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Review

Risk factors for early-onset pancreatic ductal adenocarcinoma: A systematic literature review

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ABSTRACT

Background: Emerging cancer trends suggest an increase in pancreatic cancer incidence in individuals younger than its typical age of onset, potentially reflecting changes in population exposures and lifestyles.
Patients and methods: We conducted a PRISMA-standard systematic literature review to identify non-heritable risk factors for early-onset pancreatic ductal adenocarcinoma (PDAC) (PROSPERO number: CRD42022299397). Systematic searches of MEDLINE and Embase bibliographic databases were performed (January 2022), and publications were screened against predetermined eligibility criteria; data were extracted using standardised data fields. The STROBE checklist was used to assess the completeness of reporting as a proxy for publication quality. Data were categorised by risk factor and analysed descriptively.
Results: In total, 24 publications were included. All publications reported observational study data; thresholds for age group comparisons ranged between 40 and 65 years. Lifestyle factors investigated included smoking, alcohol consumption, obesity, physical inactivity, meat intake, socioeconomic status and geographical residence. Clinical factors investigated included pancreatitis, diabetes/insulin resistance, prior cancer and cancer stage at diagnosis, hepatitis B infection, metabolic syndrome and long-term proton pump inhibitor exposure. Publication STROBE scores were 6–21 (maximum, 22). Eight studies reported results adjusted for confounders. Potential non-heritable risk factors for early-onset PDAC that warrant further investigation included smoking, alcohol consumption, pancreatitis and hepatitis B infection.
Conclusion: Evidence for non-heritable risk factors for early-onset PDAC is heterogeneous, but four factors were identified that might aid the identification of at-risk individuals who may benefit from screening and risk reduction strategies.

1. Introduction

Pancreatic cancer is a difficult-to-treat cancer with a poor prognosis. The non-specific nature of early pancreatic cancer symptoms and its aggressive nature contribute to a high proportion of patients (51%) having metastatic disease at the time of diagnosis [1–3]. Five-year survival for pancreatic cancer varies from 44.3% for patients with localised disease to only 3.2% for the high proportion of patients diagnosed with metastatic disease [1]. Therefore, increasing the proportion of patients whose cancer is detected at an early stage, when treatment is likely to be more successful, could improve pancreatic cancer outcomes.

Pancreatic cancer usually affects people later in life; the median age of onset in the USA is 70 years and, globally, incidence peaks between the ages of 65 and 79 years [1,4–6]. Overall, the incidence of pancreatic cancer has increased over recent decades, and there is evidence that this increase has been greatest in individuals younger than 50 or 55 years of age [1,6–10]. Potentially owing to the diagnosis being less likely to be considered in these individuals than in people in the typical age group for its onset, the most common form of pancreatic cancer (pancreatic ductal adenocarcinoma [PDAC] [2]) is more likely to be diagnosed at a

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later stage in younger versus older adults [11]. Therefore, there is growing interest in the aetiology and pathology of 'early-onset' disease (diagnosed at younger ages) and in opportunities to aid its early detection [2,12].

PDAC accounts for approximately 80% of pancreatic cancer cases [2]. Several risk factors for PDAC have been recognised, such as demographic characteristics (e.g. increasing age, black race and male sex), environmental and lifestyle factors (e.g. any history of tobacco smoking and obesity), comorbidities (e.g. presence of diabetes mellitus, chronic pancreatitis and *Helicobacter pylori* infection) and genetic factors (e.g. presence of hereditary pancreatic cancer genes and some genetic cancer syndromes) [1,4,13–15]. There is evidence of distinctive genomic/-transcriptomic changes in early-onset PDAC. For example, patients with early-onset PDAC are more likely to have wild-type *RAS* tumours than the general PDAC population [16], have a higher frequency of biallelic mutations in the *CDKN2* gene through homozygous copy loss and overexpress the transcription factor *FOXC2* (correlated with upregulation of *VIM* , *CDH11* and *CDH2*, which control the epithelial-to-mesenchymal transition) compared with patients with an intermediate or average age of PDAC onset (>55 years) [17], and have a lower frequency of mutations in the *SMAD4* tumour suppressor gene than patients with late-onset PDAC (≥70 years) [18].

Importantly for interventional healthcare strategies, approximately one-third of the PDAC burden can be attributed to the two-thirds of recognised risk factors that are potentially modifiable (e.g. smoking, alcohol consumption, obesity, physical inactivity and diet) [2,19]. Many environmental and lifestyle factors are known to be associated with increased cancer risks; for example, smoking, alcohol consumption, some dietary carcinogens, obesity and some infections may induce oxidative stress and inflammation that may contribute to tumourigenesis [20]. In addition, environmental pollutants have been found to increase the risk of a range of cancers including PDAC [20,21]. Further, increased exposure over recent decades to such factors may compound the risk of PDAC in individuals who have genetic risk factors. The causes of PDAC are, however, insufficiently understood, and further research and evidence syntheses are required to improve our understanding of the aetiology and risk factors for PDAC, in order to optimise screening and primary prevention strategies [2,13,14].

It has been hypothesised that early-onset PDAC (defined variously within the literature as cases diagnosed between the ages of 40 and 55 years [22,23]) may represent a distinct clinical and/or biological disease phenotype with specific aetiological factors (such as genetic and behavioural characteristics) and prognostic implications [11–13]. Indeed, it has been suggested that the more rapid increase in pancreatic cancer incidence in young (<50 years) versus older (≥50 years) adults reported in the USA between 1995 and 2014 [8], may reflect changes in carcinogenic exposures and lifestyle factors, such as obesity and smoking [8,24]. In 2014, 17% of pancreatic cancer cases diagnosed in the USA in patients at least 30 years old were estimated to be attributable to excess body weight and 10% to cigarette smoking [25]. Early-onset PDAC constitutes only a small proportion of PDAC cases (for example, 10% of patients younger than 55 years of age), but it contributes substantially to the pancreatic cancer disease burden. For example, in the USA, it has been estimated that it accounts for at least 20% of potential years of life lost owing to the disease and approximately 6% of all cancer deaths in this age group [1,26,27].

To help inform future PDAC screening and prevention strategies, we conducted a systematic literature review to identify evidence for non-heritable, potentially modifiable risk factors for early-onset PDAC.

2. Methods

2.1. Registration and methodology

The protocol for this systematic literature review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number, CRD42022299397) [28]. The review was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29,30].

2.2. Search strategy and selection criteria

Publications of interest were those reporting empirical data on non-heritable risk factors for early-onset PDAC (as defined by the authors of each publication). Publication eligibility included studies of pancreatic cancer, pancreatic adenocarcinoma and PDAC. This inclusive approach was taken in recognition that PDAC accounts for the majority of pancreatic cancer cases, but that the terminology used to describe pancreatic cancers within the literature varies. Studies investigating populations with pancreatic neuroendocrine tumours were excluded. Risk factors included demographic, socioeconomic, environmental and clinical (including presence of comorbid conditions) characteristics. Early-onset disease was determined by explicit reference to early-onset disease within the abstract text and/or by the reporting of age-stratified relative risks and/or data for age-defined populations. Non-empirical data sources (reviews, conference abstracts and protocols) were excluded, as well as animal, preclinical and case studies and articles in languages other than English. No country or date restrictions were applied. Publication eligibility criteria are summarised in Table 1.

Eligible publications were identified by systematic searches using the Ovid bibliographic research platform [31]. Targeted searches were run in the MEDLINE (Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, and OVID MEDLINE Daily and Versions and Embase databases. All publications in these databases published between 1946 (MEDLINE) or 1974 (Embase) and the search date of 20 January 2022 were searched (see Supplementary Tables S1a and S1b for full search string and screening details).

Supplementary manual searching of the proceedings of the following pre-agreed congresses held over the past 2 years was performed to identify relevant research abstracts: American Society of Clinical Oncology (ASCO), ASCO Gastrointestinal Cancers Symposium,

Table 1
Eligibility criteria for studies identified by systematic literature review.

Category	Inclusion criteria
Population	Patients with: • PDAC[a] • early-onset disease[b]
Interventions	• Any/none
Comparator	• Any/none
Outcomes	• Empirical, quantitative data on risk factors (excluding genetic factors) for early-onset PDAC[c]
Study designs	• Human clinical studies, including clinical trials, retrospective studies and observational studies • Animal, preclinical and case studies excluded
Date restrictions	• Full-text publications not restricted by date • Publications from pre-identified target congresses: 2019–2021[d]
Country restrictions	• No restriction
Language	• English language (including those translated into English)

[a]Including pancreatic cancer and pancreatic adenocarcinoma populations; excluding pancreatic neuroendocrine tumour populations.
[b]Determined by explicit reference to early-onset disease within the text and/or by the reporting of age-stratified relative risks and/or data for age-defined populations.
[c]Including demographic, socioeconomic, environmental, clinical (e.g. presence of comorbid conditions) characteristics.
[d]Congress publications of interest restricted to those presented at congresses in 2019–2021 (relevant research of interest presented earlier than this assumed to have since been published as full-text articles identified by the full-text Ovid searches).
PDAC, pancreatic ductal adenocarcinoma.

European Society for Medical Oncology and Digestive Disease Week.

2.3. Publication eligibility

Publications identified by the searches were screened against predefined inclusion and exclusion criteria in accordance with the PRISMA 2020 guidelines [29]. The title and abstract of all identified publications were screened for eligibility against the criteria stipulated in the study protocol; in addition, publications that reported data on genetic risk factors were excluded (summarised in Table 1). Short-listed publications underwent full-text review to confirm eligibility. Screening was carried out in parallel by two reviewers. To quality check the screening process, 15 randomly selected titles and abstracts were double-blind screened. The reviewers then compared their findings to ensure alignment in adherence to the inclusion criteria. Citation searching was not performed.

2.4. Data extraction

Standardised data on non-heritable risk factors were extracted from selected publications by two independent researchers and recorded in a data extraction table (Microsoft Excel).

2.5. Study and reporting quality and risk of bias assessment

The reporting quality of included publications was appraised using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist [32,33]. The checklist is designed to evaluate the reporting of observational epidemiological studies and is not explicitly a quality assessment tool, but it was used as a proxy for study quality because of its relevance to the epidemiological design of the included studies, and on the basis that completeness of study reporting may infer robustness of study design. A higher STROBE score indicates more complete reporting of key study aspects.

2.6. Data analysis

All extracted data were grouped by (and described for) each risk factor. Study size, STROBE score and use of statistical methods to control for sources of potential bias were noted and used as proxies for potential strength of evidence. A sensitivity analysis was carried out to explore the consistency (vs variation) in identified risk factors for early-onset PDAC across different age thresholds for early-onset disease (45, 55 and 65 years). No meta-analyses were planned or conducted owing to the heterogeneity in study designs and in the definitions used for early-onset

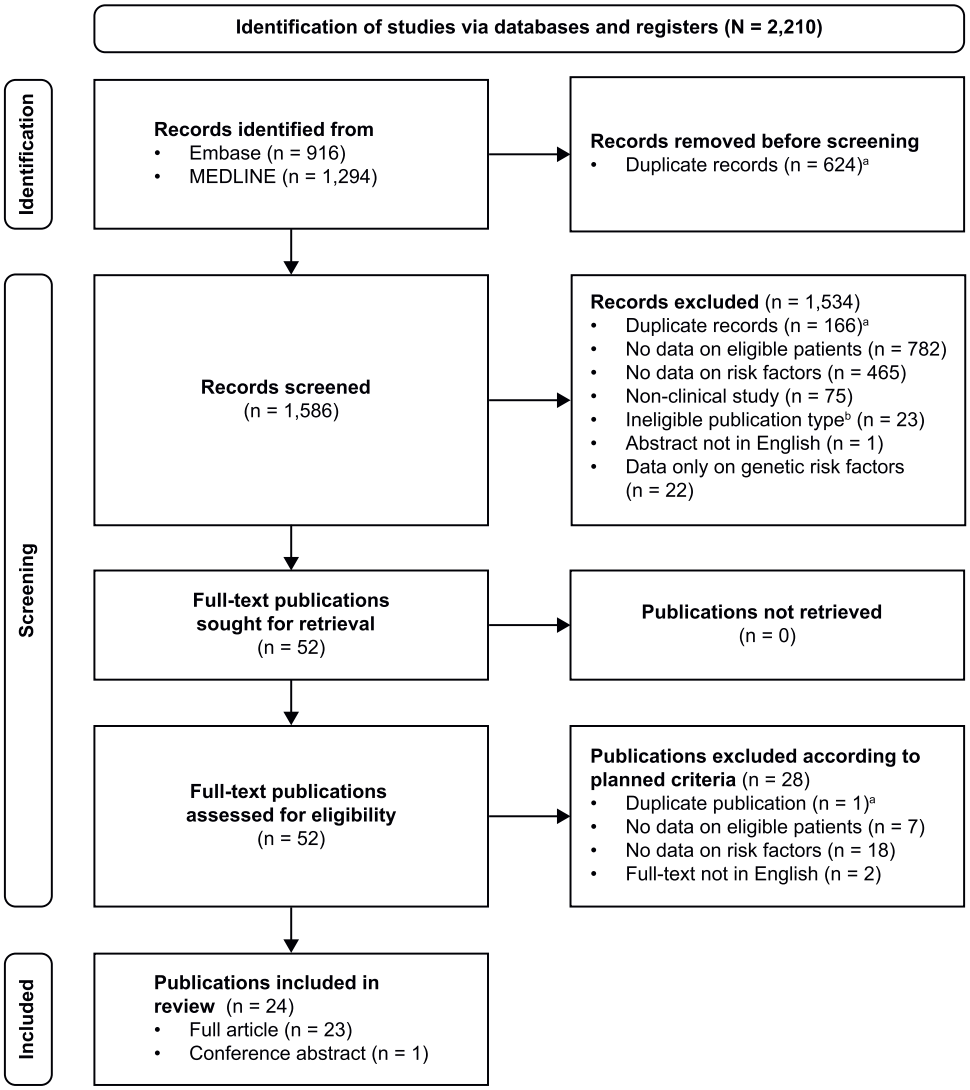

Fig. 1. PRISMA diagram of included and excluded studies in the systematic literature review. [a]Duplicate publications were excluded at more than one stage. [b]Pre-2019 conference abstract, review article, expert opinion, comment, letter to editor, case study. PRISMA, Preferred Reporting for Systematic Reviews and Meta-Analyses.

Table 2
Study characteristics and quality assessment of included studies that reported comparative data or relative risks stratified by age.

First author name Publication year Publication type	Country	Study period	Study design	Data source	Diagnosis (confirmation method)[a]	N (total patients in study)	Age groups (n)	Risk factors evaluated	Type of analysis and adjustment factors	STROBE score[b] (max, 22)
Studies reporting comparative risk for different age-defined subgroups[c]										
Desai et al. 2018 [35] Full-text article	USA	2013–2014	Retrospective review	National Inpatient Sample database –Healthcare Cost and Utilization Project (population-based data)	PC (ICD-9-CM)	69,210	• 11–25 years (1950) • 26–40 years (24,405) • 41–55 years (36,135) • 56–70 years (6720)	• Hepatitis B infection	ORs from multivariate regression analysis adjusted for: • age • sex • race • income • diabetes • obesity • smoking • alcohol history • GI cancer family history	16
Eguchi et al. 2016 [36] Full-text article	Japan	Registry started 1981	Retrospective review	Pancreatic Cancer Registry – Japan Pancreas Society (population-based data)	PDAC	36,145	• 10–39 years (526) • 40–99 years (35,619)	• Smoking • Alcohol consumption • Pancreatitis • Cancer stage	Unadjusted	9
Duell et al. 2012 [53] Full-text article	USA, Canada, Italy, Netherlands, Poland, China, Australia	1983–2009	Individual-level pooled analysis from 10 case–control studies (retrospective review)	Pancreatic Cancer Case–Control Consortium (PanC4); regional and hospital cancer registries (case–control data)	PC (clinical diagnosis)	4674 patients with PC (10,703 patients without PC)	Patients with PC • <65 years (2369) • ≥65 years (2305) • Healthy individuals • <65 years (6028) • ≥65 years (4675)	• Pancreatitis	Pooled ORs from unconditional multiple logistic regression analysis adjusted for: • age • sex • race/ethnicity • education • BMI • smoking • alcohol • history of diabetes • study region	19
Dzeletovic et al. 2014 [42] Full-text article	USA	Jan 1992–Sept 2011	Retrospective review	Mayo Clinic Biospecimen Resource for Pancreas Research	Pancreatic adenocarcinoma (pathology, medical records, self report or death certificate)	2573		• Pancreatitis	Unadjusted	17
Jiang et al. 2017 [44] Full-text article	China	Jan 1999– Dec 2014 (PDAC diagnosis)	Retrospective chart review	Medical records (single centre)	PDAC (histology)	1789	• ≤45 years (156) • >45 years (1633) • (age at diagnosis)	• Smoking • Alcohol consumption • Obesity	Unadjusted	13
Ohmoto et al. 2016 [45] Full-text article	Japan	2002–2013 (diagnosis)	Retrospective review	National Cancer Center Hospital database (single centre)	PDAC (pathology)	908	≤40 years (17)	• Smoking • Prior cancer	Unadjusted	13

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Table 2 (*continued*)

First author name Publication year Publication type	Country	Study period	Study design	Data source	Diagnosis (confirmation method)[a]	N (total patients in study)	Age groups (n)	Risk factors evaluated	Type of analysis and adjustment factors	STROBE score[b] (max, 22)
							• >40 years (891)			
Li et al. 2009 [54] Full-text article	USA	2004–2008	Case–control study (retrospective review of medical records)	Institutional tumour registry; structured questionnaire and medical records (case–control data from single centre)	PDAC (pathology)	841 patients with PC (754 healthy individuals)	Patients with PC <40 years (16) 40–49 years (85) • 50–59 years (228) • 60–69 years (318) • ≥70 years (194) Healthy individuals < 40 years (15) 40–49 years (85) • 50–59 years (233) • 60–69 years (271) • ≥70 years (150)	• Obesity	ORs from multivariable unconditional linear regression analysis adjusted for: • age • sex • race • smoking • alcohol • diabetes • family history of cancer	20
Salem et al. 2019 [46] Conference abstract	USA	2013–2017	Retrospective review	Institutional tumour registry database (single centre)	PDAC	516	≤50 years (73) • ≥70 years (443)	• Smoking • Obesity • History of cancer	Unadjusted	NA
Wang et al. 2012 [47] Full-text article	China	1 Jan 1998–30 Dec 2010	Retrospective review	Hospital records (single centre)	Pancreatic adenocarcinoma (histology)	488	• <65 years (338) • ≥65 years (150)	• Hepatitis B infection • Metabolic syndrome	Unadjusted	14
Huang et al. 2013 [43] Full-text article	China	Jan 2000–June 2010	Retrospective review	Medical records (single centre)	PC, all types (histopathology)	331		• Smoking • Alcohol consumption	Unadjusted	15
Dugnani et al. 2016 [57] Full-text article	Italy	Jan 2008– Dec 2012	Prospective observational study, case–cohort study design	Inpatient and outpatient records (single centre)	PDAC	296		• Diabetes	Unadjusted	18
Bunduc et al. 2018 [41] Full-text article	Romania	1 Jan 2015– 31 Dec 2017 (diagnosis)	Retrospective review	Hospital database (single centre)	PDAC (histology)	148	≤45 years (24) • >45 years (124) (age at diagnosis)	• Smoking • Alcohol consumption • Obesity • Pancreatitis	Unadjusted	10
Augustine et al. 1992 [40] Full-text article	India	Before 1992 (8 years)	Retrospective review	Hospital records (single centre)	Pancreatic adenocarcinoma (histology)	98 with PDAC, including 22 with tropical pancreatitis (82 with tropical		• Pancreatitis	Unadjusted	6

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Table 2 (*continued*)

First author name Publication year Publication type	Country	Study period	Study design	Data source	Diagnosis (confirmation method)[a]	N (total patients in study)	Age groups (n)	Risk factors evaluated	Type of analysis and adjustment factors	STROBE score[b] (max, 22)
						pancreatitis without PDAC)				
Noor et al. 2016 [38] Full-text article	UK	1993–1997 (recruitment); 2010 (end of follow-up)	Prospective case–cohort study	European Prospective Investigation of Cancer (EPIC)-Norfolk database (questionnaire), Norfolk Health Authority hospitalisation records, Eastern Region Cancer Registry (population-based case–control data)	PC (clinical review of medical notes)	88 patients with PC (3970 patients without PC)	Patients with PC • Activity at <60 years (29) Activity at ≥60 years (59) Healthy individuals • Activity at <60 years (2067) • Activity at ≥60 years (1903) (at recruitment)	• History of physical inactivity	HRs from multivariate Cox regression analysis adjusted for: • age • sex • smoking • diabetes • BMI	18
Studies reporting relative risk stratified by age[d]										
Alese et al. 2020 [34] Full-text article	USA	2004–2013	Retrospective review	National Cancer Database (population-based data)	PDAC	124,442	• ≤50 years (9657) • >50 years (114,785)	• Socioeconomic status • Urban/rural living	Unadjusted	15
Brusselaers et al. 2020 [37] Full-text article	Sweden	1 July 2005–31 Dec 2012 (enrolment); 31 Dec 2012 (end of follow-up)	Cohort study	Swedish Prescribed Drug Registry and Swedish Cancer Registry (population-based data)	PC (ICD-10 C25) and pancreatic adenocarcinoma (ICD-10 C25, 096; 80.4%)	1733 long-term PPI users with PC 1394 long-term PPI users with PDAC (794 759 long-term PPI users without PC)	Long-term PPI users with PC <40 years (10) 40–49 years (65) • 50–59 years (230) • 60–69 years (602) • ≥70 years (826) Long-term PPI users without PC • <40 years (88,765) • 40–49 years (103,719) • 50–59 years (155,395) • 60–69 years (177,008) • ≥70 years (269,872)	• Long-term PPI exposure • (≥180 days)	• Incidence RRs standardised for: • country • age • sex • calendar period	20

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Table 2 (*continued*)

First author name Publication year Publication type	Country	Study period	Study design	Data source	Diagnosis (confirmation method)[a]	N (total patients in study)	Age groups (n)	Risk factors evaluated	Type of analysis and adjustment factors	STROBE score[b] (max, 22)
Gupta et al. 2006 [52] Full-text article	USA	1999–2004	Retrospective cohort study	Veterans Health Administration National Patient Care Database (healthcare system data)	PC (ICD9 157.0–157.9)	149 with PC and DM (36,482 with DM only)	• 40–44 years • 45–49 years • 50–54 years • 55–59 years • 60–64 years • 65–69 years • 70–74 years • 75–79 years • 80–84 years • ≥85 years	• Diabetes	RRs from Poisson regression analysis using incidences adjusted for: • age • sex • race/ • ethnicity	21
Beaney et al. 2017 [39] Full-text article	UK	1993–1997 (recruitment); June 2010 (end of follow-up)	Prospective case–cohort study	European Prospective Investigation of Cancer (EPIC)-Norfolk database (questionnaire), Norfolk Health Authority hospitalisation records, Eastern Region Cancer Registry and Information Centre (population-based case–control data)	PC (clinical review of symptoms and radiological investigations)	86 patients with PC (3970 patients without PC)	Patients with PC <60 years (28) ≥60 years (58) Healthy individuals • <60 years (2067) • ≥60 years (1903) (at recruitment)	• Meat intake	HRs from multivariable regression analysis adjusted for: • age at recruitment • sex • smoking • diabetes • total energy intake	17
Studies reporting both comparative risk for different age groups[c] and relative risk stratified by age[d]										
McWilliams et al. 2016 [55] Full-text article	USA, Australia, Canada, Netherlands, Poland, Italy	1995–2011	Pooled analysis of 8 case–control studies (retrospective review)	Pancreatic Cancer Case–Control Consortium (PanC4) (case–control data)	PDAC (histology) or PC (clinical diagnosis)	1954 patients with PC (3278 healthy individuals)	Patients with PC • <45 years (226) • <60 years (1954) - <45 years (226) - 45–49 years (318) - 50–54 years (580) - 55–59 years (830) Healthy individuals • < 45 years (589) • <60 years (3278) - <45 years (589) - 45–49 years (528)	• Smoking • Alcohol consumption • Obesity • Pancreatitis • Diabetes	ORs from multivariable logistic regression analysis adjusted for: • family history of PC • diabetes • sex • smoking • alcohol • adult BMI • study site	19

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Table 2 (*continued*)

First author name Publication year Publication type	Country	Study period	Study design	Data source	Diagnosis (confirmation method)[a]	N (total patients in study)	Age groups (n)	Risk factors evaluated	Type of analysis and adjustment factors	STROBE score[b] (max, 22)
							- 50–54 years (986) - 55–59 years (1175)			
Rulyak et al. 2003 [56] Full-text article	USA	1996–2001	Nested case–control study	University of Washington Seattle pancreatic cancer surveillance program (single centre)	PC (pathology, medical records, death certificate, proxy confirmation)	83 patients with PC (158 controls from 28 familial PC kindreds)	Patients with PC <50 years (20) 50–69 years (34) ≥70 years (29) Healthy individuals <50 years (12) 50–69 years (65) • ≥70 years (81)	• Smoking	ORs from multivariate regression analysis adjusted for: • age • family history of PC • prior non-pancreatic cancer diagnosis • diabetes history • male sex	20

[a]Confirmation method included if reported.
[b]Number of fulfilled items out of 22 items on the STROBE checklist [32,33].
[c]Comparative data: comparative risk factor prevalence across age groups or comparative age of populations with versus without specific risk factors.
[d]Relative risks in age strata without direct comparison between age strata.
[f]STROBE checklist not applicable because of publication type (conference abstract or brief report). BMI, body mass index; CM, Clinical Modification; DM, diabetes mellitus; GI, gastrointestinal; HR, hazard ratio; ICD, International Classification of Diseases; max, maximum; NA, not applicable; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma; PC, pancreatic cancer; PPI, proton pump inhibitor; RR, rate ratio; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology.

Table 3
Relationship between modifiable/lifestyle risk factors and young age of PDAC onset.

First author name	N • Age groups (n)	Comparative data: comparison of RF prevalence between age groups or comparison of mean age of groups with vs without specific RFs n (%) of young patients with RF vs n (%) of old patients with RF p value for young vs old patients Other data as stated	Relative risks in age strata (without direct comparison between age strata) n (%) of young patients with RF vs n (%) of old patients with RF Other data as stated
Smoking			
Eguchi [36]	36,145 • 10–39 years (526) • 40–99 years (35,619)	Smokers: 26 (4.9) vs 2332 (6.5) Former smokers: 15 (2.9) vs 1681 (4.7) Never smokers: 48 (9.1) vs 6302 (17.7) Unknown: 437 (83.1) vs 25,304 (71.0) p = 0.293 Brinkman index (cigarette smoke exposure) Median (SD): 119.1 (181.7) vs 294.1 (513.3) p = 0.3990	–
McWilliams [55]	1954 patients with PDAC • <45 years (226) • <60 years (1954) 3278 healthy people • <45 years (589) • <60 years (3278)	**PDAC cases vs controls, <45 years** OR (95% CI) ref 0 pack-years: 1–19 pack-years: 1.39 (0.90–2.16) **20–39 pack-years: 1.87 (1.08–3.23)** ≥40 pack-years: 2.23 (0.91–5.47) **PDAC cases vs controls, <60 years** **OR (95% CI) ref 0 pack-years:** **1–19 pack-years: 1.40 (1.18–1.65)** **20–39 pack-years: 2.29 (1.89–2.76)** **≥40 pack-years: 2.79 (2.24–3.48)** Interaction between smoking and age at PDAC onset (<45 years vs <60 years), p = 0.20	<45 years vs <60 years 0 pack-years: 79 (35) vs 569 (29) 1–19 pack-years: 78 (35) vs 517 (26) 20–39 pack-years: 39 (17) vs 404 (21) ≥40 pack-years: 14 (6) vs 292 (15) Unknown pack-years: 16 (7) vs 172 (9)
Jiang [44]	1789 • ≤45 years (156) • >45 years (1633)	**Ever smokers: 54 (34.6) vs 423 (25.9)** **p = 0.024** Daily cigarette consumption, mean 19.3 vs 18.1 p = 0.709	–
Ohmoto [45]	908 • ≤40 years (17) • >40 years (891)	Smoking history: 10 (58.8) vs 436 (48.9) No smoking history: 7 (41.2) vs 443 (49.7) Unknown: NA vs 12 (1.3) p = 0.475	–
Salem [46]	516 • ≤50 years (73) • ≥70 years (443)	**Current/prior smokers: 64% vs 47%** **p = 0.03**	–
Huang [43]	331	**Mean age at PDAC diagnosis** **Smokers: 59.04 years** **Non-smokers: 61.51 years** **p = 0.026**	–
Bunduc [41]	148 • ≤45 years (24) • >45 years (124)	Smokers: 50.00% vs 28.92% Non-smokers: 50.00% vs 79.92% p = 0.06	–
Rulyak [56]	83 patients with PDAC • <50 years (20) • 50–69 years (34) • ≥70 years (29) 158 healthy people • <50 years (12) • 50–69 years (65) • ≥70 years (81)	*Adjusted multivariate analysis* **OR for ever vs never smokers (95% CI): 3.7 (1.8–7.6)** Patients <50 years of age: 10.4 Patients ≥70 years of age: 1.4 Likelihood ratio test, p = 0.35 **Mean age of PDAC onset** **Ever smokers: 59.6 years** **Never smokers: 69.1 years** **p = 0.01**	**In patients with PDAC confirmed by pathology or medical records (32)** **OR (95% CI) for ever vs never smokers:** **Patients <50 years of age: 14.0 (1.1–692.2)** Patients ≥70 years of age: 5.7 (0.9–59.9) *Adjusted bivariate analysis (adjusted for family history)* **OR for ever vs never smokers (95% CI): 4.0 (2.3–7.2)** **Patients <50 years of age, n (%)** **Ever smokers with PDAC: 17 (85.0)** **Never smokers with PDAC: 3 (15.0)** **Ever smokers without PDAC: 5 (41.7)** **Never smokers without PDAC: 7 (58.3)**

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Table 3 (*continued*)

First author name	N • Age groups (n)	Comparative data: comparison of RF prevalence between age groups or comparison of mean age of groups with vs without specific RFs n (%) of young patients with RF vs n (%) of old patients with RF p value for young vs old patients Other data as stated	Relative risks in age strata (without direct comparison between age strata) n (%) of young patients with RF vs n (%) of old patients with RF Other data as stated
			OR for ever vs never smokers (95% CI): 7.6 (1.3–43.0) **Patients 50–69 years of age, n (%)** **Ever smokers with PDAC: 25 (73.5)** **Never smokers with PDAC: 9 (26.5)** **Ever smokers without PDAC: 29 (44.6)** **Never smokers without PDAC: 36 (55.4)** **OR for ever vs never smokers (95% CI): 3.4 (1.3–9.0)** **Patients ≥70 years of age** **Ever smokers with PDAC: 18 (62.1)** **Never smokers with PDAC: 11 (37.9)** **Ever smokers without PDAC: 28 (34.6)** **Never smokers without PDAC: 53 (65.4)** **OR for ever vs never smokers (95% CI): 2.9 (1.1–7.4)**
Alcohol consumption			
Eguchi [36]	36,145 • 10–39 years (526) • 40–99 years (35 619)	Alcohol consumption: frequency 0–1 × /week: 62 (11.8) vs 7556 (21.2) Every day: 18 (3.4) vs 2503 (7.0) Unknown: 446 (84.8) vs 25,560 (71.8) p = 0.623 Alcohol consumption: amount (units/day × frequency × years) Mean (SD): 38.6 (71.5) vs 90.3 (290.3) p = 0.8530	–
McWilliams [55]	1954 patients with PDAC • <45 years (226) • <60 years (1954) 3278 healthy people • <45 years (589) • <60 years (3278)	**PDAC cases vs controls, <45 years** **OR (95% CI) ref <26 g/day:** **≥26 g/day, 2.18 (1.17–4.09)** **PDAC cases vs controls, <60 years** **OR (95% CI) ref <26 g/day:** **≥26 g/day, 1.49 (1.21–1.84)** Interaction between alcohol and age at PDAC onset (<45 years vs <60 years), p = 0.20 PDAC cases vs controls, <60 years OR (95% CI) ref <26 g/day: 26–51 g/day, 1.01 (0.77–1.32) **52–77 g/day, 2.24 (1.45–3.44)** **78–103 g/day, 2.26 (1.21–4.23)** **> 104 g/day, 4.60 (2.48–8.56)**	<45 years vs <60 years ≥26 g ethanol/day: 25 (11) vs 213 (11) <26 g ethanol/day: 146 (65) vs 1257 (64) Unknown g/day: 55 (24) vs 484 (25)
Jiang [44]	1789 • ≤45 years (156) • >45 years (1633)	Ever drinkers (≥12.5 g of alcohol/day for ≥1 year, or lower amount for >1 year) 55 (35.3) vs 479 (29.3) p = 0.122 Mean daily alcohol consumption, units 3.4 vs 3.8 p = 0.697	–
Huang [43]	331	**Mean age at PDAC diagnosis** **Patients who consumed alcohol 1 × /week for ≥1 year: 57.96 years** **Patients not consuming alcohol: 61.37 years** **p = 0.022**	–
Bunduc [41]	148 • ≤45 years (24) • >45 years (124)	**Patients who consumed alcohol: 42.86% vs 5.41%** **Patients not consuming alcohol: 57.14% vs 94.49%** **p = 0.01**	–
Obesity and BMI			
McWilliams [55]	1954 patients with PDAC • <45 years (226) • <60 years (1954)	Usual BMI (kg/m^2) PDAC cases vs controls, < 45 years OR (95% CI) ref <30:	Usual BMI (kg/m^2), <45 years vs <60 years ≥30: 43 (19) vs 461 (24)

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Table 3 (*continued*)

First author name	N • Age groups (n)	Comparative data: comparison of RF prevalence between age groups or comparison of mean age of groups with vs without specific RFs n (%) of young patients with RF vs n (%) of old patients with RF p value for young vs old patients Other data as stated	Relative risks in age strata (without direct comparison between age strata) n (%) of young patients with RF vs n (%) of old patients with RF Other data as stated
	3278 healthy people • <45 years (589) • <60 years (3278)	≥30, 1.13 (0.67–1.90) **PDAC cases vs controls, <60 years** **OR (95% CI) ref <30:** **≥30, 1.28 (1.08–1.52)** Interaction with age at PDAC onset (<45 years vs <60 years), p = 0.52	<30: 170 (75) vs 1366 (70) Unknown: 13 (6) vs 127 (6)
Jiang [44]	1789 • ≤45 years (156) • >45 years (1633)	BMI >28 kg/m^2: 26 (16.7) vs 226 (13.8) p = 0.317 Mean BMI (kg/m^2) 24.28 vs 24.51 p = 0.826 Weight loss before PDAC diagnosis: 72 (46.2) vs 653 (40.0) p = 0.134	–
Li [54]	841 patients with PDAC • <40 years (16) • 40–49 years (85) • 50–59 years (228) • 60–69 years (318) • ≥70 years (194) 754 healthy people • <40 years (15) • 40–49 years (85) • 50–59 years (233) • 60–69 years (271) • ≥70 years (150)	**Median age at PDAC diagnosis** **Patients with normal weight when 20–49 years: 64 years** **Patients overweight when 20–49 years: 61 years** **p = 0.02** **Patients obese when 20–49 years: 59 years** **p < 0.001** Mean (SD) age, years, at PDAC diagnosis, *adjusted OR (95% CI)* Patients never overweight/obese: 63.1 (11.1) (ref) **Patients overweight when 14–19 years: 59.4 (10.4), p = 0.01, *2.03 (1.41–2.92)*** Patients overweight when 20–29 years: 60.6 (9.4), p = 0.39, ***1.65 (1.16–2.36)*** Patients overweight when 30–39 years: 60.8 (10.9), p = 0.56, *1.27 (0.90–1.79)* Patients overweight when 40–49 years: 62.0 (9.4), p > 0.99, *0.91 (0.65–1.27)* Patients overweight when 50–59 years: 64.8 (7.3), p > 0.99, *0.95 (0.67–1.35)* Patients obese when 14–19 years: 57.3 (13.3), p = 0.28, *1.83 (0.81–4.15)* **Patients obese when 20–29 years: 56.0 (10.2), p = 0.003, *2.17 (1.15–4.07)*** Patients obese when 30–39 years: 58.3 (10.1), p = 0.06, ***2.31 (1.32–4.02)*** Patients obese when 40–49 years: 60.3 (9.8), p = 0.71, *1.47 (0.97–2.24)* Patients obese when 50–59 years: 62.3 (5.9), p > 0.99, *0.68 (0.45–1.02)* Mean (SD) age, years, at PDAC diagnosis Normal weight when 14–19 years: 62.4 (10.1) (ref) **Overweight when 14–19 years: 59.7 (9.9), p = 0.004** Obese when 14–19 years: 57.3 (13.3), p = 0.18 Normal weight when 20–29 years: 62.5 (10.4) (ref) **Overweight when 20–29 years: 60.9 (9.4), p = 0.006** **Obese when 20–29 years: 56.9 (10.7), p < 0.001** Normal weight when 30–39 years: 63.2 (10.0) (ref) **Overweight when 30–39 years: 61.3 (9.8), p = 0.01** **Obese when 30–39 years: 57.6 (9.9), p < 0.001** Normal weight when 40–49 years: 64.4 (9.3) (ref) **Overweight when 40–49 years: 62.2 (9.1), p = 0.004** **Obese when 40–49 years: 60.1 (9.1), p < 0.001** Normal weight when 50–59 years: 67.2 (8.0) (ref) **Overweight when 50–59 years: 65.2 (7.4), p = 0.008** **Obese when 50–59 years: 63.3 (7.0), p < 0.001**	–
Salem [46]	516 • ≤50 years (73) • ≥70 years (443)	Median BMI (kg/m^2) at presentation: 27.1 vs 25.4 p = 0.06	–
Bunduc [41]	148 • ≤45 years (24)	Obese: 0% vs 7.89% Not obese: 100% vs 92.11% p = 1	–

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Table 3 (*continued*)

First author name	N • Age groups (n)	Comparative data: comparison of RF prevalence between age groups or comparison of mean age of groups with vs without specific RFs n (%) of young patients with RF vs n (%) of old patients with RF p value for young vs old patients Other data as stated	Relative risks in age strata (without direct comparison between age strata) n (%) of young patients with RF vs n (%) of old patients with RF Other data as stated
	• >45 years (124)		
History of physical inactivity			
Noor [38]	88 patients with PDAC • Activity at <60 years (29) • Activity at ≥60 years (59) 3970 healthy people • Activity at <60 years (2067) • Activity at ≥60 years (1903) at recruitment	*Multivariate analysis adjusted for age, sex, smoking, diabetes, BMI* HR (95% CI) for no PDAC vs PDAC for patients Inactive at <60 years: 1.00 Moderately inactive at <60 years: 0.46 (0.16–1.27) Moderately active at <60 years: 0.73 (0.30–1.77) **Active at <60 years: 0.25 (0.07–0.93)** HR trend across categories = 0.73 (0.51–1.04), p = 0.08 HR (95% CI) for no PDAC vs PDAC for patients Inactive at ≥60 years: 1.00 Moderately inactive at ≥60 years: 0.91 (0.47–1.77) Moderately active at ≥60 years: 1.18 (0.56–2.49) Active at ≥60 years: 1.89 (0.89–4.00) HR trend across categories = 1.21 (0.94–1.55), p = 0.13	–
Meat intake			
Beaney [39]	86 patients with PDAC • <60 years (28) • ≥60 years (58) 3970 healthy people • <60 years (2067) • ≥60 years (1903)	–	HR (95% CI) for PDAC by red meat intake (g/day) in patients <60 years Q1 (0 to <8.6): 1.00 (ref) Q2 (8.6 to <23.1): 3.23 (0.65–16.12) Q3 (23.1 to <36.8): 2.13 (0.39–11.73) Q4 (36.8 to <55.7): 4.32 (0.91–20.59) Q5 (55.7–349.3): 4.62 (0.96–22.30), p = 0.06 vs Q1 **HR trend across quintiles: 1.33 (1.01–1.77), p <0.05** HR (95% CI) for PDAC by processed meat intake (g/day) in patients <60 years Q1 (0 to <5.4): 1.00 (ref) Q2 (5.4 to <14.2): 1.56 (0.35–7.01) Q3 (14.2 to <23.1): 2.64 (0.66–10.62) Q4 (23.1 to <36.1): 3.35 (0.86–13.09) Q5 (36.1–192.0): 3.73 (0.95–14.66), p = 0.06 vs Q1 **HR trend across quintiles: 1.37 (1.04–1.82), p <0.05** HR (95% CI) for PDAC by white meat intake (g/day) in patients <60 years Q1 (0 to <0.2): 1.00 (ref) Q2 (0.2 to <14.3): 1.60 (0.53–4.81) Q3 (14.3 to <25.3): NA Q4 (25.3 to <41.4): 1.94 (0.70–5.38) Q5 (41.4–347.8): 0.96 (0.29–3.16) HR trend across quintiles: p > 0.05 HR (95% CI) for PDAC by red meat intake (g/day) in patients ≥60 years Q1 (0 to <8.6): 1.00 (ref) Q2 (8.6 to <23.1): 0.51 (0.23–1.12) Q3 (23.1 to <36.8): 0.38 (0.16–0.89) Q4 (36.8 to <55.7): 0.80 (0.41–1.57) Q5 (55.7–349.3): 0.24 (0.08–0.67) HR trend across quintiles: p > 0.05 HR (95% CI) for PDAC by processed meat intake (g/day) in patients ≥60 years Q1 (0 to <5.4): 1.00 (ref) Q2 (5.4 to <14.2): 1.21 (0.55–2.68)

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Table 3 (*continued*)

First author name	N • Age groups (n)	Comparative data: comparison of RF prevalence between age groups or comparison of mean age of groups with vs without specific RFs n (%) of young patients with RF vs n (%) of old patients with RF p value for young vs old patients Other data as stated	Relative risks in age strata (without direct comparison between age strata) n (%) of young patients with RF vs n (%) of old patients with RF Other data as stated
			Q3 (14.2 to <23.1): 0.81 (0.34–1.92) Q4 (23.1 to <36.1): 0.75 (0.31–1.83) Q5 (36.1–192.0): 0.90 (0.37–2.17) HR trend across quintiles: $p > 0.05$ HR (95% CI) for PDAC by white meat intake (g/day) in patients ≥60 years Q1 (0 to <0.2): 1.00 (ref) Q2 (0.2 to <14.3): 3.40 (1.32–8.77) Q3 (14.3 to <25.3): 2.19 (0.80–5.96) Q4 (25.3 to <41.4): 3.05 (1.19–7.82) Q5 (41.4–347.8): 2.06 (0.73–5.81) HR trend across quintiles: $p > 0.05$
Socioeconomic status			
Alese [34]	124,442 • ≤50 years (9657) • >50 years (114,785)	–	Median income quartiles in 2000, US$ <30,000: 1452 (15.77) vs 15,429 (14.08) 30,000–35,999: 1737 (18.87) vs 19,963 (18.21) 36,000–45, 999: 2632 (28.59) vs 30,294 (27.64) ≥46,000: 3385 (36.77) vs 436,914 (40.07) Between quartiles: $p < 0.001$
Geographical residence			
Alese [34]	124,442 • ≤50 years (9657) • >50 years (114,785)	–	Metro: 7694 (83.29) vs 91,523 (83.54) Urban: 1378 (14.92) vs 15,918 (14.53) Rural 166 (1.8) vs 2113 (1.93) Urban vs metro vs rural: $p = 0.425$

Statistically significant data in bold.

BMI, body mass index; CI, confidence interval; HR, hazard ratio; metro, metropolitan; NA, not applicable; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma; Q, quintile; ref, reference; RF, risk factor; SD, standard deviation.

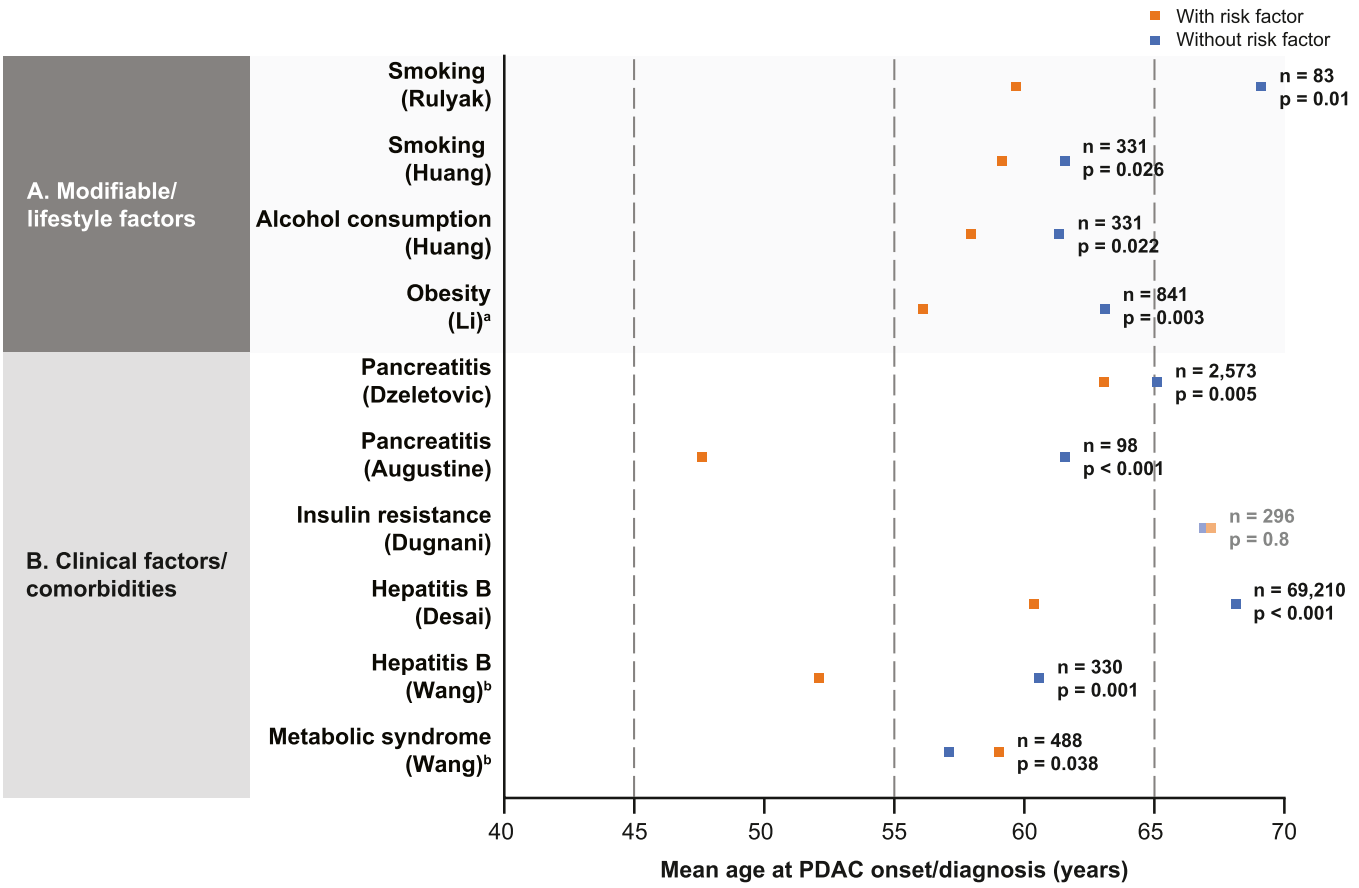

Fig. 2. Mean age at PDAC onset/diagnosis in patients with and without specific modifiable/lifestyle factors (A) and clinical factors/comorbidities (B). Statistically significant data in bold. [a]Obesity at 20–29 years of age vs never overweight/obese. [b]Median age. PDAC, pancreatic adenocarcinoma.

disease.

3. Results

3.1. Search results

The systematic searches identified 1586 publications after initial deduplication from a total of 2210 publications. Of these, 52 were short-listed for full-text screening based on title and abstract review. Twenty-four publications were confirmed as eligible for inclusion and data extraction based on full-text review (23 peer-reviewed journal articles, including one brief report and one conference abstract). Publication identification and screening are summarised in the PRISMA flow chart (Figure 1).

3.2. Characteristics of included studies

All 24 publications included in this review reported data from observational studies; six of them reported population-based data (i.e. data representing overall regional/national populations) [34–39]. Most publications (17/24) reported retrospective cohort studies [34–37, 40–52], four reported retrospective case–control studies [53–56] and three reported prospective cohort studies [38,39,57]. Details of the included studies are summarised in Table 2 and Supplementary Table S2.

The included studies reported a range of age-related risk data: nine studies compared risk factor prevalence across different age groups [36, 41,44–47,53,55,56]; eight compared the age of populations with versus without specific risk factors [35,40,42,43,47,54,56,57]; six reported relative PDAC risk stratified by age [34,37,39,52,55,56]; one study compared PDAC risk for populations defined by history of potential risk factor exposure [38] (Table 2); and five studies described risk factor prevalence in populations predefined as having early-onset PDAC without any risk comparisons [44,48–51] (Supplementary Table S2). Three publications reported more than one type of age-related risk data [44,55,56] (one of these publications reported both comparative data [Table 2] and descriptive data [Supplementary Table S2] [44]).

Eight studies included statistical adjustments to control for potential confounding and/or colinear factors [35,38,39,52–56]. Adjustment factors within the literature included: smoking, alcohol consumption, body mass index (BMI)/obesity, total energy intake, household income, level of education, presence/absence of diabetes mellitus, sex, race/-ethnicity, family history of cancer (any, pancreatic and gastrointestinal), hepatitis B infection, study site/region and age at recruitment [35,38,39, 52–56]. One additional publication reported incidence rate ratios that were simultaneously standardised for country, age, sex and calendar period, but no specific adjustment for potential risk factors was included [37].

A wide range of age thresholds were used within the identified literature to investigate young- or early-onset PDAC – diagnosis before, or at, the age of: 40 years in three studies [36,45,49], 45 years in six studies [41,44,48,50,51,55], 50 years in three studies [34,46,56], 60 years in two studies [38,39], and 65 years in two studies [47,53]. In addition, two studies reported data for multiple age groups (5- or 10-year age groups between 40 and ≥85 years of age) [37,52] and eight studies compared the mean ages of patient groups with/without specific risk factors [35,40,42,43,47,54,56,57].

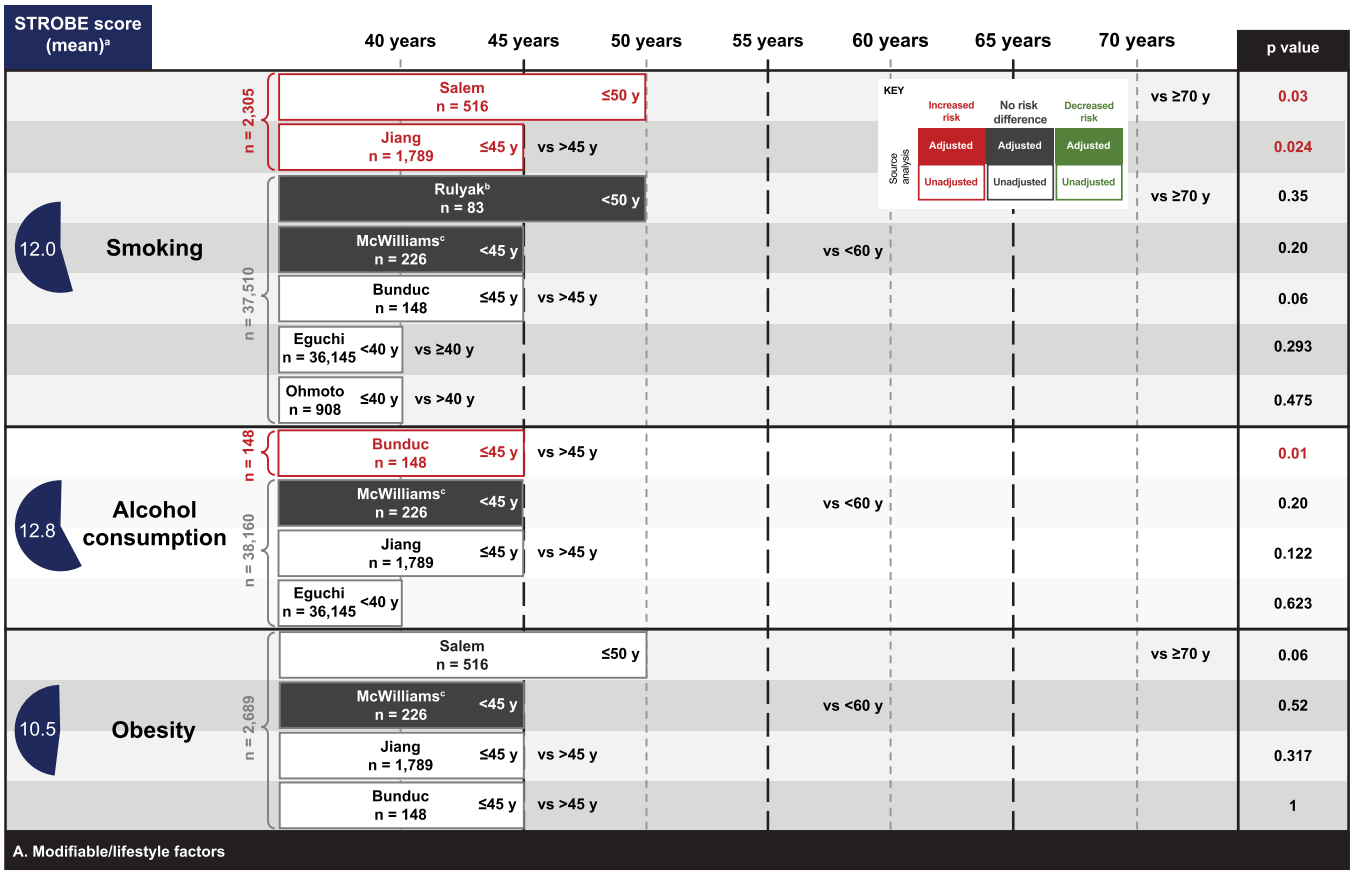

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Fig. 3. Risk of pancreatic cancer in young patients versus old patients: modifiable/lifestyle factors (A) and clinical factors/comorbidities (B). [a]Maximum STROBE score possible, 22. [b]Multivariate regression analysis of the interaction of smoking with age and sex; conditional logistic regression model adjusted for ever smoking, number of affected first-degree relatives, history of diabetes, male sex, age, number of affected second-degree relatives, prior diagnosis of non-pancreatic cancer, relationship to affected relatives. [c]Multivariable model includes factors statistically associated with increased risk in univariable modelling: first-degree family history of pancreatic cancer (no/yes/unknown); diabetes mellitus diagnosis (yes/no); sex (male/female); smoking intensity; alcohol consumption; usual adult BMI; study site (Mayo Clinic/non-Mayo Clinic in USA/non-Mayo Clinic outside USA). [d]Unconditional multiple logistic regression model adjusted for: age (<50/50–54/55–59/60–64/65–69/70–74/≥75 years); sex; race/ethnicity (non-Hispanic White, Hispanic, non-Hispanic Black, others); education (≤8th grade/9th–11th grade/12th grade or high school/college/≥1 year of graduate or professional school), BMI (<20/20 to <25/25 to <30/≥30 kg/m^2); tobacco smoking (never/products other than cigarettes/1 to ≤20 cigarettes per day/≥20 cigarettes per day/>10 years since quitting cigarettes/1 to ≤10 years since quitting cigarettes); alcohol intake (never/<1 drink per day/1–4 drinks per day/≥4 drinks per day); history of diabetes; study centre. BMI, body mass index; STROBE, STrengthening the Reporting of OBservational Studies in Epidemiology; y, years.,.

3.3. Study and reporting quality of included studies

The included publications were evaluated using the STROBE checklist [32]. Two publications could not be evaluated because they were not full research articles (one conference abstract and one brief report [46,49]). Out of 22 items on the STROBE checklist, the number of items that were fulfilled within each study report ranged from 6 to 21, indicating wide variation in the level of completeness of study reporting and potentially research quality (Table 2 and Supplementary Table S2).

3.4. Modifiable and lifestyle risk factors

The results of 12 publications reporting comparative data and stratified relative risk data for age-related modifiable and lifestyle factors associated with PDAC are summarised in Table 3. The descriptive analyses of modifiable and lifestyle risk factors in young patients with PDAC are presented in Supplementary Table S3.

3.4.1. Smoking

Eight publications investigated the potential relationship between smoking status and age of PDAC onset/diagnosis. Of these publications, four (50%) reported an apparent association between smoking and young age of PDAC onset/diagnosis (Table 3, Figures 2A and 3A) [43,44,46,56].

In two of the included studies, the mean age of PDAC onset in patients with a history of smoking was lower than in patients with no such history. In a US case–control study by Rulyak et al, smokers developed PDAC on average 10 years earlier than non-smokers (59.6 years vs 69.1 years; p = 0.01) [56]. Similarly, in a retrospective cohort study conducted in China (N = 331), the mean age of PDAC diagnosis was 59.0 years in smokers compared with 61.5 years in non-smokers (p = 0.026) [43] (Table 3 and Figure 2A).

When smoking was investigated as a specific risk factor for early-onset PDAC, however, only two of seven studies found evidence of a statistically significant association (Table 3 and Figure 3A). These two studies were retrospective cohort studies (N = 1789 and N = 516) that reported higher proportions of ever smokers among young than older patients with PDAC (≤45 years vs >45 years [p = 0.024] and ≤50 years vs ≥70 years [p = 0.03], respectively) [44,46].

In contrast, five retrospective cohort studies found no evidence of an association between smoking and early-onset disease [36,41,45,55,56]. Briefly, the US nested case–control study of families with a history of PDAC (without known cancer syndromes) found no significant difference between the adjusted odds ratios (ORs) for patients younger than 50 years and those older than 70 years (10.4 vs 1.4, respectively; likelihood ratio test, p = 0.35; 83 patients with PDAC) [56].

Similarly, a multivariable analysis of data from eight pooled case–control studies by McWilliams et al [55] (N = 1954) found no evidence of an increased risk associated with smoking in patients aged <45 years compared with those aged <60 years after adjustment for family history of PDAC, diabetes mellitus, sex, smoking intensity, alcohol consumption, BMI and study site (p = 0.20). This study did, however, corroborate smoking as a general (age-agnostic) risk factor for PDAC, reporting increased PDAC risk among smokers versus non-smokers in both age groups investigated (<60 years and <45 years) [55].

Finally, three retrospective cohort studies (N = 148, N = 908, and N = 36,145 for an analysis of population-based data from a national cancer registry) reported no apparent association between smoking status and age of PDAC onset (younger vs older than 45 years, 40 years and 40 years, respectively) [36,41,45].

3.4.2. Alcohol consumption

Five publications reported data on the relationship between alcohol consumption and age of PDAC onset/diagnosis; two of these (40%) supported a possible association between alcohol consumption and young age of PDAC onset/diagnosis (Table 3, Figures 2A and 3A) [41,43].

Among the included publications was a small retrospective cohort study from China (N = 331) that reported that patients who regularly consumed alcohol were significantly younger at the time of PDAC diagnosis than those who did not (57.96 years vs 61.37 years; p = 0.022) [43] (Table 3 and Figure 2A).

Of the four studies that investigated alcohol consumption as a specific risk factor for early-onset PDAC, only one reported increased PDAC risk in young versus old patients who consumed alcohol (Table 3 and Figure 3A). In this small cohort study from Romania (N = 148), a larger proportion of young patients than older patients with PDAC consumed alcohol (43% of those aged ≤45 years vs 5% of those aged >45 years; p = 0.01) [41].

The three studies that found no evidence of an association between alcohol consumption and early-onset PDAC included the previously described multivariable analysis of data from eight case–control studies (including 1954 PDAC cases) [55]. This study reported that PDAC risk was not significantly higher in patients aged <45 years than in those aged <60 years after adjustments (p = 0.20). However, this analysis showed that alcohol consumption of more than 26 g/day (vs ≤ 26 g/day) was associated with an increased risk of PDAC in both age groups, with a trend towards a greater magnitude of risk in patients younger than 45 years (OR 2.18, 95% CI 1.17–4.09) versus younger than 60 years (OR 1.49, 95% CI 1.21–1.84) [55].

Finally, no differences in alcohol consumption were observed between patients diagnosed with PDAC earlier in life (<40 years and <45 years, respectively) compared with those diagnosed later in a retrospective analysis of population-based data from the Japanese Cancer Registry (N = 36,145) [36] and in a retrospective chart review conducted at a cancer hospital in China (N = 1789) [44].

3.4.3. Obesity and BMI

Five publications reported results of analyses investigating whether obesity or increased BMI is associated with age of PDAC onset/diagnosis; only one of these (20%) supported a potential association (Table 3, Figures 2A and 3A) [54].

Li et al [54] reported an inverse linear relationship between BMI and age of sporadic PDAC diagnosis in a case–control study involving 841 patients with PDAC and 754 controls matched for age, race and sex. This finding was based on the results of multivariable linear regression modelling that reported ORs adjusted for age, race, sex, smoking status, alcohol consumption, diabetes status and family history of cancer. The

Table 4
Relationship between clinical factors/comorbid conditions and young age of PDAC onset.

First author name	N • Age groups (n)	Comparative data: comparison of RF prevalence between age groups or comparison of mean age between groups with vs without specific RFs n (%) of young patients with RF vs n (%) of old patients with RF p value for young vs old patients Other data as stated	Relative risks in age strata (without direct comparison between age strata) n (%) of young patients with RF vs n (%) of old patients with RF Other data as stated
Pancreatitis			
Eguchi [36]	36,145 • 10–39 years (526) • 40–99 years (35,619)	Chronic pancreatitis With chronic pancreatitis: 16 (3.0) vs 942 (2.6) Without chronic pancreatitis: 490 (93.2) vs 33,000 (92.6) Unknown: 20 (3.8) vs 1677 (4.7) p = 0.600	–
Duell [53]	4674 patients with PDAC and history of pancreatitis • <65 years (2369) • ≥65 years (2305) 10,703 healthy people with history of pancreatitis • <65 years (6028) • ≥65 years (4675)	*Adjusted unconditional multiple logistic regression analysis* **Association between PDAC and history of pancreatitis (>2 years before PDAC)** **In patients <65 years of age: OR (95% CI): 3.91 (2.53–6.04)** **In patients ≥65 years of age: OR (95% CI): 1.68 (1.02–2.76)** **p for interaction = 0.006**	–
Dzeletovic [42]	2573	**Mean (SD) age at PDAC diagnosis** **Patients with history of pancreatitis: 63 (12) years** **Patients without history of pancreatitis (≥10 days before PDAC diagnosis): 65 (10) years** **p = 0.005**	–
McWilliams [55]	1954 patients with PDAC • <45 years (226) • <60 years (1954) 3278 healthy people • <45 years (589) • <60 years (3278)	Pancreatitis ≥3 years before PDAC diagnosis/study recruitment PDAC cases vs controls, <45 years OR (95% CI) ref patients without pancreatitis history: Patients with pancreatitis history: 2.66 (0.19–37.9) **PDAC cases vs controls, <60 years** **OR (95% CI) ref patients without pancreatitis history:** **Patients with pancreatitis history: 4.71 (2.03–10.9)**	Pancreatitis ≥3 years before PDAC diagnosis/study recruitment, <45 years vs < 60 years: Patients with pancreatitis history: 3 (1) vs 35 (2) Patients without pancreatitis history: 160 (71) vs 1381 (71) Unknown: 63 (28) vs 538 (28)
Bunduc [41]	148 • ≤45 years (24) • >45 years (124)	Chronic pancreatitis With chronic pancreatitis: 0% vs 6.03% Without chronic pancreatitis: 100% vs 93.97% p = 0.59	–
Augustine [40]	98 with PDAC (including 22 with tropical pancreatitis) 82 with tropical pancreatitis without PDAC	**Mean (SD) age** **1) Patients with benign tropical pancreatitis: 39 (14.83) years** **2) Patients with tropical pancreatitis and PDAC: 47.5 (10.9) years** **1 vs 2: p = 0.0035** **3) Patients with *de novo* PDAC: 61.5 (7.2) years** **2 vs 3: p < 0.001**	–
Diabetes mellitus/insulin resistance			
McWilliams [55]	1954 patients with PDAC • <45 years (226) • <60 years (1954) 3278 healthy people • <45 years (589) • <60 years (3278)	DM history ≥ 3 years before PDAC diagnosis/study recruitment PDAC cases vs controls, < 45 years OR (95% CI) ref non-DM: DM: 0.85 (0.25–2.93) **PDAC cases vs controls, < 60 years** **OR (95% CI) ref non-DM:** **DM, 1.55 (1.16–2.06)** Interaction with age at PDAC onset (<45 years vs <60 years), p = 0.84	DM history ≥3 years before PDAC diagnosis/study recruitment, <45 years vs <60 years: DM: 6 (3) vs 137 (7) No DM: 193 (85) vs 1577 (81) Unknown: 27 (12) vs 240 (12)
Dugnani [57]	296	At PDAC diagnosis, 99 (33%) patients had IR Mean age ± SD at PDAC diagnosis Patients without IR: 66.8 ± 10 years Patients with IR: 67.1 ± 9 years p = 0.8 Patients without known DM at PDAC diagnosis and without IR: 64.6 ± 11 years	–

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Table 4 (*continued*)

First author name	N • Age groups (n)	Comparative data: comparison of RF prevalence between age groups or comparison of mean age between groups with vs without specific RFs n (%) of young patients with RF vs n (%) of old patients with RF p value for young vs old patients Other data as stated	Relative risks in age strata (without direct comparison between age strata) n (%) of young patients with RF vs n (%) of old patients with RF Other data as stated
		Patients without known DM at PDAC diagnosis and with IR: 65.5 ± 10 years p = 0.68 Patients with DM without IR: 68 ± 8.3 years Patients with DM with IR: 70.2 ± 7.9 years p = 0.103	
Gupta [52]	149 patients with PDAC and DM 36,482 patients with DM only • 40–44 years • 45–49 years • 50–54 years • 55–59 years • 60–64 years • 65–69 years • 70–74 years • 75–79 years • 80–84 years • ≥85 years	–	Rate ratios (95% CI) for first-year incidence of PDAC in patients with new-onset DM vs those without DM **Overall: 3.91 (2.93–5.23), p < 0.0001** 40–44 years: 0.00 (NA), p = NA **45–49 years: 16.91 (6.10–46.83), p < 0.0001** **50–54 years: 4.73 (2.02–11.06), p = 0.0003** **55–59 years: 5.52 (2.48. 12.28), p < 0.0001** 60–64 years: 1.77 (0.55–5.69), p = 0.3362 **65–69 years: 3.15 (1.44–6.86), p = 0.0039** **70–74 years: 2.42 (1.12–5.22), p = 0.0247** **75–79 years: 3.45 (1.67–7.14), p = 0.0008** **80–84 years: 6.74 (2.85–15.93), p < 0.0001 ≥ 85 years: 10.54 (2.30–48.24), p = 0.0024** Overall trend in rate ratio (new-onset DM: no DM) between increasing age and rate of PDAC: p = 0.07
Prior cancer and cancer stage			
Eguchi [36]	36,145 • 10–39 years (526) • 40–99 years (35,619)	**Cancer in organ other than pancreas** **Synchronous: 6 (1.1) vs 1150 (3.2)** **Metachronous: 4 (0.8) vs 2507 (7.0)** **No cancer in another organ: 492 (93.5) vs 30,755 (86.3)** **Unknown: 24 (4.6) vs 1207 (3.4)** **p < 0.0001** **UICC metastatic status** **M0: 185 (35.2) vs 16,187 (45.4)** **M1: 239 (45.4) vs 12,837 (36.0)** **Mx/unknown: 102 (19.4) vs 6595 (18.5)** **p < 0.0001** **UICC stage** **0: 0 (0.0) vs 20 (0.1)** **Ia: 7 (1.3) vs 652 (1.8)** **Ib: 9 (1.7) vs 885 (2.5)** **IIa: 24 (4.6) vs 2564 (7.2)** **IIb: 43 (8.2) vs 4726 (13.3)** **III: 77 (14.6) vs 5317 (14.9)** **IV: 239 (45.4) vs 12,836 (36.0)** **Unknown: 127 (24.1) vs 8619 (24.2)** **p < 0.0001**	–
Ohmoto [45]	908 ≤40 years (17) • >40 years (891)	Medical history of any cancer With history of cancer: 1 (5.8) vs 144 (16.2) Without history of cancer: 16 (94.1) vs 747 (83.8) p = 0.499	–
Salem [46]	516 ≤50 years (73) • ≥70 years (443)	Metastatic disease status at initial presentation p = 0.2	–
Hepatitis B infection			
Desai [35]	69,210 • 11–25 years (1950) • 26–40 years (24,405)	**Mean (SD) age at admission** **Patients with PDAC with HepB: 60.4 (7.4) years** **Patients with PDAC without HepB: 68.2 (12.1) years**	–

(*continued on next page*)

Table 4 (*continued*)

First author name	N • Age groups (n)	Comparative data: comparison of RF prevalence between age groups or comparison of mean age between groups with vs without specific RFs n (%) of young patients with RF vs n (%) of old patients with RF p value for young vs old patients Other data as stated	Relative risks in age strata (without direct comparison between age strata) n (%) of young patients with RF vs n (%) of old patients with RF Other data as stated
	• 41–55 years (36,135) • 56–70 years (6720)	**p < 0.001** **Patients with PDAC and HepB who were 26–40 years of age: 125/175 (71.4%)** **Patients with PDAC without HepB who were 26–40 years of age: 24,280/69,035 (35.2%)** **p < 0.001** **Adjusted ORs (95% CI)** Age: 1.032 (1.032–1.033) HepB: 1.237 (1.056–1.449)	
Wang [47]	330 • <65 years (224) • ≥65 years (106)	**Chronic HepB infection** **Carriers: 55 (24.6) vs 9 (8.5)** **Non-carriers: 169 (75.4) vs 97 (91.5)** **p = 0.001** **Median (SD) age at PDAC onset** **Carriers: 52.00 (11.155)** **Non-carriers: 60.50 (10.747)** **p = 0.001**	–
Metabolic syndrome			
Wang [47]	488 • <65 years (338) • ≥65 years (150)	**Patients with MetS: 43 (12.7) vs 30 (20.0)** **Patients without MetS: 295 (87.3) vs 120 (80.0)** **p = 0.038** **Median (SD) age at PDAC onset** **Patients with MetS: 59.00 (11.185)** **Patients without MetS: 57.00 (10.974)** **p = 0.038**	–
Long-term PPI exposure			
Brusselaers [37]	1733 PPI users with PC 1394 PPI users with PDAC 796,492 PPI users • <40 years (88,775) • 40–49 years (103,784) • 50–59 years (155,625) • 60–69 years (177,610) • ≥70 years (270,698)	–	**Standardised incidence rate ratios (95% CI) in adults with long-term PPI exposure** **For PC vs no PC** **<40 years: 8.90 (4.26–16.37)** **40–49 years: 5.93 (4.58–7.56)** **50–59 years: 3.36 (2.94–3.82)** **60–69 years: 2.46 (2.26–2.66)** **≥70 years: 1.81 (1.69–1.94)** **For PDAC vs no PDAC** **<40 years: 12.30 (4.93–25.34)** **40–49 years: 6.62 (4.97–8.63)** **50–59 years: 3.29 (2.84–3.80)** **60–69 years: 2.47 (2.27–2.70)** **≥70 years: 1.83 (1.69–1.98)**

Statistically significant data in bold.

CI, confidence interval; DM, diabetes mellitus; HepB, hepatitis B; IQR, interquartile range; IR, insulin resistance;M0, no metastasis present; M1, metastasis present; Mx, metastasis cannot be measured; MetS, metabolic syndrome; NA, not applicable; OR, odds ratio; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PPI, proton pump inhibitor; ref, reference; RF, risk factor; SD, standard deviation; UICC, Union Internationale Contre le Cancer.

mean age of PDAC diagnosis was 7 years younger for patients who had obesity at 20–29 years of age than for those who had never been overweight or had obesity (56 years vs 63 years, p = 0.003; adjusted OR [95% CI] 2.17 [1.15–4.07]) [54] (Table 3 and Figure 2A).

The four studies that investigated obesity as a specific risk factor for early-onset PDAC found no statistically significant evidence of an association (Table 3 and Figure 3A). The multivariable analysis conducted by McWilliams et al [55] (N = 1954) reported that there was no significant difference in OR between patients younger than 45 years versus those younger than 60 years after adjustments (p = 0.52). Although obesity was associated with PDAC in patients younger than 60 years of age (OR 1.28, 95% CI 1.08–1.52), it was not associated with PDAC in those younger than 45 years (OR 1.13, 95% CI 0.67–1.90) [55].

In addition, three retrospective cohort studies reported no significant differences in BMI between younger patients with PDAC (≤45 years or ≤50 years) and older patients with PDAC (N = 148, N = 1789 and N = 516) [41,44,46].

3.4.4. History of physical inactivity

One study investigated whether physical activity level at certain ages was associated with PDAC risk, but it did not examine the effect of history of physical inactivity/activity on age of PDAC development. In this multivariate case–control analysis of 88 patients who developed PDAC and 3970 healthy individuals from the population-based European Prospective Investigation of Cancer (EPIC)-Norfolk Study, Noor et al [38] reported that physical inactivity (vs activity) before the age of 60 years was associated with increased PDAC risk for PDAC versus active individuals (hazard ratio [HR] 4.0, 95% CI 1.1–14.3) (Table 3). This association was not observed in individuals who were physically inactive after the age of 60 years [38].

3.4.5. Meat intake

One study identified for inclusion in this review investigated the association between meat intake and PDAC in patients younger than 60 years, but it did not include direct risk comparison between age groups. Multivariable case–control analysis of 86 patients who developed PDAC and 3970 healthy individuals in the population-based EPIC-Norfolk Study, found a positive association between red and processed meat intake and PDAC in patients younger than 60 years (p < 0.05 for HR trends across daily intake quintiles), but not in those older than 60 years (Table 3). HRs were adjusted for age at recruitment, sex, smoking, diabetes mellitus and total energy intake in this analysis [39].

3.4.6. Socioeconomic status and geographical residence

One retrospective analysis of the population-based US National Cancer Database investigated the impact of income level on risk of PDAC in patients younger than 50 years, but no direct risk comparisons between age groups were reported. Alese et al [34] included 124,442 patients diagnosed with PDAC between 2004 and 2013. The distributions of patients across income quartiles (<US$30,000; US$30,000–35,999; US$36,000–45,999; >US$46,000), and between metropolitan, urban and rural residence locations were similar for younger (≤50 years) and older (>50 years) patients with PDAC (Table 3) [34].

3.5. Clinical factors and comorbid conditions

The results of the 12 publications reporting comparative data and stratified relative risk data for age-related clinical factors and comorbid conditions associated with PDAC are summarised in Table 4. The descriptive analyses on clinical and comorbid factors in young patients with PDAC are presented in Supplementary Table S3.

3.5.1. Pancreatitis

Six publications reported analyses investigating a possible relationship between pancreatitis and age of PDAC onset. Of these, three publications (50%) reported an apparent association between a history of pancreatitis and younger age of PDAC onset (Table 4, Figures 2B and 3B) [40,42,53].

Among these publications, a retrospective cohort study from a centre in India (98 PDAC cases and 82 controls) found that patients with a diagnosis of PDAC and tropical pancreatitis were younger than those with PDAC alone (47.5 years vs 61.5 years; p < 0.001) [40]. Similarly, one retrospective study (N = 2573) from a single US centre found that patients with a history of pancreatitis were significantly younger (63 years vs 65 years; p = 0.005) at the time of PDAC diagnosis than those without such a history [42] (Table 4 and Figure 2B).

Of three studies that compared PDAC risk associated with history of pancreatitis between age groups, only one reported an association in younger versus older individuals. This pooled analysis of ten case–control studies (4674 cases and 10,703 controls) found that a history of pancreatitis of longer than 2 years was associated with risk of PDAC in patients younger than 65 years of age (Table 4 and Figure 3B). In addition, multivariable logistic regression analysis found that patients younger than 65 years of age were more likely to have a history of pancreatitis than those older than 65 years (p = 0.006 following adjustment for age, sex, race/ethnicity, education, BMI, smoking, alcohol consumption, history of diabetes mellitus and study region) [53].

In contrast, no differences in the frequency of chronic pancreatitis were found between younger and older patients with PDAC in a cohort study from Romania (N = 148; ≤45 years vs >45 years) [41], or between younger (<40 years) and older (≥40 years) patients in a retrospective analysis of the population-based Japanese Cancer Registry (N = 36,145) [36].

In addition, the multivariable logistic regression analysis of eight case–control studies by McWilliams et al [55] (N = 1954) found that the interaction between pancreatitis history and age of PDAC onset did not reach statistical significance, possibly due to the small number of patients with PDAC and the requisite history (n = 38). While a history of pancreatitis of at least 3 years was significantly associated with a PDAC diagnosis before 60 years of age, the association with a PDAC diagnosis before 45 years of age did not reach statistical significance after adjustments [55].

3.5.2. Diabetes mellitus/insulin resistance

Three studies investigated the possibility of an association between diabetes mellitus/insulin resistance and age of PDAC onset/diagnosis (Table 4, Figures 2B and 3B) [52,55,57]. None of these reported that diabetes-related PDAC risk was significantly higher in younger than older patients.

No significant difference in mean age of PDAC onset was reported for patients with and without insulin resistance in a prospective study in Italy (67.1 years and 66.8 years, respectively; p = 0.8; N = 296) (Table 4 and Figure 2B) [57].

In the only study that compared PDAC risk associated with diabetes between age groups, there was no significant interaction between diabetes and age at PDAC onset (<45 years vs <60 years; p = 0.84; N = 1954), although comorbid diabetes mellitus was associated with increased risk of PDAC before 60 years of age, but not before 45 years of age according to adjusted ORs (Table 4 and Figure 3B) [55].

A retrospective analysis of the US Veterans Health Administration National Patient Care Database (149 patients with PDAC among 36,631 patients with new-onset diabetes) that estimated incidences of PDAC for patients with and without new-onset diabetes using direct standardisation to adjust for age, sex and race/ethnicity, and Poisson regression reported that although new-onset diabetes was significantly associated with PDAC for patients aged 45–59 years and ≥65 years, a trend between increasing age and the rate of PDAC was insignificant (p for trend = 0.07) (Table 4) [52].

3.5.3. Prior cancer and cancer stage at diagnosis

One study examined the potential association between a previous

cancer diagnosis and age of PDAC onset [45], and two investigated a potential association between age and cancer stage at time of PDAC onset [36,46] (Table 4 and Figure 3B). One of these three studies (33%) was a retrospective analysis of the Japan Pancreas Society's nationwide Pancreatic Cancer Registry that reported a significantly lower burden of metastatic sites and a significantly lower frequency of non-pancreatic cancers in younger (<40 years) than in older (≥40 years) patients with PDAC ($p < 0.0001$; N = 36,145) [36].

In contrast, in their retrospective analysis of 908 patients diagnosed with pathologically proven PDAC between 2002 and 2013 in the database of the National Cancer Center Hospital in Japan, Ohmoto et al [45] found no significant difference in the proportion of patients with a medical history of previous cancer in the subgroups of patients younger and older than 40 years of age (5.8% vs 16.2%, respectively; $p = 0.499$). Further, in terms of PDAC stage at time of disease onset, a conference abstract by Salem et al [46] reported no significant difference in the presence of metastatic disease between patients with PDAC at 50 years of age or younger compared with those with PDAC at 70 years of age or older (N = 516 with PDAC, institutional tumour registry study).

3.5.4. Hepatitis B infection

Two studies reported a positive association between hepatitis B infection and increased risk of PDAC in younger versus older patients (Table 4, Figures 2B and 3B) [35,47]. Both studies reported that, among patients with PDAC, those with hepatitis B infection were younger than those without it. In a retrospective analysis of patient records (N = 330) from a Chinese hospital, chronic carriers of hepatitis B infection were significantly younger than those without hepatitis B at the time of PDAC diagnosis (median age, 52.0 vs 60.5 years; $p = 0.001$) [47]. The second study was a retrospective analysis of the population-based US National Inpatient Sample (for the years 2013–2014), which included 69,210 patients with PDAC. This study reported that patients with hepatitis B were younger than those without the infection (mean age, 60.4 years vs 68.2 years; $p < 0.001$) [35] (Table 4 and Figure 2B).

In addition, chronic hepatitis B infection was more common in patients with PDAC who were younger than 65 years of age than in those who were 65 years of age or older (24.6% vs 8.5%; $p = 0.001$) in the Chinese patient cohort [47] (Table 4 and Figure 3B). The population-based US study found that the 26–40 years age group accounted for a greater proportion of the cohort with PDAC and hepatitis B than of the cohort with PDAC alone (71.4% vs 35.2%; $p < 0.001$) [35].

3.5.5. Metabolic syndrome

The same retrospective analysis of patient records from a Chinese hospital found that, in patients with histologically confirmed PDAC (N = 488), those with metabolic syndrome were older at the time of PDAC onset than those without metabolic syndrome (59.0 years vs 57.0 years; $p = 0.038$) (Figure 2B). This study also found that a metabolic syndrome diagnosis was less common in patients younger than 65 years than in those aged 65 years or older (12.7% vs 20.0%; $p = 0.038$) (Table 4, Figures 2B and 3B) [47].

3.5.6. Long-term proton pump inhibitor (PPI) exposure

A population-based nationwide Swedish cohort study involving adults using chronic PPI medication (including 1733 pancreatic cancer cases and 1394 PDAC cases) found that long-term PPI exposure (≥180 days) was associated with an increased risk of PDAC, although PDAC risk was not directly compared between age groups. The risk of PDAC among patients with long-term PPI exposure was, however, greater in younger age groups than in older age groups, with unadjusted standardised incidence rate ratios (95% CI) (standardised for country, age, sex and calendar period) ranging from 12.30 (4.93–25.34) for individuals younger than 40 years of age to 1.83 (1.69–1.98) for those 70 years of age or older (Table 4) [37].

3.6. Impact of risk factors for PDAC before the ages of 45, 55 and 65 years (sensitivity analysis)

We conducted a sensitivity analysis to explore whether potential risk factors for early-onset PDAC varied for different definitions of early-onset disease, specifically diagnoses at/before 45 years, 55 years and 65 years (Figures 2 and 3). In summary, the only factors we found evidence for being associated with higher PDAC risk in individuals younger versus older than 45 years of age were smoking and alcohol consumption [41,44]; in addition, we found evidence that smoking, pancreatitis and hepatitis B infection increased PDAC risk more in individuals younger than 55 and 65 years of age than in older individuals [35,40,46,47,53,56]. However, even with all the inherent limitations of indirect comparisons between studies, the insufficient and/or inconsistent data did not support strong conclusions on the role of any non-heritable risk factors in the development of PDAC before a particular age.

4. Discussion

We examined the published evidence for non-heritable risk factors for early-onset PDAC motivated by the medical, economic and societal burdens associated with a young age of diagnosis. Understanding the role of non-heritable risk factors for early-onset PDAC may help to inform effective screening programmes and thus improve the overall health and survival of patients with this condition. Risk profiling early-onset PDAC is also important in light of assertions that affected individuals may constitute a distinct patient phenotype [11–13].

From systematic MEDLINE and Embase databases searches, we identified 24 publications reporting observational study data for almost 250,000 patients from around the world [34–57]. The small number of eligible publications identified highlights the scope for further research in this area, particularly given that 50,000 people under the age of 55 years are estimated to be diagnosed with PDAC each year [1,58].

In the absence of an agreed definition of 'early-onset' PDAC [22,23,59], we included all publications reporting data offering insight into age-related risk factors. Among the publications included, the most frequently used age threshold for early-onset disease was 45 years, but lower (40 years) and higher (50, 60 and 65 years) thresholds were also used. The 25-year range spanned by these cut-off ages highlights the surprising lack of a consensus definition of early-onset PDAC, which severely limits synthesis of the current evidence. An important finding of this review is therefore that future research in this area would be considerably strengthened by an agreed, clinically relevant definition of early-onset PDAC.

There was substantial heterogeneity in the design of the studies included; some studies compared risk factor prevalence between age groups, or the age of patients with and without risk factors, while some reported relative risks in a range of age groups (Tables 2, 3 and 4), and others considered risk factor prevalence in populations identified a priori as having early-onset disease with no comparator group (Supplementary tables S2 and S3). Another notable limitation of the evidence was that only a minority of the studies (33%) reported results adjusted for potential confounders; most were unadjusted descriptive statistics. Further, the wide range of STROBE score (6−21) reflects inconsistent study reporting and potentially an overall lack of robustness in the epidemiological PDAC studies reviewed.

Despite the discussed data limitations, there was evidence for a potential association between younger (vs older) age of disease onset and: smoking exposure, alcohol consumption, history of pancreatitis and hepatitis B infection. Although the associations between these factors and early-onset PDAC were not strong, they warrant further investigation in future research.

4.1. Modifiable and lifestyle risk factors: smoking and alcohol

Smoking is known to be a risk factor for developing PDAC [14].

Among the studies identified by our searches, smoking was the risk factor investigated by the highest number of studies. Eight studies reported mixed evidence of its impact on PDAC risk in young patients: there was evidence that smoking increases PDAC risk in individuals younger than 45, 55 and 65 years of age [43,44,46,56], and that it does not significantly affect PDAC risk in individuals younger than 40, 45 and 50 years of age [36,41,45,55]. While these data do not support a strong conclusion that smoking differentially increases the risk of PDAC in younger versus older patients, they indicate that, as an important modifiable risk factor for PDAC in general, its impact on the risk of early-onset PDAC warrants further examination.

An international study involving 3280 patients with PDAC that was published after the date of our systematic searches has reported a weak tendency for a current (vs never) smoking status to have a stronger effect on PDAC risk in individuals younger than 50 years old (OR 2.92, 95% CI 1.69–5.04, $p < 0.001$) than in older individuals (OR 1.51, 95% CI 1.12–2.03, $p = 0.006$; both adjusted for sex and country) [60]. The magnitude of the effect in people younger than 50 years was smaller in this study than in the US nested case–control study by Rulyak et al included in this review (adjusted ORs 2.9 and 10.4, respectively) [56]. This finding adds to the weak evidence for smoking as a risk factor for early-onset PDAC identified by our systematic searches. In a Spanish, single-centre, retrospective cohort study published after our search date, patients with PDAC aged 50 years or younger were more likely to be current smokers than those aged 70 years or older ($N = 336$; $p = 0.03$) [61].

There is published evidence that high levels of alcohol consumption increase the risk of PDAC [14]. Only two studies identified by our searches found an association between alcohol consumption and risk of early-onset PDAC: one small study reported that PDAC risk was greater in patients younger versus older than 45 years of age [41], and another study reported a 3-year reduction in age of PDAC diagnosis to 58 years of age [43]. Three studies, however, found no association [36,44,55]. These findings suggest that although alcohol consumption may have a greater effect on younger than older patients, the association needs to be investigated in a larger population. Interestingly, since we performed our systematic searches, a small pilot study in Taiwan of 24 patients with pancreatic cancer has reported a significant correlation between age at which alcohol consumption started and age of PDAC diagnosis ($r = 0.8124$, $p = 0.0043$) [62]. However, this finding cannot be compared with data extracted from the studies identified in our systematic searches as none of them analysed the effect of the age of starting alcohol consumption on age-related PDAC risk.

Our searches identified studies on the impact of five other modifiable risk factors on the age of PDAC onset: obesity, physical inactivity, meat intake, socioeconomic status and geographic residence [34,38,39,41,44,46,54,55]. None of these factors, however, was found to significantly increase PDAC risk in young versus older patients.

4.2. Clinical and comorbidity risk factors: pancreatitis and hepatitis B

While pancreatitis is a recognised risk factor for PDAC, it is important to consider that its occurrence within a short time (potentially up to 3 years) before PDAC onset may be an early sign of PDAC rather than a risk factor [14,62]. Of the six studies that examined the impact of pancreatitis on risk of early-onset PDAC, one reported that patients with PDAC who had tropical pancreatitis were 14 years younger (48 years old) than those without tropical pancreatitis, and a second study found that pancreatitis was associated with higher PDAC risk in individuals younger than 65 years of age than in older individuals [40,53]. Another study reported a 2-year reduction in age of PDAC onset to 63 years [42], and three other studies reported no association between history of pancreatitis and age of PDAC onset [36,41,55]. There is therefore no strong evidence that pancreatitis poses a greater risk of PDAC to young than old patients, but the available data suggest that it is a risk factor that needs further evaluation with regards to age. A conference abstract published since our searches reported a multivariable analysis of US data in which patients with acute pancreatitis younger than 50 years old had lower odds of developing PDAC within 3 years than those aged 50–60 years [63].

Hepatitis B infection has previously been reported to be associated with risk of PDAC in several studies, mostly from China [64–67]. The two studies identified by our searches that investigated hepatitis B infection as a risk factor for early-onset PDAC, from China and the USA, respectively, found that it increased PDAC risk in patients younger than 55 and 65 years of age [35,47]. It may be valuable to examine the association of hepatitis B infection with PDAC risk in patients younger than these ages.

The other clinical factors identified by our searches were diabetes/insulin resistance, prior cancer and cancer stage, metabolic syndrome and long-term PPI use; none of these reported data that supported roles for these factors in increasing PDAC risk more in young versus older patients [36,37,45–47,52,55,57]. In the Spanish retrospective cohort study published after our search date, type 2 diabetes mellitus and a personal history of cancer were less common in patients with PDAC aged 50 years or younger than in those aged 70 years or older ($N = 336$; $p < 0.01$ for both) [61].

4.3. Clinical, public health and research implications

Overall, we found insufficient data to formulate a non-heritable risk profile for early-onset PDAC that could be used to inform targeted screening or risk reduction strategies. This supports the current recommendation to screen only individuals who are at high risk of developing the disease because of a known genetic predisposition (for example, Peutz–Jeghers syndrome or hereditary pancreatitis) or a family history of PDAC [68]. Screening of asymptomatic individuals in the general population is not recommended as it is considered to be difficult (involving imaging-based methods such as endoscopic ultrasonography) and not cost-effective due to its low incidence [69,70]. The development of artificial intelligence methodologies for analysing primary healthcare data may, however, aid the identification of a sub-population of patients at high risk of PDAC for screening [71].

Our findings that pancreatitis and hepatitis B infection may increase PDAC risk more in younger than in older patients are important in light of the fact that individuals with a history of these conditions are not routinely screened for PDAC, despite suggestions that patients with acute pancreatitis or viral liver infections may benefit from being monitored for PDAC [70,72–76]. The evaluation of factors (such as pancreatitis susceptibility genes, long duration of pancreatitis and autoimmune pancreatitis) that may contribute to increased risk of PDAC associated with pancreatitis may help to characterise a subgroup of patients, potentially including those younger than the typical age of PDAC onset, who could derive particular benefit from screening [68,72–74,77–79].

In light of the lack of strong evidence for non-heritable risk factors in our study, investigating other potential risk factors is a research priority for understanding the basis of early-onset PDAC. Of particular interest are factors that may have changed over recent decades, especially in younger age groups. Environmental exposures, for example, are one potential area of investigation, but are quite hard to evaluate. Assessment of their potential contribution might include integration of data from public health (such as “clean air”) programmes and personal location data. Other factors that may contribute to the risk of early-onset PDAC include environmental conditions (such as climate change and urban migration), and socioeconomic and political factors. In addition, patient factors, such as diet (for example, organic and vegan diets, health and herbal supplement use, nutritional and non-alcoholic beverage consumption, dietary changes that impact the microbiome), recreational substance use (for example, smoking of non-tobacco products such as vaping), use of technology, and exercise patterns, may also play a role. Dietary factors are also challenging to isolate because they

are so subject to confounding; future cohort studies could potentially characterize patients according to different dietary profiles. In reality, however, high-quality longitudinal data on these potential risk factors are difficult to obtain.

Well-designed, large-scale studies comparing the age of PDAC onset or diagnosis between patients with and without specific risk factors are required to evaluate the relative contribution of each potential factor to the risk of developing PDAC before its typical age of onset. Given the lack of consensus on the age threshold defining early-onset PDAC, analysis of age as a continuous variable is necessary to avoid the selection of an arbitrary age threshold, which may bias or weaken the results. A pilot study with such a design has confirmed the feasibility of this approach; the results of this pilot study demonstrate the importance of performing an analysis of the correlation between age of risk factor exposure and age of PDAC onset, and also a mediation analysis for disease-related factors that may represent mediators of tumourigenesis [62].

5. Conclusions

In this systematic literature review, the published evidence for non-heritable, age-related risk factors for PDAC varied in terms of source study design and data quality. A lack of consensus on the age threshold defining early-onset PDAC precluded formal meta-analysis of the data. Although no strong evidence was identified for specific non-heritable factors being determinants of early-onset PDAC, we identified four factors that may increase the risk of PDAC in patients younger than its typical age of onset: smoking, alcohol consumption, history of pancreatitis and hepatitis B infection. The further evaluation of potential PDAC risk factors using age as a continuous variable may aid the identification of individuals with an elevated risk of developing PDAC before its typical age of onset, specifically those who may benefit from screening and risk reduction strategies.

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CRediT authorship contribution statement

SR Chandana: Conceptulisation, Methodology, Visualisation, Writing – review & editing. **LM Woods:** Conceptulisation, Methodology, Visualisation, Writing – review & editing. **F Maxwell:** Conceptulisation, Methodology, Visualisation, Writing – review & editing. **R Gandolfo:** Conceptulisation, Methodology, Visualisation, Writing – original draft, Writing – review & editing. **T Bekaii-Saab:** Conceptulisation, Methodology, Visualisation, Writing – review & editing.

Declaration of Competing Interest

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L Woods has no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113471.

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Corrigendum

Corrigendum to "Risk factors for early-onset pancreatic ductal adenocarcinoma: A systematic literature review" [Eur J Cancer 198 (2024) 113471]

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The authors regret that Dr Zhimin Xiao's involvement as an author of this manuscript was unfortunately overlooked. We, the authors, would like to include Dr Zhimin Xiao, who was employed by Ipsen during manuscript development. We propose to include Dr Zhimin Xiao as the fourth author. Dr Zhimin Xiao made significant contributions to the development of this manuscript. The author details for Dr Zhimin Xiao are as follows: previously an employee of Ipsen; no other conflicts of interest. His contributions include: Conceptualisation; Methodology; Visualisation; Writing - review & editing.

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