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Global epidemiology and holistic prevention of pancreatitis

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Abstract

Knowledge of pancreatitis in the 20th century was shaped predominantly by animal data and clinical trials. Several large general population-based cohort studies and comprehensive systematic literature reviews in the 21st century have had a major effect on our understanding of pancreatitis and its sequelae. This Review provides precise and up-to-date data on the burden of acute pancreatitis, chronic pancreatitis and post-pancreatitis diabetes mellitus. Exocrine pancreatic insufficiency and altered bone metabolism following pancreatitis are also discussed. Furthermore, the article introduces a framework for the holistic prevention of pancreatitis with a view to providing guidance on strategies and intervention objectives at primary, secondary and tertiary levels. Concerted efforts by not only gastroenterologists and surgeons but also primary care physicians, endocrinologists, radiologists, pain specialists, dietitians, epidemiologists and public health specialists will be required to reduce meaningfully the burden of pancreatitis and its sequelae over the ensuing decades.

Pancreatitis refers to autodigestion of the pancreas, in which pancreatic enzymes injure pancreas tissue and lead to dysfunction of the gland, as well as remote organs and systems. The epidemiology of diseases often changes with time — for pancreatitis, this aspect is certainly true. The reasons for such changes are many: population growth and migration, change in patterns of alcohol consumption and tobacco smoking, rising rates of obesity and recognition of metabolic causes of pancreatitis, and increasing use and improving quality of imaging modalities[1,2]. Emerging studies have also shown that acute, recurrent acute and chronic pancreatitis often represent a disease continuum[3,4]. In addition, there is a growing appreciation of the effect of pancreatitis on development of metabolic disorders, such as diabetes, exocrine pancreatic insufficiency (EPI) and altered bone metabolism[57]. Hence, this Review focuses on up-to-date epidemiological data from the perspective of pancreatic

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inflammation as a continuum (including its sequelae). We also outline strategies that might have an effect on reducing the burden of pancreatitis and resulting metabolic disorders. Epidemiological studies are prone to biases, of which the most common is selection bias (for example, studies limited only to women or individuals of a certain ethnicity)[8]. Thus, throughout this Review, priority is given to population-based cohort studies conducted in general populations and comprehensive systematic literature reviews to minimize the risk of selection bias and report the most robust estimates. If such studies are not available, the most recent relevant research is reviewed.

Epidemiology of pancreatitis worldwide

Incidence.

The global incidence of pancreatitis cited in previous reviews was invariably presented as a wide range of estimates, mainly because they were based on a mix of primary studies that had heterogeneous study populations and varying methodological quality A systematic review by Xiao et al.[9] addressed this issue by pooling data from high quality studies only — specifically, population-based cohort studies conducted in general populations. This article reported that the global pooled incidence of acute pancreatitis is 34 cases (95% confidence interval (Cl) 23–49) per 100,000 general population per year, with no statistically significant difference between men and women[9]. The disease predominantly affects those who are middle-aged or older[10,11] (FIG. 1). Throughout the world, there are differences in the incidence of acute pancreatitis. The high incidence regions (that is, those with incidence more than 34 cases per 100,000 general population per year) are the North America and Western Pacific regions (as defined by the WHO). Europe as a whole is a low incidence region (29 cases per 100,000 general population per year), although it was suggested that incidence of acute pancreatitis varies across the continent with Northern and Eastern Europe being most affected[12]. However, it is currently difficult to compare the incidence of acute pancreatitis across Europe in a robust manner because of the lack of high quality studies from Eastern and Southern Europe. Notably, population-based data on incidence of acute pancreatitis are not available from the South America, Africa, South-East Asia and Eastern Mediterranean regions. Population-based cohort studies from these regions are eagerly awaited to appreciate fully the burden of acute pancreatitis around the globe (BOX 1).

The frequency of transition from the first episode of acute pancreatitis to recurrent acute pancreatitis and chronic pancreatitis was quantified in a 2015 systematic review of high quality cohort studies with at least 1 year of follow up[3]. Importantly, interventional studies were excluded as interventions might modify the natural course of transition from acute to chronic pancreatitis. Recurrent acute pancreatitis developed in 21% (95% Cl 17–26%) of patients after the first episode of acute pancreatitis, and chronic pancreatitis developed in 36% (95% Cl 20–53%) of patients after recurrent acute pancreatitis (FIG. 2). The rates of transition were higher in men than women and in patients with alcohol-induced versus biliary pancreatitis. Age, severity of acute pancreatitis and duration of follow-up did not seem to affect the rate of transition.

According to the systematic review by Xiao et al., the global pooled incidence of chronic pancreatitis is 10 cases (95% Cl 8–12) per 100,000 general population per year[9]. Notably,

the incidence is statistically significantly higher among men than women, at 12 cases (95% CI 8–17) and 6 cases (95% Cl 4–8) per 100,000 general population per year, respectively. Similar to acute pancreatitis, chronic pancreatitis predominantly affects patients who are middle-aged and older[10,11] (FIG. 1b). Studies that investigate variations in incidence of chronic pancreatitis in general populations across the globe are lacking and should be priorities for future research (BOX 1).

Prevalence.

The notion of prevalence is typically considered in the context of chronic diseases, yet the prevalence of acute conditions can also be of importance. An article published in 2016 suggests that prevalence of antibodies can be used to project the burden of infectious disease and vaccination needs in the general population[13]. Estimating the prevalence of acute pancreatitis has not been the focus for pancreatologists thus far, at least in part because it was believed that the overwhelming majority of patients do not develop long-term consequences. However, data suggest that even patients with mild acute pancreatitis (who represent the majority of patients with acute pancreatitis) have at least twofold higher long-term risk of diabetes mellitus than people in the general population without a history of acute pancreatitis[14,15]. The rising incidence of acute pancreatitis[4] might further increase the frequency of dysfunction of several systems (including endocrine, exocrine and altered bone metabolism, covered in detail later) long after clinical resolution of pancreatitis. Thus, a knowledge of prevalence (that is, cases with a prior history of acute pancreatitis) might enable quantification of the predicted burden of sequelae attributable to acute pancreatitis in the general population and guide the effective allocation of health care resources. Epidemiological studies on the prevalence of acute pancreatitis are now warranted (BOX 1).

Population-based data on the prevalence of chronic pancreatitis in the general population are scarce. In a population-based evaluation from Olmsted County, Minnesota, USA, where a prospective administrative database was interrogated to identify the cases followed by a formal review of records, the prevalence of chronic pancreatitis in 2006 was 42 per 100,000 persons[16]. The prevalence was highest in the 45–74 years of age group, and in men when compared with women (52 versus 34 per 100,000 persons). Based on a nationwide survey, the estimated prevalence in the Japanese population in 2011 was similar (52 per 100,000 persons)[17]. The lack of data on the burden of chronic pancreatitis in most populations of the world makes this an important area for future research to better understand the similarities and differences between populations (BOX 1).

Mortality.

The pooled mortality from an episode of acute pancreatitis in seven population-based cohort studies evaluated in the systematic review by Xiao et al. was 1.16 (95% Cl 0.85–1.58) per 100,000 general population per year[9]. Although subgroup analyses and meta-regression was not feasible in the systematic review, determinants for increased risk for mortality in acute pancreatitis are well-established and include persistent organ failure and infected pancreatic necrosis[18–20]. Importantly, although there has been a general trend towards decreasing case-fatality of acute pancreatitis, the population mortality from acute pancreatitis remains the same[21,22].

Case-fatality from recurrent acute pancreatitis (typically <1% in modern studies) is lower than from the first attack (typically <10% in modern studies). It is possible that parenchymal damage from a prior attack affects the ability of the pancreas to mount a similar inflammatory response[23]. In a 2006 systematic review of population-based studies, nine out of 10 studies reported lower case-fatality in patients who suffered from a recurrent attack than those suffering the first attack[22].

Xiao et al. found that the crude mortality from chronic pancreatitis was 0.09 (95% Cl 0.02–0.47) per 100,000 person-years[9]. In the majority of patients with chronic pancreatitis, deaths are attributed to non-pancreatitis causes — most frequently, cancers and cardiovascular diseases. Pancreatitis is attributed as a potential cause in <25% deaths[16,24].

Sequelae of pancreatitis

Post-pancreatitis diabetes mellitus.

Metabolic abnormalities are an important and frequent sequelae of pancreatitis. Diabetes of the exocrine pancreas (DEP) and its 3 subtypes — post-pancreatitis diabetes mellitus (PPDM), pancreatic cancer-related diabetes (PCRD) and cystic fibrosis-related diabetes (CFRD) — have been suggested as a uniform nomenclature[25]. The rationale, definitions and exclusions for these subtypes are presented in detail elsewhere[25]. Importantly, not every case of hyper-glycaemia in the context of acute or chronic pancreatitis should be regarded as PPDM[26]. Furthermore, PPDM and other types of diabetes cannot coexist even though some elements of the pathogenesis can overlap (for example, insulin resistance in both type 2 diabetes and PPDM). This aspect is in line with the American Diabetes Association classification of diabetes, which recognizes that all types of diabetes possess unique aetiologies, but not necessarily elements of pathogenesis. In that regard, PPDM should be afforded the same considerations as gestational diabetes and post-transplantation diabetes mellitus, which are both integral parts of the American Diabetes Association diabetes classification[25,27]. A proposed algorithm to diagnose PPDM is presented in FIG. 3. Specific markers for PPDM (and DEP in general) will probably be discovered in the future (BOX 1).

The pathogenesis of post-chronic pancreatitis diabetes mellitus (PPDM-C) is quite straightforward — worsening insulin deficiency is induced by progressive fibrosis of the exocrine tissue and a persistent pro-inflammatory milieu. As such, the frequency of this condition is generally a function of duration of chronic pancreatitis[28]. For example, a single-center follow-up study of 445 patients with chronic pancreatitis conducted in China showed that the frequency of diabetes at the onset of chronic pancreatitis was 3.6%; at 1 year after diagnosis of chronic pancreatitis, the frequency was 7.5%, and at 10 years and 20 years after diagnosis it was 28% and 52%, respectively[29]. A similar time-dependent increase was reported in a study of 656 patients with chronic pancreatitis conducted in Japan, in which the frequency of diabetes at the onset of chronic pancreatitis was 10%. At 10 years after chronic pancreatitis diagnosis the frequency of diabetes was 50%, and after 25 years it was 83%[30].

Although historically the majority of evidence related to PPDM was in the context of chronic pancreatitis, a 2014 systematic review by Das et al. assessed post-acute pancreatitis diabetes mellitus (PPDM-A)[31]. This study pooled data from prospective clinical studies of

1,102 patients with a first attack of acute pancreatitis who had been followed up for newly developed abnormalities of blood glucose metabolism. Importantly, the study excluded patients who had previous history of diabetes or prediabetes, cohorts limited to patients who underwent pancreatic surgery, and cohorts limited to patients with chronic, autoimmune or hereditary pancreatitis. The study made three main inferences. First, frequency of PPDM-A in individuals after a single episode of acute pancreatitis is markedly higher than in the general population without history of acute pancreatitis. Second, the frequency of PPDM-A is not substantially affected by the severity of acute pancreatitis and, hence, its burden is non-negligible as patients with non-necrotizing pancreatitis (who constitute the majority of patients with acute pancreatitis) are also at a high risk of developing PPDM. Third, a considerable fraction of individuals with PPDM-A receive insulin therapy and, contrary to earlier beliefs, elevated levels of fasting plasma glucose are not transient and not inconsequential. These inferences were subsequently confirmed in several larger scale high-quality population-based studies that compared the risk of developing diabetes in people after first episode of acute pancreatitis and in general population using complementary epidemiological approaches, all adjusting for key covariates.

The study by Shen et al. included 2,966 individuals after acute pancreatitis and 11,864 control individuals from the general population matched for age and sex (who had no prior diagnosis of diabetes or disease of the exocrine pancreas)[15]. This study showed that the adjusted risk of PPDM was 2.54 (95% Cl 2.13–3.04) times higher among those who had an attack of acute pancreatitis than those who had not. Another study by Lee et al., which included a total of 3,187 individuals who had had acute pancreatitis and 709,259 randomly selected control individuals from the general population (who had no prior diagnosis of diabetes or acute pancreatitis), found that the adjusted risk ofPPDM was 2.1 (95% Cl 1.92–2.41) times higher among those who had an episode of acute pancreatitis[14]. Furthermore, the results of the two population-based studies conducted in Taiwan corroborate the findings of the earlier meta-analysis by Das et al. that included a total of 24 prospective follow-up studies from around the world[31]. Taken together, these data indicate that individuals with a history of acute pancreatitis are a high-risk group for the development of diabetes, with the risk being at least 2 times higher than in individuals in the general population who do not have a history of acute pancreatitis.

The two studies mentioned above also confirmed that the high-risk of PPDM-A is not limited to patients with non-mild acute pancreatitis. Specifically, Shen et al. showed that using a sensitivity analysis constrained to individuals with mild acute pancreatitis only (81.4% of all cases in their study) yields a 2.49 (95% Cl 2.04–3.04) times higher risk of new-onset diabetes in comparison with the general population[15]. Lee et al. used a complementary approach and constrained their sensitivity analysis to individuals with non-mild acute pancreatitis only (8.7% of all cases in their study). Individuals with non-mild acute pancreatitis had a 2.22 (95% Cl 1.50–3.29) times higher risk of new-onset diabetes than individuals in the general population[14]. Taken together, these data suggest that, contrary to common belief, mechanical destruction of the islets of Langerhans as a result of pancreatic necrosis (with or without surgery) is not the only cause of PPDM-A. The pathogenesis of PPDM-A is being actively investigated, with the key mechanisms identified

thus far being persistent low-grade inflammation[32–34], dysfunction of the pancreas-gut-brain axis[35–37], lipolysis of adipose tissue[38–40] and insulin resistance[41–43].

High frequency of insulin therapy in individuals with a history of pancreatitis was confirmed in a 2017 study by Woodmansey et al.[44]. The authors searched a large database of patients (*n* = 2,360,631) in the UK who had been registered at primary care practices and identified 31,789 new-diagnoses of adult-onset diabetes, of which 502 cases were DEP (including 361 cases of PPDM-A). At 1 year after diagnosis of diabetes, 1.4% (95% Cl 1.3–1.6) of individuals with type 2 diabetes required insulin compared with 9.7% (95% Cl 6.8–13.7) of individuals with PPDM-A and 16.3% (95% Cl 13.1–20.0) of individuals with DEP overall. At 5 years after diagnosis, 4.1% (95% Cl 3.8–4.4) of those with type 2 diabetes required insulin compared with 20.9% (95% Cl 14.6%−28.9%) of individuals with PPDM-A and 29.6% (95% Cl 23.6–36.4) of individuals with DEP overall. Owing to more frequent administration of insulin therapy, individuals with PPDM might need closer monitoring than individuals with type 2 diabetes. The absence of a management protocol specifically tailored to individuals with PPDM is a substantial clinical practice gap (BOX 1).

Two large population-based studies in tertiary care and primary care settings have used complementary approaches to determine the incidence of DEP and the frequency of its subtypes. The study by Pendharkar et al.[10] identified cases of new diagnoses of diseases of the exocrine pancreas and DEP (as well as its subtypes) among nearly 3 million residents of New Zealand, whereas the study by Woodmansey et al.[44] (described earlier) identified cases of new diagnoses of adult-onset diabetes and DEP (as well as its subtypes) among more than 2 million UK residents. The incidence of DEP in the primary care setting in the UK was 2.59 (95% Cl 2.38–2.81) per 100,000 general population per year[44] whereas its incidence in the tertiary care setting in New Zealand was 10.00 (95% Cl 9.66–10.34) per 100,000 general population per year[11]. Until population-based studies from other parts of the world are completed, it is reasonable to assume that the incidence of DEP worldwide is ~6 per 100,000 general population per year. The new epidemiological data derived from these studies indicate that DEP constitutes 1.6% of all cases of diabetes in adults (which makes it the second most common type of adult-onset diabetes), four out of five patients (80%) develop DEP after pancreatitis (with PCRD contributing 18% and CFRD contributing 2% to DEP frequency), and the contribution of acute pancreatitis to PPDM risk is considerably larger (83% versus 17%) than that of chronic pancreatitis (FIG. 4).

Exocrine pancreatic dysfunction.

Similar to endocrine dysfunction, abnormalities in pancreatic exocrine function were initially considered only in the context of chronic pancreatitis. In classic natural history studies, up to 80% patients develop EPI during the course of disease[45–47]. The probability increases with disease duration, reflecting progressive destruction of the pancreatic parenchyma from inflammatory and fibrotic changes. In physiological studies, clinical signs of EPI (the main sign of which is steatorrhoea) are expected with ~90% loss of pancreatic exocrine tissue[48,49].

Exocrine dysfunction after acute pancreatitis is typically associated with the extent of pancreatic damage (that is, pancreatic necrosis). A systematic review evaluated the

coexistence of EPI and PPDM after acute pancreatitis[50]. This review included eight studies comprising 234 patients that evaluated both exocrine and endocrine functions of the pancreas, with a follow-up at the time of assessment of 12–179 months. EPI was determined in a variety of ways, including direct pancreatic function testing, measurement of faecal elastase or faecal fat levels and need for oral pancreatic enzyme replacement therapy. In seven of the eight studies, all patients had either severe or necrotizing pancreatitis, with a varying fraction having had a necrosectomy as part of treatment of their disease. The prevalence of EPI after acute pancreatitis was 29% and nearly 40% of individuals with PPDM also had concomitant EPI. Interestingly, the prevalence of EPI among patients with diabetes mellitus decreased over time.

In an earlier study, pancreatic function was assessed by two methods in 75 patients at least 4 months after an episode of acute pancreatitis. In 18 patients (8 with alcohol-related pancreatitis and 10 with biliary pancreatitis), duodenal aspiration for 30 minutes was used to evaluate lipase, chymotrypsin and bicarbonate output following intravenous infusion of secretin and the oligopeptide cerulein. In 57 patients (28 with alcohol-related pancreatitis and 29 with biliary pancreatitis), the assessment was made using plasma amino acid levels taken at different intervals before and after a one hour infusion of cerulein (known as the amino acid consumption test)[51]. In 46 of the 57 patients who underwent the amino acid consumption test, the test was repeated after 1 year. The authors found that pancreatic function was decreased in 85% patients with alcoholic acute pancreatitis irrespective of severity, whereas in those with biliary pancreatitis it was affected only in patients with necrotizing pancreatitis but at a much lower frequency (22%). Upon repeat testing a year later, patients with alcohol-related pancreatitis and those with necrotizing pancreatitis showed continued abnormality, whereas the only patient with mild biliary pancreatitis and borderline exocrine dysfunction of the pancreas showed improvement. These data suggest that clinically relevant EPI is relatively common after acute necrotizing pancreatitis, and more frequent in patients with alcohol-induced disease. In contrast to endocrine dysfunction, the risk of which progressively increases over time, loss of exocrine function after acute pancreatitis seems to be steady. A limitation of published data is the lack of uniform criteria to define exocrine function. Thus, modern, adequately powered clinical studies in patients with varying severity using uniform definitions are needed to investigate the prevalence and factors associated with exocrine dysfunction after acute pancreatitis.

Osteoporosis.

The importance of bone health in chronic pancreatitis is gaining attention. In a systematic review of 10 studies comprising 513 patients with chronic pancreatitis, the prevalence of osteoporosis was 23.4% and 65% for osteoporosis or osteopenia[52]. Owing to the small sample sizes of primary studies, stratified analyses were not possible, although it seemed that the rates were not influenced by age, sex and geographic region. Risk of fractures, the clinical consequence of low bone density, was assessed in three large cohorts. In a tertiary care center study of 3,192 patients with chronic pancreatitis conducted in the USA, the prevalence of low fragility fractures in those with chronic pancreatitis was higher than in control individuals who did not carry a diagnosis of chronic pancreatitis, coeliac disease, Crohn’s disease, cirrhosis or post-gastrectomy state (4.8% versus 1.1%). The odds of a

fracture in patients with chronic pancreatitis were 2.4 fold higher than control individuals after adjusting for age, sex and race, and were similar to other gastrointestinal conditions with well-recognized increased risk of osteoporosis and fractures (mentioned earlier)[53]. In a study of 453,912 veterans in the USA, of whom 3,257 had chronic pancreatitis, the prevalence of any fracture (vertebrae, hip and wrist) in patients with chronic pancreatitis was 4.7% versus 2.07% in control individuals, and the odds of having a fracture in patients with pancreatitis were 1.7-fold greater after adjusting for age, sex, race and aetiology[54]. A large population-based study of 11,972 patients with chronic pancreatitis from Denmark, of which 33% were women, identified bone fractures in 2,594 (21.7%) patients[55]. Furthermore, the adjusted hazard ratio for any fracture was 1.7 (95% Cl, 1.6–1.8) in patients with chronic pancreatitis compared with control individuals matched for age and sex. The high frequency of osteoporosis, osteopenia and fractures warrants appropriate and timely screening of patients with pancreatitis. Similar to other gastrointestinal diseases, a European guideline published in 2017 suggested that patients with chronic pancreatitis with a history of low trauma fractures, those with malabsorption, postmenopausal women, and men >50 years of age should undergo bone density testing by dual X-ray absorptiometry[56].

EPI can lead to maldigestion and malabsorption, and five of nine studies in the systematic review noted an association between pancreatic enzyme insufficiency and osteoporosis[52]. One consequence of malabsorption is deficiency of vitamin D, which has an important role in bone health. Interestingly, in a systematic review of nine studies, although the prevalence of vitamin D deficiency in patients with chronic pancreatitis was relatively high, it was not statistically significantly different from the prevalence in control individuals[57]. Also, the population-based study from Denmark mentioned earlier[55] found, somewhat expectedly, that patients with chronic pancreatitis receiving pancreatic enzyme supplementation for fat malabsorption had a 20% lower risk of fractures than other patients with chronic pancreatitis. However, what was unexpected is that increased duration of pancreatic enzyme supplementation was associated with an increased risk of fracture, perhaps because of the effect of an unknown confounding factor. These findings highlight the need for well-designed physiological studies to investigate the intricate relationship between pancreatic function and bone metabolism (BOX 1).

Similar to diabetes mellitus and EPI, osteoporosis was initially deemed to not be a sequelae of acute pancreatitis. However, a population-based study of 4,016 patients from Taiwan with acute pancreatitis, published in 2017, found a statistically significant increase in incident diagnosis of osteoporosis in patients with acute pancreatitis when compared with propensity-matched control individuals, with an adjusted hazard ratio of 1.27 (95% Cl 1.02–1.58)[58]. The adjusted hazard ratio was even higher in patients who had recurrent acute pancreatitis attacks (4.8-fold higher in patients with more than 3 attacks), suggesting that the increased risk is, at least in part, driven by disease progression towards chronic pancreatitis. If these results are confirmed in subsequent population-based studies, investigations of the pathological mechanisms that lead to osteoporosis following acute pancreatitis will be warranted.

Holistic prevention of pancreatitis

The epidemiological burden of pancreatitis and its sequelae underscores the need for a comprehensive approach to its prevention. Prevention approaches are classically categorized as primary, secondary and tertiary in terms of the intervention time point and target population. In primary prevention, intervention is applied to the general population who do not have a disease of interest. These strategies typically aim to reduce disease incidence. Secondary prevention involves early identification of individuals with an existing disease of interest. The purpose of secondary prevention is to apply effective intervention early and reduce morbidity. Tertiary prevention is applied after a disease of interest is established, aiming at minimizing its sequelae and resulting burden[59,60].

The concept of multi-level prevention has been known since the 1980s and has proven to be useful in reducing the burden of several diseases (for example, cardiovascular diseases, tuberculosis and asthma)[61–63]. However, the opportunity to apply this concept holisti-cally to diseases of the pancreas has been overlooked as most early research in pancreatology was focused on a single aspect of prevention — reducing the number of recurrences of pancreatitis. By aetiology, the preventive interventions included cholecystectomy for biliary pancreatitis[64], alcohol counselling (for example, using structured 30-minute talks at outpatient clinics every 6 months) for alcohol-induced pancreatitis[65] and tight control of lipidaemia for hypertriglyceridaemia-induced pancreatitis[66]. Here, we propose the holistic prevention of pancreatitis (HPP) framework, which is based on the above core principles of prevention applied, for the first time, broadly and holistically to pancreatitis. As shown in FIG. 5, each prevention level has its corresponding main target population: the general population for primary prevention, patients in the early stage of acute pancreatitis and chronic pancreatitis for secondary prevention, and patients with any form of pancreatitis who are at risk of sequelae (such as PPDM or EPI) for tertiary prevention.

Opportunities for multi-level prevention are available for all elements of the HPP framework. Implementation of HPP requires the concerted contributions of health care professionals from various disciplines, including primary care physicians, gastroenterologists, surgeons, radiologists, pain specialists, endocrinologists, dietitians and public health specialists. Details of the prevention strategies, intervention objectives and responsible health care sectors are outlined in TABLE 1. The following sections are focused on examples of emerging advances in pancreatology as they are applied to primary, secondary and tertiary prevention of pancreatitis.

Primary prevention.

A comprehensive systematic review of general population-based studies evaluated more than 30 factors associated with diseases of the exocrine pancreas[8]. This study estimated that more than half of pancreatitis cases could have been prevented if all people in the general population were non-smokers, nearly one-fourth of cases if all individuals in the general population were a normal weight (BMI 18–25 kg/m^2), and nearly one-fifth of cases if they had limited alcohol consumption. The review also emphasized that consumption of vegetables and fruits is associated with a nearly 30% reduced risk of all diseases of the exocrine pancreas[8]. Specifically, vegetable consumption was associated with a statistically

significantly reduced risk of acute pancreatitis (OR 0.64, 95% Cl 0.50–0.82)[8]. The open question is how best to use these data on primary prevention of pancreatitis at population level as associations between diet, obesity, smoking, alcohol and risk of other major diseases of the pancreas (pancreatic cancer) are well known[67,68], but these findings have not yet been translated into actionable steps.

The form of acute pancreatitis particularly amenable to primary prevention by gastroenterologists is pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). Avoidance of futile ERCP and the appropriate choice of sedation for ERCP[69,70], rectal administration of nonsteroidal anti-inflammatory drugs[71,72] and optimization of cannulation technique in patients at high-risk (for example, in those with clinical suspicion of sphincter of Oddi dysfunction, pancreatic sphincterotomy, precut sphincterotomy or ampullec-tomy)[73] have proven to be beneficial. Pharmacological interventions (statins in particular) are being trialled as a means of primary prevention of recurrent acute pancreatitis[74] and results are eagerly awaited (TABLE 1).

Secondary prevention.

The emerging aspect of secondary prevention of acute pancreatitis is epitomized in the concept of gut rousing', which has replaced the pancreas rest' concept that dominated the field in the 20th century[75]. The new concept has been developed to prevent progression of acute pancreatitis severity by optimizing the use of the three mainstays of early management — opiates, fluids and nutrition[76]. The concept postulates that the presence of gut dysfunction worsens the outcomes of patients with acute pancreatitis, and the key factors that affect gut function are both pathogenic and iatrogenic (specifically, liberal administration of opiates and fluids)[77]. The concept also recognizes that in acute pancreatitis the gastrointestinal tract should be afforded the same considerations as the other vital systems (respiratory, cardiovascular and renal), and it should be targeted by appropriate therapies. In particular, timely administration of apposite feed into the lumen stimulates (rouses) the gut, mitigates gut dysfunction and restores normal gut function. Neglecting the gut (for example by resting the pancreas) or administering feed at a wrong time leads to worsen outcomes[78].

An emerging example of secondary prevention of chronic pancreatitis is the identification of biomarker signatures that can accurately detect early stage disease[79]. These signatures will not only uncover the specific pathogenic bases of chronic pancreatitis but will also enable tailored selection of patients for future clinical studies, including but not limited to those investigating anti-inflammatory and anti-fibrotic drugs (BOX 1). In that regard, a draft proposal has offered a new mechanistic definition of chronic pancreatitis as: "a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress"[80]. This definition holds promise as it might enable a platform for future research to understand markers of different stages of the disease.

Tertiary prevention.

Although time from an episode of pancreatitis to developing its sequelae varies in the published studies, there is clearly a large window of opportunity for their prevention. For example, two large studies investigated factors associated with PPDM. A study by Ho et al.[81] included a total of 12,284 patients with first attack acute pancreatitis. Alcohol-related acute pancreatitis, more recurrences of acute pancreatitis, male sex and age ≥ 65 years were associated with diabetes after acute pancreatitis in multivariable analyses. Conversely, severity of acute pancreatitis, Charlson comorbidity score and monthly income were not associated with diabetes after acute pancreatitis[81]. A multi-centre study by Beilin et al.[82] included a total of 1,171 patients with chronic pancreatitis. Overweight or obesity, EPI, pancreatic calcifications, prior pancreas surgery, family history of diabetes, male sex, age and duration of pancreatitis were associated with the presence of diabetes in patients with chronic pancreatitis in multivariable analyses, whereas heavy alcohol intake and smoking were not associated with the presence of diabetes. However, the studies by Ho et al.[81] and Beilin et al.[82] did not investigate the relative weights of risk factors. This aspect was addressed in the derivation of the Prediabetes self-assEssment scReening Score aftEr acUte pancreatitis (PERSEUS)[83], which is the first screening instrument to identify patients after an episode of acute pancreatitis who are at high risk of developing prediabetes (and ultimately diabetes). The score is intended for use by patients after hospital discharge to self-assess their probability of having impaired glucose homeostasis. Development of the score began with a comprehensive review of published screening scores for type 2 diabetes and prediabetes, which identified four main domains — anthropometric data, sociodemographic factors, lifestyle-related factors and personal and family health history[84]. PERSEUS was then developed and validated in two independent cohorts, resulting in area under the receiver operating characteristic of 0.88 and 0.81 in the training and validation cohorts, respectively[83]. Importantly, all variables included in the score are readily available to individuals and do not require laboratory testing. Two variables — tobacco smoking and abdominal adiposity — are modifiable risk factors that are worth targeting with a view to reducing the incidence of PPDM.

Conclusions

Epidemiological estimates of the burden of pancreatitis have now become more accurate owing to several large cohort studies conducted in general populations. The sequelae of not only chronic pancreatitis but also acute pancreatitis have become better appreciated, and their effect is formidable. Addressing the most pressing research priorities (BOX 1) will help to lessen the burden of pancreatitis and its sequelae. Contrary to the common belief among gastroenterologists and surgeons, there are already ways to prevent pancreatitis at primary, secondary and tertiary levels. Adoption of the HPP framework will open up many more opportunities by harmonizing efforts of health care specialists from various disciplines for the benefit of patients with pancreatitis worldwide.

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Key points

- Per 100,000 people in the general population, the yearly global incidence of acute pancreatitis is 34 cases, chronic pancreatitis is 10 cases and post-pancreatitis diabetes mellitus is 6 cases.
- The global transition rate from the first episode of acute pancreatitis to a recurrent episode is −20% and, from recurrent acute pancreatitis to chronic pancreatitis, the rate is-35%.
- Acute pancreatitis (including its non-necrotizing form) leads to a number of sequelae long after clinical resolution and, hence, should no longer be considered a self-limited disease.
- Post-pancreatitis diabetes mellitus is the most frequent sequelae of pancreatitis, caused by acute and recurrent acute pancreatitis in −80% and chronic pancreatitis in −20% of cases.
- Patients with pancreatitis have a greater than twofold higher lifetime risk of developing new onset diabetes than individuals in the general population without a history of pancreatitis.
- The holistic prevention of pancreatitis (HPP) concept postulates that primary, secondary and tertiary prevention strategies need to be systematically employed to lessen the effect of pancreatitis and its sequelae.

Box 1|

Knowledge gaps and research opportunities

Epidemiology of pancreatitis

- Acute pancreatitis incidence in Eastern and Southern Europe, South America, South-East Asia, Africa, and the Eastern Mediterranean
- Acute pancreatitis prevalence
- Chronic pancreatitis incidence and prevalence in general populations of most regions of the world
- Ethnic and racial variations

Sequelae of pancreatitis

- Pathogenesis of post-pancreatitis diabetes mellitus (PPDM) and identification of individuals at high risk for PPDM
- Diagnostic markers for diabetes of the exocrine pancreas and its subtypes
- Relationship between the endocrine and exocrine functions of the pancreas, and between the exocrine function and bone metabolism
- Optimal management of post-pancreatitis diabetes mellitus, exocrine pancreatic dysfunction and osteoporosis

Holistic prevention of pancreatitis

- Preventing and /or mitigating gut dysfunction and resulting severity in acute pancreatitis
- Identification of markers of different stages of chronic pancreatitis
- Identification of individuals at risk of recurrences and progression of pancreatitis
- Pharmacological (or other) interventions to prevent recurrences of pancreatitis or progression of chronic pancreatitis

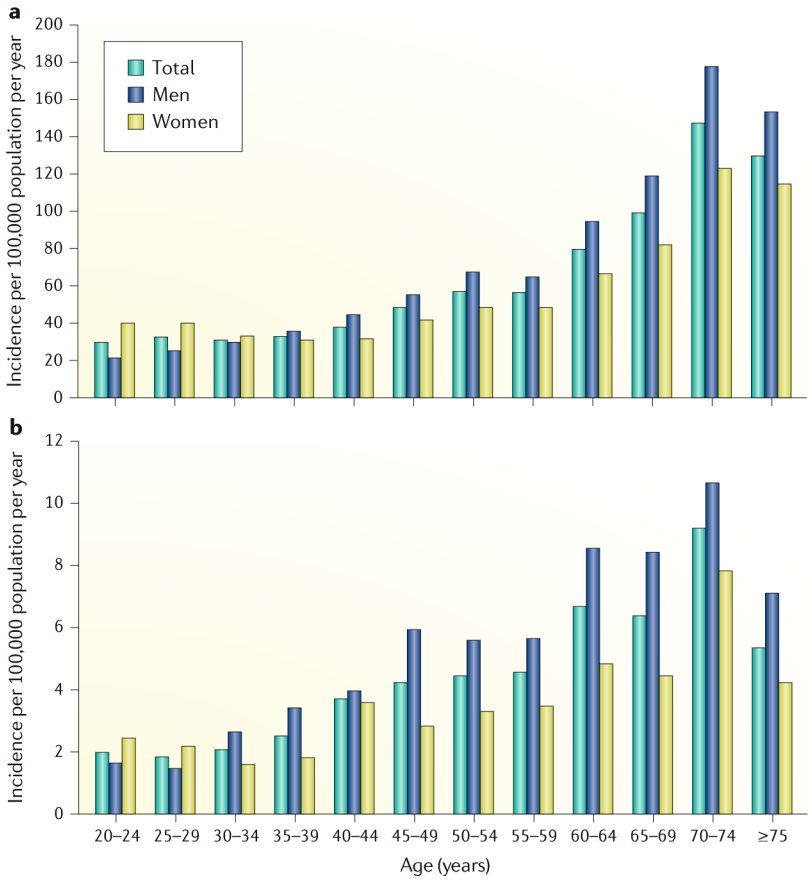

Fig. 1|. Incidence of pancreatitis in the general population.

a | Incidence of acute pancreatitis stratified by age and sex. **b** | Incidence of chronic pancreatitis stratified by age and sex. Data are derived from Pendharkar et al.[10,11].

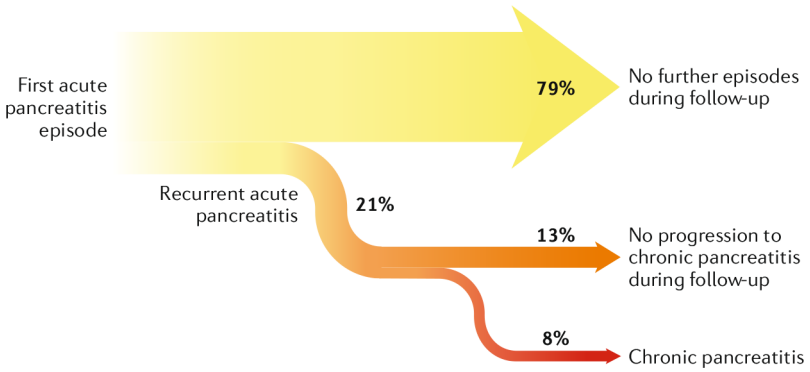

Fig. 2 |. Frequency of transition from first episode of acute pancreatitis to chronic pancreatitis through recurrent acute pancreatitis.

Around 21% of patients suffering a first episode of acute pancreatitis will develop recurrent acute pancreatitis. Of those developing recurrent acute pancreatitis, ~36% will develop chronic pancreatitis. Data are derived from Sankaran et al.[3].

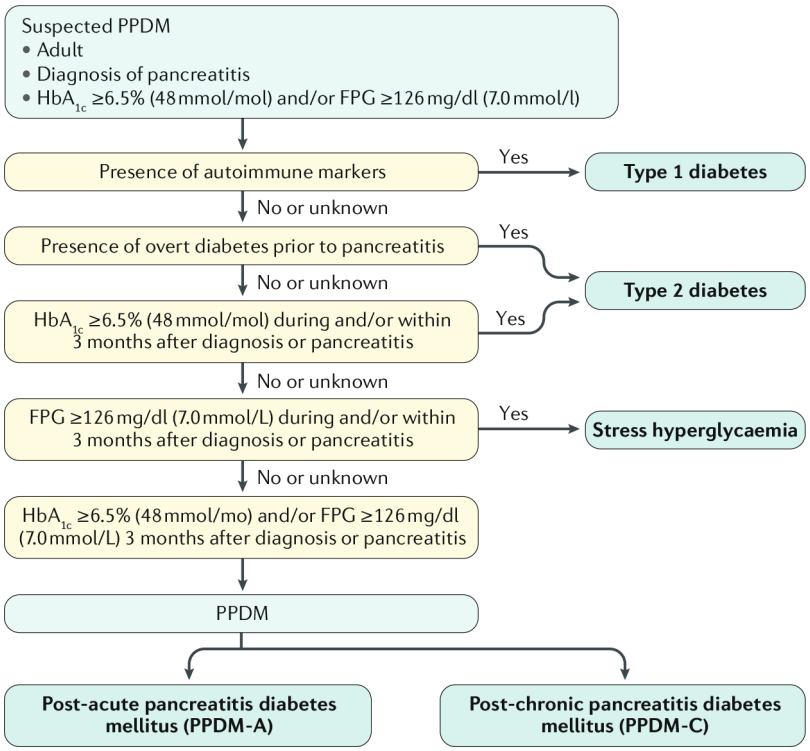

Fig. 3 |. Diagnostic algorithm to identify individuals with PPDM.

Post-pancreatitis diabetes mellitus (PPDM) should be suspected in all adults with a history of pancreatitis who meet the diagnostic criteria for diabetes by the American Diabetes Association. Confirmed type 1 diabetes, or type 2 diabetes prior to first attack of pancreatitis, or stress hyperglycaemia during (or within 3 months after) pancreatitis rules out the diagnosis of PPDM. The 3-month threshold is applied because glycated haemoglobin (HbA_{lc}) level reflects average plasma glucose over the previous 8–12 weeks. The term 'New-onset diabetes after pancreatitis' (NODAP) is reserved for individuals with PPDM who had documented normal glucose homeostasis at baseline (as evidenced by available HbA_{lc} and/or fasting plasma glucose (FPG) data). The algorithm has been devised by the authors. The glycated haemoglobin HbAlc test should be performed using a method that is certified by the National Glycohaemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay. Fasting is defined as no caloric intake for at least 8 h. Autoimmune markers include islet cell autoantibodies and autoantibodies to glutamic acid decarboxylase, insulin, the tyrosine phosphatases IA-2 and IA-2b and zinc transporter antigen. The oral glucose tolerance test can also be used to diagnose diabetes, if it is deemed practical and time-efficient in a given hospital.

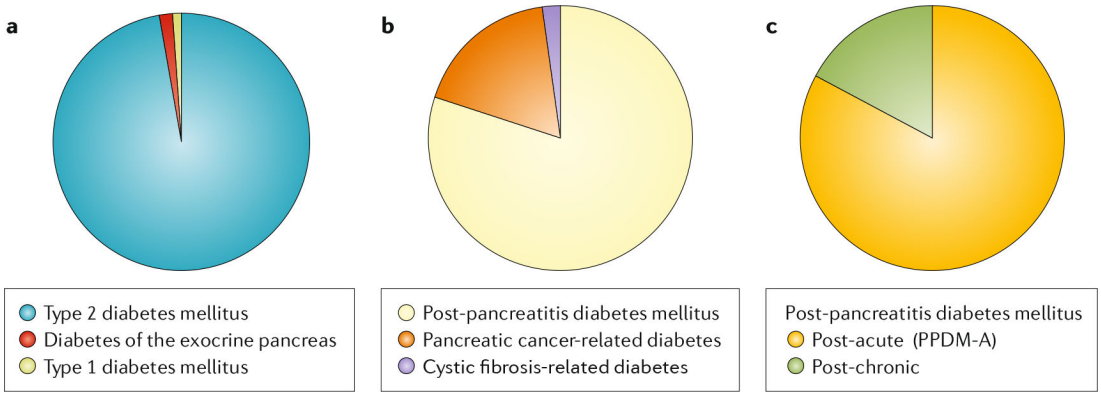

Fig. 4 |. Epidemiology of diabetes of the exocrine pancreas.

a | Frequency of diabetes of the exocrine pancreas in adults, **b** I Frequency of subtypes of diabetes of the exocrine pancreas, **c** | Frequency of subtypes of post-pancreatitis diabetes mellitus. Data are derived from the pooled estimates reported by Woodmansey et al.[44] and Pendharkar et al.[10–11]. Post-acute pancreatitis diabetes mellitus includes cases with diabetes after both first acute pancreatitis episode and recurrent acute pancreatitis.

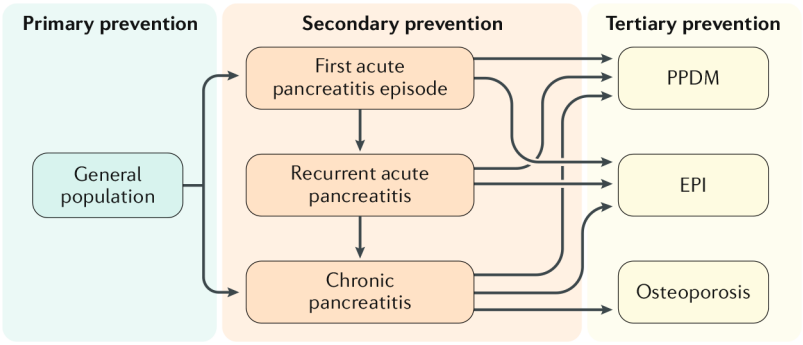

Fig. 5 |. The holistic prevention of pancreatitis framework.

Primary, secondary and tertiary levels of prevention applied holistically to acute, recurrent acute and chronic pancreatitis and as a disease continuum. EPI, exocrine pancreatic insufficiency; PPDM, post-pancreatitis diabetes mellitus.

Table 1 |

prevention levels and targets applied to pancreatitis

	primary prevention	Secondary prevention	Tertiary prevention
First acute pancreatitis episode			
Prevention strategies	• Education of general population • Avoidance of high-risk medications and futile ERCP	• Effective algorithms for early identification and effective in-hospital management of AP	• Screening of patients at high risk
Intervention objectives	• Reducing heavy alcohol use, smoking and obesity • Increasing intake of vegetables • Judicious use of drugs known to induce AP • Restricted use of ERCP	• Early detection of AP and removal of known aetiologies (for example, cholecystectomy, control triglycerides, discontinuation of drugs that induced AP, alcohol, smoking) • Judicious use of opiates, nutrition and fluids to prevent progression of AP severity	• Early detection and management of sequelae (for example, PPDM, EPI) via regular follow-ups • Administration of preventative medications (for example, metformin for PPDM)[a]
Responsible sector	• Public health specialists • Primary care physicians • Gastroenterologists	• Primary care physicians • Gastroenterologists • Surgeons • Radiologists	• Primary care physicians • Gastroenterologists • Dietitians • Endocrinologists
Recurrent acute pancreatitis			
Prevention strategies	• Education of general population and individuals with prior attack of AP	• Effective in-hospital management of AP	• Screening of high-risk patients
Intervention objectives	• Reducing heavy alcohol use, smoking and obesity • Increasing intake of vegetables • Judicious use of drugs known to induce AP • Avoidance of futile ERCP • Administration of preventative medications (for example, statins)[a]	• Removal of known aetiologies (for example, cholecystectomy, control triglycerides, discontinuation of drugs that induced AP, alcohol, smoking) • Judicious use of opiates, nutrition and fluids to prevent progression of AP severity	• Early detection and management of sequelae (for example, PPDM, EPI) via regular follow-ups • Administration of preventative medications (for example, metformin for PPDM)[a]
Responsible sector	• Public health specialists • Primary care physicians • Gastroenterologists • Surgeons	• Gastroenterologists • Surgeons	• Primary care physicians • Gastroenterologists • Dietitians • Endocrinologists
Chronic pancreatitis			
Prevention strategies	• Education of general population and individuals with prior attack of AP	• Effective algorithms of early identification of CP	• Screening of high-risk patients • Professional health consultancy for patients with CP • Chronic pain management
Intervention objectives	• Reducing heavy alcohol use, smoking and obesity • Increasing intake of vegetables • Administration of preventive medications (for example, statins)[a]	• Early detection of CP • Removal of known aetiologies (for example, alcohol, smoking) • Treatment of pancreatic strictures and stones • Discontinuation of alcohol and smoking	• Early detection and management of sequelae (for example, PPDM, EPI) via regular follow-ups • Patient behaviour change • Administration of preventative medications (for example, calcium and vitamin D for osteoporosis, metformin for PPDM[a])
Responsible sector	• Public health specialists • Primary care physicians • Gastroenterologists •Surgeons	• Primary care physicians • Gastroenterologists • Surgeons • Radiologists	• Primary care physicians • Gastroenterologists • Endocrinologists • Pain specialists

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primary prevention	Secondary prevention	Tertiary prevention
		• Dietitians

AP, acute pancreatitis; CP, chronic pancreatitis; EPI, exocrine pancreatic insufficiency; ERCP, endoscopic retrograde cholangiopancreatography; PPDM, post-pancreatitis diabetes mellitus.

[a] If confirmed in future studies.