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The association between obesity and outcomes in acute pancreatitis: an individual patient data meta-analysis

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Objectives There are data to suggest that obesity is associated with local and systemic complications as well as mortality in acute pancreatitis (AP). Cohort studies to date, however, have shown conflicting results from mostly unadjusted analyses. Therefore, we performed an individual patient data meta-analysis with the primary aim to investigate the association between obesity and mortality in AP. Our secondary aim was to investigate the association between obesity and necrosis, organ failure, multiple organ failure, and invasive intervention.

Patients and methods We systematically searched four electronic databases for prospective studies on obesity and outcomes in AP. Researchers of eligible studies were invited to share individual patient data using a standardized data collection form. All end points were investigated with a one-stage mixed effects Poisson model with random intercepts and forced entry of relevant confounders.

Results We included five databases with 1302 patients, of whom 418 (32%) were obese. In total, 466 (36%) patients had necrosis, 328 (25%) had organ failure, 188 (14%) had multiple organ failure, 210 (16%) had an intervention, and 84 (7%) patients died. We found no significant association between obesity and mortality [relative risk (RR) 1.40, 95% confidence interval (CI): 0.89–2.20], necrosis (RR: 1.08, 95% CI: 0.90–1.31) or invasive intervention (RR: 1.10, 95% CI: 0.83–1.47) after adjustment for confounders. However, obesity was independently associated with the development of organ failure (RR: 1.38, 95% CI: 1.11–1.73) and multiple organ failure (RR: 1.81, 95% CI: 1.35–2.42).

Conclusion Obesity is independently associated with the development of organ failure and multiple organ failure in AP. However, there is no association between obesity and mortality, necrosis, and an intervention. Eur J Gastroenterol Hepatol 31:316–322

Introduction

Acute pancreatitis (AP) has an annual incidence of 13 to 45/100 000, and it is the third most common gastrointestinal discharge diagnosis in the USA [1,2]. Approximately 80% of AP cases are mild and self-limiting, but in 20% of cases, the disease progresses to necrotizing pancreatitis with a high risk of organ failure and a mortality rate up to 20% [3]. AP is one of the leading causes of death owing to gastrointestinal and liver diseases [2].

The incidence of AP is increasing, and this is in part owing to the rising prevalence of obesity: a high BMI stimulates gallstone formation and increases hyperlipidemia, both causing AP [1,4–6]. The prevalence of obesity, defined by the WHO as a BMI of at least 30 kg/m^2, has doubled between 1980 and 2014. In 2014, 11% of adult males and 15% of adult women were obese, predominantly in high-income countries [7].

There are data to suggest that obesity is also associated with local and systemic complications as well as mortality in AP. Pancreatic enzymes released in AP digest adipocytes, causing an outflux of unsaturated fatty acids that can contribute to local and systemic complications [8–10]. Furthermore, obesity is thought to promote the excessive inflammatory response in AP [11]. Alternatively, it is possible that the association between obesity and mortality in severe AP is explained by the so-called 'obesity paradox': the finding that critically ill patients with overweight or moderate obesity have a lower mortality compared to patients with a normal weight or morbid obesity [12].

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Because of these contradictory findings, it is not surprising that a systematic review on the association between obesity and outcomes in AP reported conflicting results [13]. However, these conflicts could also arise owing to heterogeneity in the study populations (e.g. only biliary etiology), adopted definitions (continuous BMI vs. WHO cutoff values) and the reporting of unadjusted analyses in 12 of 19 included studies. As a result, the question whether obesity is an independent prognostic factor in AP remains unanswered. Furthermore, traditional meta-analyses can only synthesize aggregate data obtained from study publications. In contrast, an individual patient data meta-analysis (IPDMA) combines raw patient data derived from published and unpublished cohorts [14]. Therefore, an IPDMA has the advantage that effect estimates can be adjusted for confounders, data for subgroup analyses can be extracted (e.g. patients with overweight or obesity subclasses), and it allows for the use of uniform definitions.

We performed an IPDMA of prospective cohort studies on AP from international expert centers. Our primary aim was to examine the association between obesity and mortality in AP. Our secondary aim was to investigate the association between obesity and four widely studied outcomes in AP: the development of necrosis, organ failure, multiple organ failure, and invasive intervention (i.e. catheter drainage or necrosectomy).

Patients and methods

Our methodology consisted of two steps. First, we systematically searched the literature for prospective cohort studies on the patient. Second, we performed an IPDMA by combining the identified cohorts. In this study, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Individual Patient Data (PRISMA-IPD) guidelines [14] (see Supplementary Table 1, Supplement 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A365*). All original patient data were collected in accordance with the declaration of Helsinki.

Systematic review

Literature search and study selection

We conducted a literature search in the electronic databases Medline, Embase, Web of Science, and Cochrane by combining the following search terms with synonyms: obese, pancreatitis, and prognosis (see Supplementary Material, Supplement 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A365* for full search strategy). Thereafter, we screened all articles on title and abstract to ensure they reported on AP and obesity. The eligibility of the remaining articles was assessed by examining the full-text papers for adherence to predefined inclusion and exclusion criteria (Table 1). Finally, we screened all eligible studies for cross-references in Web of Science. Two investigators (I.K. and K.G.) independently executed all screenings. Disagreements were resolved after discussion with a third author (E.v.G.).

Data collection and individual patient data integrity

We invited the primary researchers of all eligible studies to share their individual patient data. When contact with the primary author failed, other co-authors or the author's department were contacted. After agreement, the authors received a standardized list of all variables and definitions of interest (see Supplementary Table 2, Supplement 3, Supplemental digital content 1, *http://links.lww.com/EJGH/A365* for study definitions). We collected the following variables: age, sex, comorbidity, BMI, etiology, predicted severity, (infected) necrosis, organ failure (circulatory, pulmonary, renal), invasive interventions for AP (percutaneous/endoscopic drainage, surgical/endoscopic necrosectomy), and mortality. The received databases were checked for completeness and internal consistency. All queries were discussed with the original investigators.

Table 1. Inclusion and exclusion criteria systematic search

Inclusion	Exclusion
Patients (>18 years) with admission to the hospital for acute pancreatitis	The risk of obesity on the development of acute pancreatitis as the purpose of the study
BMI as primary or secondary determinant	Chronic pancreatitis (or acute-on-chronic pancreatitis), pancreatic cancer or autoimmune pancreatitis as an etiology of acute pancreatitis
Clinical outcome: mortality	Animal studies
Original, human in-vivo studies	Case reports, letters, editorials, comments, and reviews
Full-text articles or abstracts of presentations	No full-text available
Publication date > 1980	
English language	
Prospective study design	

Quality assessment

The quality of all eligible articles, regardless of data sharing, was critically appraised using the Quality In Prognosis Studies tool [15]. As advocated by the designers of Quality In Prognosis Studies, we optimized the tool for the specific research questions of the current study (see Supplementary Table 3, Supplement 4, Supplemental digital content 1, *http://links.lww.com/EJGH/A365*). For each domain, we designated whether the study had a low, moderate, or high risk of bias. The critical appraisal was performed independently by two investigators (I.K. and X.S.). Disagreements were resolved after discussion with a third author (E.v.G.). We made funnel plots to assess possible publication bias.

Individual patient data meta-analysis

Outcomes

The primary endpoint was AP-related mortality. In our first analysis, we investigated the influence of obesity on mortality in the entire cohort and in subgroups of patients with organ failure and multiple organ failure. In our second analysis, we investigated whether the relationship between BMI and mortality follows that of the obesity paradox. To that end, we categorized patients according to the WHO BMI categories (Supplementary Table 2, Supplement 3, Supplemental digital content 1, *http://links.lww.com/EJGH/A365*). For each category, we calculated the relative risk (RR) for mortality with normal weight as a reference. Because the obesity paradox is specifically for critically ill patients, we performed our analyses in three subgroups with severe disease: (i) patients with predicted severe AP, (ii) patients with organ failure, and (iii) patients with multiple organ failure. We did not analyze the subgroup of ICU patients because indications for ICU admission are variable and subjective.

The secondary end points were presence of pancreatic necrosis, organ failure, multiple organ failure, and invasive intervention. All results are expressed as RR with 95% confidence interval (CI).

Synthesis methods

After integrating all contributed databases to one final database, missing values were managed by multiple (20×) imputation by chained equations and predictive mean matching [16]. For all analyses, including the subgroup analyses and analyses of secondary end points, we used a one-stage approach in which the meta-analytical effect estimate is derived from the source data of all studies simultaneously. As advocated by the PRISMA-IPD guidelines [14], we accounted for clustering of patients within studies by using a mixed effects model with random intercepts. Because we wanted to report relative risks instead of odds ratios, we used a Poisson model. By forced entry, we accounted for the potential confounder's age, sex, comorbidity, aetiology, necrosis, organ failure, and intervention in all analyses.

A two-tailed *P* value below 0.05 was regarded as statistically significant. The statistical analyses were performed with R (R Foundation for Statistical Computing, Vienna, Austria). Funnel plots were made with Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Systematic review and individual patient data collection

The systematic review yielded 1303 results, after removal of duplicates (Fig. 1). We excluded 1176 studies on the basis of title and abstract. Of the 127 remaining studies, 109 were excluded based on full-text evaluation. Finally, our data set consisted of 18 studies [17–34]. We were not able to retrieve individual data of 13 studies, mostly because the databases were no longer available. Characteristics of all eligible studies are found in Supplementary Table 4, Supplement 5 (Supplemental digital content 1, *http://links.lww.com/EJGH/A365*).

Five authors provided individual patient data [30–34]. Three cohorts [31–33] included unpublished data. All authors confirmed that the additional data were collected in accordance with the methodology of the original manuscript. We found no inconsistencies in data integrity. The sample sizes ranged from 120 to 400 patients, with 1302 patients in total. The studies were conducted in mostly a western population between 1997 and 2008. Two studies [30,34] collected data from multiple centres. The prevalence of obesity ranged from 26 to 40%.

Baseline characteristics

The baseline characteristics of the 1302 patients are given in Table 2. The mean age of the patients was 53 years, 602 (46%) were female, and 651 (50%) had comorbidity. The median BMI was 27.2 (range: 13.6–77.9). A total of 418 (32%) patients in the cohort were obese. Biliary etiology was the most prevalent, in 515 (40%) patients. A total of 684 (53%) patients had a predicted severe disease course, 466 (36%) developed necrotizing pancreatitis, and 328 (25%) developed organ failure. In total, 84 (7%) patients died. Data were missing in four of the 11 baseline variables. Necrosis was missing in 278 (21%) patients, mainly

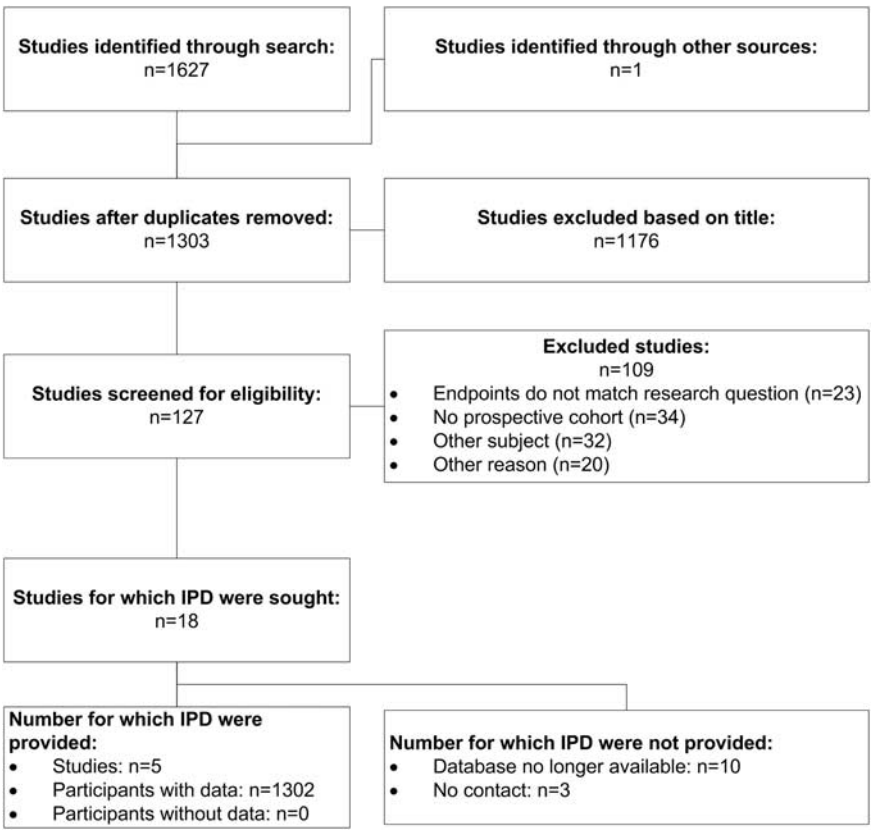

Fig. 1. Flow chart. IPD, individual patient data.

Table 2. Baseline characteristics and differences between nonobese and obese patients

	Total ($N=1302$)	Nonobese ($n=871$)	Obese ($n=418$)	*P* value	Missing
Age (years)	53 (17)	54 (18)	52 (16)	0.194	0 (0)
Sex (female)	602 (46)	393 (45)	203 (49)	0.246	0 (0)
Comorbidity	651 (50)	442 (51)	203 (49)	0.463	0 (0)
BMI	27.2 (13.6–77.9)	25.0 (13.6–29.9)	35.7 (30.0–77.9)	<0.001	13 (1)
Etiology				<0.001	5 (0.4)
Biliary	515 (40)	307 (35)	205 (49)		
Alcohol	239 (18)	177 (20)	58 (14)		
Idiopathic	210 (16)	142 (16)	67 (16)		
Other	333 (26)	241 (28)	87 (21)		
Predicted severe	684 (53)	472 (54)	209 (50)	0.158	0 (0)
Necrosis	466 (36)	306 (44)	159 (49)	0.166	278 (21)
Organ failure	328 (25)	196 (23)	131 (31)	0.001	0 (0)
Multiple organ failure	188 (14)	102 (12)	85 (20)	<0.001	0 (0)
Invasive intervention	210 (16)	128 (16)	82 (21)	0.045	120 (9)
Mortality	84 (7)	47 (5)	36 (9)	0.028	0 (0)

Values represent number of patients (percentage of total in column) [*n* (%)], mean (SD), or median (range). Numbers of nonobese and obese patients do not always add up to the total number of patients owing to missing BMI data in 13 patients.

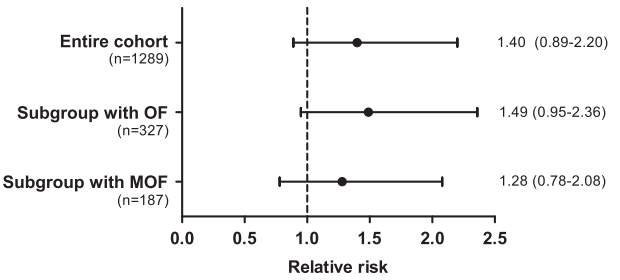

Fig. 2. Forest plot depicting relative risk of obesity for mortality in subgroups. Values represent relative risk (95% confidence interval). In all subgroup analyses, we adjusted for age, sex, comorbidity, etiology, necrosis, and intervention. In the analysis of the entire cohort, we also adjusted for organ failure. MOF, multiple organ failure; OF, organ failure.

because the decision to perform a computed tomography scan (to assess necrosis) in four cohorts [31–34] was left to the discretion of the treating physician, as is the common practice in these countries. Univariable analyses showed there were significant differences between nonobese and obese patients with respect to etiology, organ failure, multiple organ failure, intervention, and mortality.

Association between obesity and mortality

For our primary analysis, we investigated the association between obesity and AP-related mortality. The results are shown in Fig. 2. After adjustment for confounders, there was no statistically significant association between obesity and mortality in any of the subgroups.

We then went on to investigate the presence of an obesity paradox in subgroups with (predicted) severe disease. The results are shown in Fig. 3. We found that BMI did not have a statistically significant effect on mortality, with the exception of an increased risk for mortality in underweight patients with predicted severe AP (RR: 3.03, 95% CI: 1.01–9.18; $P=0.048$). Therefore, we found no evidence for an obesity paradox, that is, the concept that critically ill patients with overweight or mild obesity have a lower risk of mortality as compared with patients with normal weight or severe obesity. This result was maintained regardless of the subgroup.

Association between obesity and morbidity or invasive intervention

In our secondary analysis, we investigated the association between obesity and AP-related morbidity or invasive intervention (Fig. 4). There was no statistically significant association between obesity and necrotizing pancreatitis or intervention after adjustment for confounders. However, obesity was independently associated with the development of organ failure (RR: 1.38, 95% CI: 1.11–1.73; $P=0.005$) and multiple organ failure (RR: 1.81, 95% CI: 1.35–2.42; $P<0.001$).

Risk of bias assessment

We assessed the risk of bias in all eligible studies (Supplementary Table 4, Supplement 4, Supplemental digital content 1, *http://links.lww.com/EJGH/A365*). The most important reasons for assigning a high risk of bias were as follows: first, six studies [17,19,23,24,30,34] targeted only a subgroup of patients with AP, which limits generalizability to the entire AP population; second, five studies [19,23,24,27,28] incorporated BMI as a continuous parameter instead of using WHO cutoff values for obesity; and third, all studies did not measure, report, or take into account relevant confounders, which increases the chances of biased results.

To assess risk of publication bias, funnel plots were made for all meta-analyses (Supplementary Figs 1–3, Supplement 4, Supplemental digital content 1, *http://links.lww.com/EJGH/A365*). For the analyses of organ failure and mortality, there is a suggestion of missing studies on the lowest end of the plot. Because this region contains studies with high as well as low significance, publication bias seems unlikely. Furthermore, the asymmetry could be explained by the relatively low number of studies and the considerable heterogeneity encountered.

Discussion

This IPDMA from five prospective cohorts with 1302 patients found that obesity is independently associated with the development of organ failure and multiple organ failure. We found no significant relationship between obesity and necrosis, an intervention, or mortality after correction for confounders. Our findings did not confirm the so-called 'obesity paradox'.

In contrast, conventional meta-analyses found that obesity is a prognostic factor for local and systemic complications as well as mortality in AP [35–38]. We believe these differences can be ascribed mainly to the fact that we could adjust for confounders. Our univariable analysis also shows a significant difference in mortality between obese and nonobese patients, which is in line with conventional meta-analyses. However, after adjustment for confounders, we found no significant difference. This argument is strengthened by the observation that studies using multivariable analyses show results similar to ours [19,39,40]. The fact that obesity was first proposed as a

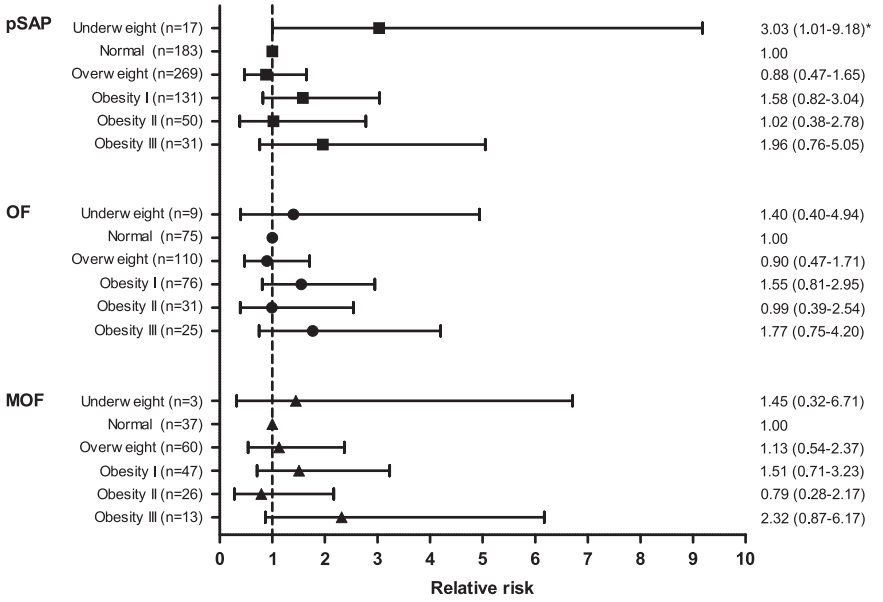

Fig. 3. Forest plot depicting relative risk for mortality per WHO BMI category in subgroups with predicted and severe acute pancreatitis. Values represent relative risk (95% confidence interval), relative to a reference of normal weight. In all subgroup analyses, we adjusted for age, sex, comorbidity, etiology, necrosis, and intervention. In the analysis of pSAP, we also adjusted for organ failure. MOF, multiple organ failure; OF, organ failure; pSAP, predicted severe acute pancreatitis. *$P = 0.048$.

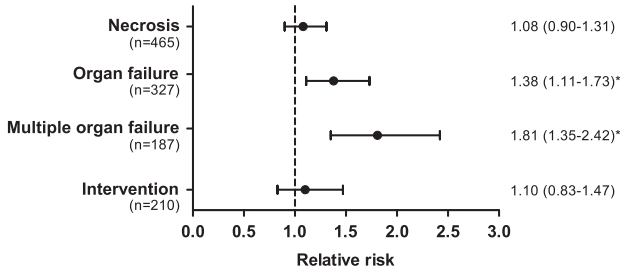

Fig. 4. Forest plot depicting relative risk of obesity for different outcomes in acute pancreatitis. Values represent relative risk (95% confidence interval). In all analyses, we adjusted for age, sex, comorbidity, and etiology. In the analysis of intervention, we also adjusted for organ failure. *$P < 0.05$.

risk factor, but was later discarded in multivariable analyses, is seen in other disease populations as well [41–44].

There are other differences between our study and conventional meta-analyses. First of all, we performed a broad search to limit the chances of missing relevant articles, which explains why we identified 1627 potentially relevant articles compared with a maximum of 286 in the other meta-analyses. Second, we did not have to exclude articles that did not report specific numbers of obese patients, used suboptimal definitions, or did not clearly report used definitions. The reason for this is that we could overcome these issues because we imposed prespecified study definitions and used original source data. In this way, we created a database with uniformly defined parameters, as opposed to standard meta-analysis that can only use original study definitions. For instance, studies included in Chen's meta-analysis [35] defined severe AP in three different ways.

An explanation that obesity is associated with a higher risk for organ failure can be found in the pathophysiology underlying the disease. Regardless of the initiating event, pancreatic acinar cells produce mediators that elicit an inflammatory response. The ensuing cytokine storm can either resolve or progress to a systemic inflammatory response syndrome with accompanying organ failure. Obesity is thought to promote this excessive inflammatory response in several ways. Proposed mechanisms include a chronic inflammatory state, increased inflammatory M1 macrophages, downregulation of anti-inflammatory cytokines, and inhibition of autophagy [11]. Furthermore, obesity is associated with pancreatic steatosis [45]. Pancreatic enzymes released in AP digest adipocytes, causing an outflux of unsaturated fatty acids. In turn, these can act as proinflammatory mediators, and they are implicated in development of systemic inflammation and multiple organ failure [8–10].

We found that obese patients are more likely to develop organ failure. Organ failure is the main determinant for mortality in AP [3,46], which suggests that obesity would be an important risk factor for mortality as well. However, in the subgroup analyses, we did not find an additional risk of mortality in obese patients with organ failure nor was higher BMI a protective factor for mortality. There is an ongoing debate whether critically ill patients (e.g. those with organ failure) with moderate obesity have a lower mortality risk [12,47] or whether this obesity paradox is the result of methodological limitations [48]. Our results suggest the latter.

The main strength of this study is our access to individual patient data. This gave us the opportunity to correct for important confounders and to adopt uniform definitions (e.g. WHO cutoff values for BMI, necrotizing pancreatitis instead of local complications in general). Indeed, our quality assessment showed that these were the main drawbacks of individual cohort studies, which cannot be corrected in conventional meta-analyses. The extensive literature search in four databases ensured comprehensive literature coverage, and by focusing on prospective studies,

we ensured a high data quality. Finally, our large sample size allowed us to perform subgroup analyses in patients with a (predicted) severe disease course.

Several limitations must be acknowledged. First, 13 of the 18 identified cohorts could not be retrieved because they were no longer available. However, for the same reason, it is unlikely that other IPDMAs will include more patients. Our sample size is comparable to conventional meta-analysis on this patient that did not depend on individual patient data [35,36]. Second, despite our large sample size, some of our subgroups were very small, as is evident from the broad confidence intervals in our analysis of the obesity paradox. It results in a higher chance of type I and II errors, and thus in a higher chance of false-positive and false-negative findings. This could explain the significantly higher RR for mortality in underweight patients with predicted severe AP. Third, three included cohorts [31–33] were from single tertiary referral centers and the remaining two cohorts included only patients with predicted severe AP [30] or necrosis [34]. Therefore, the study population of our cohort may be biased toward more severe disease. Although this does not influence our internal validity, it could limit external validity. Fourth, we were unable to investigate the influence of obesity on persistent organ failure owing to unavailability of data. It is mainly the persistent nature of organ failure that is linked to mortality [49]. However, patients with multiple organ failure usually have persistent organ failure [50]. It is therefore likely that obesity is associated with higher rates of persistent organ failure as well. Fifth, BMI is a suboptimal surrogate marker for visceral fat and body composition, whereas android fat distribution has been implicated as a strong risk factor for severe AP [51]. It is likely that a more direct measurement, for instance by computed tomography scan, would result in a more accurate prediction of disease severity [48,52,53]. Finally, despite our adjustment for important confounders, observational studies have an inherent risk of residual confounding that cannot be fully corrected.

Regardless of these limitations, our study shows that BMI has significant predictive properties in AP. It can be regarded as a useful surrogate marker of pancreatic fat that can be easily incorporated in clinical practice. The question is how BMI can be used in clinical practice to predict severity of pancreatitis. Johnson *et al.* [20] addressed this question by adding a score depending on BMI class to the APACHE II: the APACHE-O. Although a higher predictive accuracy was found (82 vs. 77%), the results failed replication [32]. This was mainly owing to the small proportion of patients who were reclassified from predicted mild to predicted severe AP by adding BMI. With this in mind, it could be useful to recalibrate the APACHE-O score.

Conclusion

This individual patient data meta-analysis showed that obesity is independently associated with development of organ failure and multiorgan failure in AP. However, we found no association with development of necrosis, intervention, or AP-related mortality. There was no evidence to support the obesity paradox in AP.

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Authors' contributions: X.S., I.K., K.G., W.K., M.B., and E.v.G. planned and designed the study. I.K. and K.G. performed the literature search. X.S. and I.K. assessed the quality of all eligible studies. X.S., I.K., and K.G. collected the data. X.S. and M.B. performed the statistical analyses. X.S. drafted the manuscript. I.K., K.G., V.S., P.B., G.P., A.D., G.R., W.K., M.B., R.V., H.v.S., J.D., M.B., and E.v.G. interpreted the data and critically reviewed the manuscript. E.v.G. supervised the study. All authors approved the final draft of the manuscript.

Conflicts of interest

There are no conflicts of interest.

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