Excess Body Weight and Pancreatic Disease

Mats L. Wiese Ali A. Aghdassi Markus M. Lerch Antje Steveling

Department of Medicine A, University Medicine Greifswald, Greifswald, Germany

Keywords

Pancreatitis · Pancreatic cancer · Obesity · Visceral fat · Mortality

Abstract

Background: Excess body weight (EBW) is a risk factor for various acute and chronic conditions. Conversely, the “obesity paradox” suggests a protective effect of higher body weight on some disease outcomes. This article discusses the role of EBW along the disease continuum of pancreatitis and pancreatic cancer (PC) in terms of incidence and outcome. **Summary:** Comparison of findings is hampered by the use of different methods to assess EBW. Nevertheless, in acute pancreatitis (AP) and PC, EBW, especially visceral obesity, presents a distinct risk factor and predictor of a negative outcome. Findings of a protective effect likely result from nonconsideration of fat distribution or other confounders. Regarding chronic pancreatitis (CP), few studies indicate lower incidence and a better outcome with higher body mass. However, there is insufficient evidence to confirm the existence of an obesity paradox. The precise mechanisms of how EBW affects the disease continuum require further elucidation but both common and disease-specific effects seem involved. **Key Messages:** EBW is associated with higher incidence and a negative outcome in AP and PC. The association with CP is less conclusive. Thus, maintaining normal weight is advisable at any stage of the disease continuum.

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Introduction

Excess body weight (EBW) generally implies an excessive accumulation of body fat, resulting from prolonged positive energy balance, that is, energy intake exceeding expenditure. If not halted, this gain of body fat initially leads to the development of overweight, and eventually obesity, which has been a pandemic-scale health problem for decades [1]. Although in the past it has been controversially discussed whether obesity is a chronic condition in itself [2], there is consensus that both overweight and obesity increase the risk of numerous noncommunicable diseases, most prominently metabolic and cardiovascular diseases as well as various types of cancer [3].

Just as EBW has been a constantly growing health-care issue, also the global burden of pancreatic diseases has increased over the past decades [4, 5]. In this context, acute pancreatitis (AP) presents the most common pancreatic disease, while pancreatic cancer (PC) is the most lethal one [6]. Clinical data accumulated from human studies confirm that AP, recurrent AP, and chronic pancreatitis (CP) form a disease continuum [7, 8]. Likewise, CP is a well-established risk factor of PC [9, 10]. Because of the parallel trends in prevalence and the established role of overweight and obesity as risk factors for numerous conditions, EBW presumably also increases the risk and worsens the outcome in these pancreatic diseases. However, in the past, the existence of a phenomenon termed “obesity paradox,” that is, obesity exerting a protective effect on an outcome in several chronic and acute diseases, has been proposed. Since then, it has been controversially discussed whether the obesity paradox is real or simply a product of residual confounding [11]. Therefore, assessing the role of EBW in the continuum of pan-

creatic diseases is highly attractive. What are the effects in terms of incidence and outcomes and what are the underlying mechanisms? Addressing these questions, this review summarizes evidence for the role of EBW in AP, CP, and PC, respectively.

Measures of EBW

Some methodological considerations regarding assessment of EBW are indicated as employment of different methods can hamper comparison of findings between studies. Beyond this, interpretation of results might be different depending on what method was employed and which disease was investigated.

There is no definitive answer to the question how to best measure EBW. Several methods exist, and all have their strengths and limitations [12, 13]. Arguably, body mass index (BMI) is the best-established metric as it can be easily assessed, even in large-scale studies, and has been proven as a reliable predictor of adverse outcomes related to EBW in many investigations. By definition, BMI between 25.0 and 30.0 kg/m² indicates overweight and values greater than 30.0 kg/m² qualify as obesity. Yet, for Asian populations, lower cutoff points, that is, 23.0 and 27.5 kg/m², have been identified to reflect increased risk and high risk of EBW, respectively [14]. Other than the issue of defining appropriate cutoff points for specific populations, BMI falls short by not accounting for body composition or fat distribution. In case of the latter, especially abdominal or, more precisely, visceral fat has been linked to chronic diseases [15–17] and adverse outcomes in acute medical conditions [18, 19]. Thus, for more specific assessment, supplemental anthropometric measures, that is, waist circumference (WC) or waist-to-hip ratio, which have shown an additional predicative value for various diseases [20, 21], are frequently employed in large-scale studies. However, these methods do not provide a quantitative measure of body fat reserves. Although there are noninvasive methods for such assessments, for example, bioelectrical impedance analysis or hydrostatic weighing, these techniques have limitations which hinder their usage in larger study settings. Furthermore, none of these methods captures fat distribution in terms of visceral obesity [22]. In contrast, imaging modalities, such as dual-energy X-ray absorptiometry, computed tomography, or magnetic resonance imaging, measure both quantity and distribution of body fat. However, as imaging modalities also have their limitations, for instance, exposure to radiation, requirement of highly trained operators, or high costs, only recently they are used more frequently outside clinical settings [13, 22].

Acute Pancreatitis

The most common causes of AP are gallstones and alcohol abuse, accounting for approximately 60–80% of all cases [23]. In the remaining cases, actual causes often remain unknown. Hypertriglyceridemia and certain medications, including drugs used for the treatment of metabolic diseases, for example, diabetes mellitus, are considered potential triggers of AP [24]. As associations with overweight and or obesity have been shown for all these factors, it is a key question whether EBW is an independent risk factor for AP.

While in the past contradictory findings have been reported on the association of BMI and risk of AP [25–32], higher WC has been consistently associated with an increased risk [27, 29]. A recent meta-analysis [33] showed that both BMI and WC are associated with an increased risk of AP in a dose-response-related manner, with a risk elevation of 18% per 5-unit increment in BMI and 36% per 10 cm increase in WC. While in case of WC, the association was linear, for BMI, a nonlinear association with a steeper risk increase when BMI exceeded 30 kg/m² was found.

With regard to the AP outcome, the relation with EBW is more complex. Several meta-analyses confirm obesity based on BMI as a relevant prognostic factor for local and systemic complications [34–38] as well as severity and mortality in AP [34–39]. According to the most recent meta-analysis [39], obese patients have a 3.6-fold risk of severe AP and a 2.9-fold mortality risk. Two meta-analyses [36, 39] also addressed overweight as a risk factor. Although a higher risk of local complications and mortality was found than in normal-weight patients, the strength of these associations was weaker than for obesity.

In contrast, findings from studies that applied multivariate analysis suggest that EBW may not necessarily be an independent predictor of outcome [40–44]. Findings of an individual patient data meta-analysis [45] corroborate these findings. After adjustment for confounding variables, an independent association of obesity was only seen with development of organ and multiple organ failure but neither with local nor systemic complications nor mortality.

Although these findings question BMI as a suitable parameter to reflect the risks inherent to EBW in AP, they do not support the concept of an obesity paradox either. Evidence for the existence of such phenomenon is scarce anyway. As of today, only few studies [46–48] have suggested that an obesity paradox may exist in AP. In fact, this may be true under certain conditions. Several studies [49–52] showed visceral fat to be a stronger predictor of severe AP than BMI. Assuming that excessive visceral fat causes negative outcomes in AP, high BMI, in the absence of abdominal obesity, could exert a protective effect. The

Fig. 1. Biochemical mechanisms of how EBW affects pathogenesis and outcome in AP, CP, and PC. AP, acute pancreatitis; CP, chronic pancreatitis; PC, pancreatic cancer; EBW, excess body weight.

fair correlation between BMI and visceral fat might explain the association between obesity based on BMI and negative outcomes in AP seen in large population-based studies and meta-analyses.

Chronic Pancreatitis

The number of studies investigating the association of EBW with the incidence of CP is very limited. A recent meta-analysis of prospective studies [33] found that a 5-unit increase in BMI lowered the risk of CP by 22%. Because only 2 studies [27, 28] were included in this analysis, with one [27] showing only a trend for this association, this finding should be considered with caution. Also, despite prospective study designs, it cannot be ruled out that reduced body weight at baseline might be the result of an early form of CP rather than a risk factor for disease.

Regarding the disease outcome, EBW may also have a protective effect, which is suggested for that reason alone that malnutrition, associated with increased morbidity and mortality, in CP is common and still challenging to treat [53]. However, there are only a few studies to actually support this hypothesis. For instance, a cohort study with a 30-year follow-up [54] found that CP patients with a BMI

$\geq 25 \text{ kg/m}^2$ had a 40% lower mortality rate than patients with BMI $< 20 \text{ kg/m}^2$. In another study [55], BMI $\geq 23 \text{ kg/m}^2$ was associated with higher islet yields and better clinical outcomes in autologous islet cell transplantation. Last, a prospective investigation in pediatric patients [56] showed that overweight or obese children with CP were less likely to undergo medical or endoscopic treatment, develop exocrine pancreatic insufficiency, and require total pancreatectomy with islet autotransplantation. Despite these findings and the lack of data revealing an association of EBW with negative outcomes or mortality, there is insufficient evidence to confirm an obesity paradox in CP.

Pancreatic Cancer

The role of EBW in the development of PC presents as a clear-cut case. Several meta-analyses [57–59] and large pooled analyses [60–62] showed a dose-dependent association between BMI and PC risk, with a risk increase of approximately 10% per 5-unit increment in BMI. Among studies that also looked at anthropometric parameters, significant associations were found with WC [57] and waist-to-hip ratio [61, 62], especially in women, indicating a relevance of body fat distribution.

With respect to mortality, the association between EBW and PC is less conclusive. A recent meta-analysis [63] indicated that EBW at diagnosis or before PC surgery is not associated with survival. On the other hand, the same study found a dose-response relationship between adult BMI and mortality resulting in an 11% higher mortality risk per 5-unit increase in BMI. These findings could be explained by the rapid progression of PC accompanied by drastic weight loss commonly occurring before diagnosis or surgery. Unfortunately, weight loss as a confounding factor has not been included in the studies looking at BMI at diagnosis or before surgery. Another study [64] also investigated the effect of body fat distribution but found no association for either BMI or visceral fat with overall survival. For now, the effect of EBW on outcome in PC remains unclear. Despite its consuming character, so far, there is no evidence for the existence of an obesity paradox in PC.

Mechanisms

The mechanisms of how EBW effect pathogenesis and outcome in pancreatic diseases are still not fully understood. The most commonly proposed biochemical mechanisms are associated with an excessive accumulation of both visceral and intra-pancreatic fat (shown in Fig. 1). Low-grade inflammation and immune dysfunction mediated by adipokines, both locally and systematically, is likely to contribute to the pathogenesis of all 3 diseases [65]. Moreover, especially in AP, increased lipolysis seems to account for adverse outcomes by setting free unsaturated fatty acids that potentiate necrosis and worsen local and systemic inflammation [66] mediated by a storm of cytokines, predominantly IL-6, IL-8, and IL-10 [67]. Diet-induced visceral fat unsaturation has therefore recently been suggested as a driver of AP severity and potential explanation for an obesity paradox [68]. By contrast, in CP, intra-pancreatic adipocytes are surrounded by fibrotic tissue, which limits lipolysis and, thus, ameliorates severity of acute exacerbations in CP [69]. This could at least partially explain the observation of an improved outcome in patients with EBW. Last, especially in PC, hormonal effects of adipose tissue seem to be involved in pathogenesis. Obesity and BMI have been associated with increased levels of insulin and insulin-like growth factor 1, which may promote pancreatic carcinogenesis by modulation of cell proliferation, apoptosis, and angiogenesis [70]. In addition, also leptin, primarily synthesized in adipocytes, has been found to enhance the invasion of PC through an increase in matrix metalloproteinase-13 production [71]. Pancreatic steatosis, resulting from progressive fatty infiltration, may also contribute to carcinogenesis by tissue remodeling and fibroinflammatory reactions [72].

Overall, the observed associations of EBW with both AP and PC suggest similar mechanisms caused by EBW that include the induction of a pro-inflammatory micro-environment in both diseases. Although CP is a known risk factor of PC, there are only a relatively small number of CP patients who eventually develop PC, which may explain that pathogenic factors for cancer development are different to chronic inflammation. However, acknowledging the lack of convincing mechanistic explanations, the alleged inverse association between EBW and CP should be considered even more cautiously.

Conclusion

The role of EBW along the continuum of pancreatic diseases is ambiguous. For AP and PC, there is convincing evidence that EBW, especially in the form of visceral obesity, increases risk and worsens the outcome. Conversely, limited data on CP suggest a protective effect. The precise mechanisms of how EBW impacts pancreatic disease require further investigation, but there seem to be both common and disease-specific effects. To reduce the risk of progression, prevention should start at the earliest stage of disease. Therefore, maintaining normal-weight stands as a recommendation that is universally applicable along the continuum of pancreatic disease.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.L.W., A.A.A., M.M.L., and A.S. conceived and drafted the manuscript. All the authors approved the final version of the manuscript, including the authorship list.

References

- 1 Egger G, Swinburn B. An “ecological” approach to the obesity pandemic. *BMJ*. 1997; 315(7106):477–80.
- 2 Bray GA, Kim KK, Wilding JPH. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obes Rev*. 2017;18(7):715–23.
- 3 Afshin A, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13–27.
- 4 GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2019;4(12):934–47.
- 5 Ouyang G, Pan G, Liu Q, Wu Y, Liu Z, Lu W, et al. The global, regional, and national burden of pancreatitis in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *BMC Med*. 2020;18(1):388.
- 6 Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. *Lancet Gastroenterol Hepatol*. 2016;1(1):45–55.
- 7 Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark CE, Petrov MS. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. *Gastroenterology*. 2015;149(6):1490–500.e1.
- 8 Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol*. 2016;14(5):738–46.
- 9 Hoffmeister A, Mayerle J, Beglinger C, Büchler MW, Büfler P, Dathe K, et al. English language version of the S3-consensus guidelines on chronic pancreatitis: definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis. *Z Gastroenterol*. 2015;53(12):1447–95.
- 10 Lohr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United European Gastroenterol J*. 2017;5(2):153–99.
- 11 Banack HR, Stokes A. The “obesity paradox” may not be a paradox at all. *Int J Obes*. 2017; 41(8):1162–3.
- 12 Andreoli A, Garaci F, Cafarelli FP, Guglielmi G. Body composition in clinical practice. *Eur J Radiol*. 2016;85(8):1461–8.
- 13 Ceniccola GD, Castro MG, Piovacari SMF, Horie LM, Corrêa FG, Barrere APN, et al. Current technologies in body composition assessment: advantages and disadvantages. *Nutrition*. 2019;62:25–31.
- 14 WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004; 363(9403):157–63.
- 15 Schulze MB, Heidemann C, Schienkiewitz A, Bergmann MM, Hoffmann K, Boeing H. Comparison of anthropometric characteristics in predicting the incidence of type 2 diabetes in the EPIC-Potsdam study. *Diabetes Care*. 2006;29(8):1921–3.
- 16 Hirani V. Generalised and abdominal adiposity are important risk factors for chronic disease in older people: results from a nationally representative survey. *J Nutr Health Aging*. 2011;15(6):469–78.
- 17 Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP, Navaneethan SD. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2011;6(10):2364–73.
- 18 Lakka HM, Lakka TA, Tuomilehto J, Salonen JT. Abdominal obesity is associated with increased risk of acute coronary events in men. *Eur Heart J*. 2002;23(9):706–13.
- 19 Paolini JB, Mancini J, Genestal M, Gonzalez H, McKay RE, Samii K, et al. Predictive value of abdominal obesity vs. body mass index for determining risk of intensive care unit mortality. *Crit Care Med*. 2010;38(5):1308–14.
- 20 Janssen I, Katzmarzyk PT, Ross R. Body mass index, waist circumference, and health risk: evidence in support of current National Institutes of Health guidelines. *Arch Intern Med*. 2002;162(18):2074–9.
- 21 Ross R, Neeland JJ, Yamashita S, Shai I, Seidell J, Magni P, et al. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. *Nat Rev Endocrinol*. 2020;16(3):177–89.
- 22 Fosbøl MØ, Zerahn B. Contemporary methods of body composition measurement. *Clin Physiol Funct Imaging*. 2015;35(2):81–97.
- 23 Wang GJ, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: etiology and common pathogenesis. *World J Gastroenterol*. 2009; 15(12):1427–30.
- 24 Weiss FU, Laemmerhirt F, Lerch MM. Etiology and risk factors of acute and chronic pancreatitis. *Visc Med*. 2019;35(2):73–81.
- 25 Hansen SEJ, Madsen CM, Varbo A, Nordestgaard BG. Body mass index, triglycerides, and risk of acute pancreatitis: a population-based study of 118 000 individuals. *J Clin Endocrinol Metab*. 2020;105(1):dgz059.
- 26 Choi JS, Yi SW, Park JW, Lee S, Jeong SH, Yi JJ, et al. Body mass index and the risk of acute pancreatitis by etiology: a prospective analysis of Korean National Screening Cohort. *J Gastroenterol Hepatol*. 2019;34(3):603–11.
- 27 Pang Y, Kartsonaki C, Turnbull I, Guo Y, Yang L, Bian Z, et al. Metabolic and lifestyle risk factors for acute pancreatitis in Chinese adults: a prospective cohort study of 0.5 million people. *PLoS Med*. 2018;15(8):e1002618.
- 28 Prizment AE, Jensen EH, Hopper AM, Virnig BA, Anderson KE. Risk factors for pancreatitis in older women: the Iowa Women’s Health Study. *Ann Epidemiol*. 2015;25(7):544–8.
- 29 Sadr-Azodi O, Orsini N, Andrén-Sandberg Å, Wolk A. Abdominal and total adiposity and the risk of acute pancreatitis: a population-based prospective cohort study. *Am J Gastroenterol*. 2013;108(1):133–9.
- 30 Gonzalez-Perez A, Schlienger RG, Rodríguez LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study. *Diabetes Care*. 2010;33(12):2580–5.
- 31 Lindkvist B, Appelros S, Manjer J, Berglund G, Borgstrom A. A prospective cohort study of smoking in acute pancreatitis. *Pancreatol*. 2008;8(1):63–70.
- 32 Morton C, Klatzky AL, Udaltsova N. Smoking, coffee, and pancreatitis. *Am J Gastroenterol*. 2004;99(4):731–8.
- 33 Aune D, Mahamat-Saleh Y, Norat T, Riboli E. High body mass index and central adiposity is associated with increased risk of acute pancreatitis: a meta-analysis. *Dig Dis Sci*. 2021; 66(4):1249–67.
- 34 Martínez J, Sánchez-Payá J, Palazón JM, Suazo-Barahona J, Robles-Díaz G, Pérez-Mateo M. Is obesity a risk factor in acute pancreatitis? A meta-analysis. *Pancreatol*. 2004;4(1):42–8.
- 35 Martínez J, Johnson CD, Sánchez-Payá J, de Madaria E, Robles-Díaz G, Pérez-Mateo M. Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated meta-analysis. *Pancreatol*. 2006;6(3):206–9.
- 36 Wang SQ, Li SJ, Feng QX, Feng XY, Xu L, Zhao QC. Overweight is an additional prognostic factor in acute pancreatitis: a meta-analysis. *Pancreatol*. 2011;11(2):92–8.
- 37 Hong S, Qiwen B, Ying J, Wei A, Chaoyang T. Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis. *Eur J Gastroenterol Hepatol*. 2011;23(12):1136–43.
- 38 Chen SM, Xiong GS, Wu SM. Is obesity an indicator of complications and mortality in acute pancreatitis? An updated meta-analysis. *J Dig Dis*. 2012;13(5):244–51.
- 39 Dobszai D, Mátrai P, Gyöngyi Z, Csopor D, Bajor J, Eröss B, et al. Body-mass index correlates with severity and mortality in acute pancreatitis: a meta-analysis. *World J Gastroenterol*. 2019;25(6):729–43.
- 40 Mentula P, Kylänpää ML, Kemppainen E, Puolakkainen P. Obesity correlates with early hyperglycemia in patients with acute pancreatitis who developed organ failure. *Pancreas*. 2008;36(1):e21–5.
- 41 Gloor B, Müller CA, Worni M, Martignoni ME, Uhl W, Büchler MW. Late mortality in patients with severe acute pancreatitis. *Br J Surg*. 2001;88(7):975–9.
- 42 Halonen KI, Leppaniemi AK, Puolakkainen PA, Lundin JE, Kemppainen EA, Hietaranta AJ, et al. Severe acute pancreatitis: prognostic factors in 270 consecutive patients. *Pancreas*. 2000;21(3):266–71.
- 43 Karimani I, Porter KA, Langevin RE, Banks PA. Prognostic factors in sterile pancreatic necrosis. *Gastroenterology*. 1992;103(5):1636–40.
- 44 Porter KA, Banks PA. Obesity as a predictor of severity in acute pancreatitis. *Int J Pancreatol*. 1991;10(3–4):247–52.
- 45 Smeets XJNM, Knoester I, Grooteman KV, Singh VK, Banks PA, Papachristou GI, et al. The association between obesity and outcomes in acute pancreatitis: an individual patient data meta-analysis. *Eur J Gastroenterol Hepatol*. 2019;31(3):316–22.

- 46 Bala S, Alkhayro A, Hila A. Obesity paradox in acute pancreatitis: 76. *Am J Gastroenterol*. 2016;31:S36–7.
- 47 van Geenen EJM, Bollen TL, Smits MM, van Santvoort HC, Besselink MG, Gooszen HG, et al. The “obesity paradox” in predicted severe acute pancreatitis. *Pancreatol*. 2013;13(2): e82.
- 48 Davis PJ, Eltawil KM, Abu-Wasel B, Walsh MJ, Topp T, Molinari M. Effect of obesity and decompressive laparotomy on mortality in acute pancreatitis requiring intensive care unit admission. *World J Surg*. 2013;37(2): 318–32.
- 49 Xie J, Xu L, Pan Y, Li P, Liu Y, Pan Y, et al. Impact of visceral adiposity on severity of acute pancreatitis: a propensity score-matched analysis. *BMC Gastroenterol*. 2019; 19(1):87.
- 50 Natu A, Stevens T, Kang L, Yasinow S, Mansoor E, Lopez R, et al. Visceral adiposity predicts severity of acute pancreatitis. *Pancreas*. 2017;46(6):776–81.
- 51 O’Leary DP, O’Neill D, McLaughlin P, O’Neill S, Myers E, Maher MM, et al. Effects of abdominal fat distribution parameters on severity of acute pancreatitis. *World J Surg*. 2012; 36(7):1679–85.
- 52 Yashima Y, Isayama H, Tsujino T, Nagano R, Yamamoto K, Mizuno S, et al. A large volume of visceral adipose tissue leads to severe acute pancreatitis. *J Gastroenterol*. 2011;46(10): 1213–8.
- 53 Wiese M, Gärtner S, Doller J, Tran TQ, Frost F, Bannert K, et al. Nutritional management of chronic pancreatitis: a systematic review and meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol*. 2021;36(3): 588–600.
- 54 Nøjgaard C. Prognosis of acute and chronic pancreatitis: a 30-year follow-up of a Danish cohort. *Dan Med Bull*. 2010;57(12):B4228.
- 55 Takita M, Naziruddin B, Matsumoto S, Noguchi H, Shimoda M, Chujo D, et al. Body mass index reflects islet isolation outcome in islet autotransplantation for patients with chronic pancreatitis. *Cell Transplant*. 2011;20(2): 313–22.
- 56 Uc A, Zimmerman MB, Wilschanski M, Werlin SL, Troendle D, Shah U, et al. Impact of obesity on pediatric acute recurrent and chronic pancreatitis. *Pancreas*. 2018;47(8): 967–73.
- 57 Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Ann Oncol*. 2012;23(4): 843–52.
- 58 Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: a meta-analysis of prospective studies. *Int J Cancer*. 2007; 120(9):1993–8.
- 59 Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. *Br J Cancer*. 2003;89(3): 519–23.
- 60 Jiao L, Berrington de Gonzalez A, Hartge P, Pfeiffer RM, Park Y, Freedman DM, et al. Body mass index, effect modifiers, and risk of pancreatic cancer: a pooled study of seven prospective cohorts. *Cancer Causes Control*. 2010;21(8):1305–14.
- 61 Genkinger JM, Spiegelman D, Anderson KE, Bernstein L, van den Brandt PA, Calle EE, et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. *Int J Cancer*. 2011;129(7):1708–17.
- 62 Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Arch Intern Med*. 2010; 170(9):791–802.
- 63 Shi YQ, Yang J, Du P, Xu T, Zhuang XH, Shen JQ, et al. Effect of body mass index on overall survival of pancreatic cancer: a meta-analysis. *Medicine* 2016;95(14):e3305.
- 64 Gaujoux S, Torres J, Olson S, Winston C, Gonen M, Brennan MF, et al. Impact of obesity and body fat distribution on survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg Oncol*. 2012;19(9): 2908–16.
- 65 Gukovsky I, Li N, Todoric J, Gukovskaya A, Karin M. Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer. *Gastroenterology*. 2013;144(6):1199–e4.
- 66 Noel P, Patel K, Durgampudi C, Trivedi RN, de Oliveira C, Crowell MD, et al. Peripancreatic fat necrosis worsens acute pancreatitis independent of pancreatic necrosis via unsaturated fatty acids increased in human pancreatic necrosis collections. *Gut*. 2016;65(1): 100–11.
- 67 Hegyi P, Szakács Z, Sahin-Tóth M. Lipotoxicity and cytokine storm in severe acute pancreatitis and COVID-19. *Gastroenterology*. 2020;159(3):824–7.
- 68 Khatua B, El-Kurdi B, Patel K, Rood C, Noel P, Crowell M, et al. Adipose saturation reduces lipotoxic systemic inflammation and explains the obesity paradox. *Sci Adv*. 2021;7(5): eabd6449.
- 69 Acharya C, Cline RA, Jaligama D, Noel P, DeLany JP, Bae K, et al. Fibrosis reduces severity of acute-on-chronic pancreatitis in humans. *Gastroenterology*. 2013;145(2):466–75.
- 70 Bracci PM. Obesity and pancreatic cancer: overview of epidemiologic evidence and biologic mechanisms. *Mol Carcinog*. 2012;51(1): 53–63.
- 71 Fan Y, Gan Y, Shen Y, Cai X, Song Y, Zhao F, et al. Leptin signaling enhances cell invasion and promotes the metastasis of human pancreatic cancer via increasing MMP-13 production. *Oncotarget*. 2015;6(18):16120–34.
- 72 Desai V, Patel K, Sheth R, Barlass U, Chan YM, Sclamborg J, et al. Pancreatic fat infiltration is associated with a higher risk of pancreatic ductal adenocarcinoma. *Visc Med*. 2020; 36(3):220–6.