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Premorbid Obesity and Mortality in Patients With Pancreatic Cancer: A Systematic Review and Meta-analysis

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Abstract

Background & Aims—Obesity is associated with an increased risk for pancreatic cancer, but it is unclear whether it affects mortality. We performed a systematic review and meta-analysis to assess the association between premorbid obesity and mortality from pancreatic cancer.

Methods—We performed a systematic search through January 2015 and identified studies of the association between premorbid obesity (at least 1 year prior to pancreatic cancer diagnosis) and pancreatic cancer–related mortality. We estimated summary adjusted hazard ratio (aHR) with 95% confidence interval (CI), comparing data from obese (body mass index [BMI] 30 kg/m²) and overweight subjects (BMI, 25.0–29.9 kg/m²) with those from individuals with a normal BMI (controls) by using random-effects model.

Results—We identified 13 studies (including 3 studies that pooled multiple cohorts); 5 studies included only patients with pancreatic cancer, whereas 8 studies evaluated pancreatic cancer–related mortality in cancer-free individuals at inception. In the meta-analysis, we observed increase in pancreatic cancer–related mortality among overweight (aHR, 1.06; 95% CI, 1.02–1.11; $I^2 = 0$) and obese individuals (aHR, 1.31; 95% CI, 1.20–1.42; $I^2 = 43\%$), compared with controls; the association remained when we analyzed data from only subjects with pancreatic cancer. Each 1 kg/m² increase in BMI was associated with 10% increase in mortality (aHR, 1.10; 95% CI, 1.05–1.15) with minimal heterogeneity ($I^2 = 0$). In the subgroup analysis, obesity was associated with increased mortality in Western populations (11 studies; aHR, 1.32; 95% CI, 1.22–1.42) but not in Asia-Pacific populations (2 studies; aHR, 0.98; 95% CI, 0.76–1.27).

Conclusions—In a systematic review and meta-analysis, we associated increasing level of obesity with increased mortality in patients with pancreatic cancer in Western but not Asia-Pacific

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populations. Strategies to reduce obesity-induced metabolic abnormalities might be developed to treat patients with pancreatic cancer.

Keywords

Survival; Adiposity; Pancreas; Malignancy

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the United States.¹ It carries a dismal prognosis with 5-year survival of 5%, in part because of late stage at time of diagnosis; however, even for surgically resectable pancreatic cancer, 5-year survival is only 10%–20%. Obesity, both overall and visceral, has been implicated as a risk factor for development of pancreatic cancer. In a systematic review of 23 prospective cohort studies, Aune et al² observed a non-linear association between body mass index (BMI) and pancreatic cancer risk, with a 10% increase for each 5-unit change in BMI after adjustment for confounding variables. This may be related to induction of chronic inflammatory state in obese individuals with increased production of proinflammatory cytokines (eg, interleukin-6) and adipocytokines (eg, adiponectin, leptin), hyperinsulinemia, insulin resistance, and elevated levels of insulin-like growth factors.^{3–7}

Recent evidence suggests that premorbid obesity may also be associated with increased mortality in patients with cancer, including colorectal,⁸ breast,⁹ prostate cancer,¹⁰ and leukemia.¹¹ Several observational studies have evaluated the association between obesity and mortality in patients with pancreatic cancer, with variable results. In a case-control study, Li et al¹² observed that obesity in adulthood was associated with reduced overall survival of pancreatic cancer, independent of disease stage and tumor resection status. In contrast, in a pooled analysis of 16 cohorts from Asian countries, Lin et al¹³ did not observe a significant association between increased BMI and pancreatic cancer–related mortality.

Hence, to better understand this association, we performed a systematic review with metaanalysis of observational studies that investigated the association between premorbid BMI and pancreatic cancer–related mortality.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and was conducted following a priori established protocol.¹⁴

Study Selection

We included observational studies that reported statistical measures of association (hazard ratio [HR], incidence rate ratio, or relative risk, with 95% confidence intervals [CIs]) between premorbid (ie, at least 1 year before diagnosis of pancreatic cancer) measures of obesity (BMI) and mortality (all-cause or cancer-related) in adults (relative to patients with normal BMI). Two types of patient populations were considered, studies performed in patients with established pancreatic cancer and those performed in cancer-free individuals at inception and followed for development of pancreatic cancer–related mortality. Inclusion was otherwise not restricted by study size, language, or publication type. When there were

multiple publications from the same cohort, only data from the most recent comprehensive report were included.

We excluded cross-sectional studies, studies only with data on BMI changes at or after diagnosis of pancreatic cancer (confounding by underlying disease), and studies that did not provide a measure of association (precluded statistical analysis).

Data Sources and Search Strategy

First, we conducted a systematic literature search of PubMed (MEDLINE), Embase, Web of Science, Cochrane Library, and Google Scholar from inception to January 31, 2015 by using a combination of keywords or medical subject headings for cancer, obesity, mortality, and prognosis. All identified studies were combined together in a single reference manager file (EndNote; Thomson Reuters, Stamford, CT), duplicates were discarded, and the title and abstracts were reviewed by 2 authors independently to exclude studies that did not report the association between obesity and mortality, which was based on pre-specified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information. Disagreements were harmonized by consensus, in conjunction with the principal investigator. Second, the reference lists from included original articles and recent reviews and meta-analyses on obesity and cancer-related mortality were hand searched to identify any additional studies. Third, conference proceedings of major gastroenterology and oncology conferences (Digestive Diseases Week, Gastrointestinal Cancers Symposium, annual meetings of the American Society of Clinical Oncology and European Society of Medical Oncology) from 2010 to 2014 were reviewed for relevant abstracts. Figure 1 shows the schematic diagram of study selection.

Data Abstraction and Quality Assessment

Two reviewers independently abstracted data on the study-related and patient-related characteristics onto a standardized form, as detailed in the Supplementary Materials.

The risk of bias in these prognostic individual studies was assessed by 2 authors independently by using the Quality In Prognosis Studies tool, which evaluates validity and bias in studies of prognostic factors across 6 domains: participation, attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting.¹⁵

Outcomes Assessed

Our primary outcome was the association between obesity and pancreatic cancer–related mortality. This was assessed by using 3 approaches. First, we compared mortality risk with the highest reported BMI category in a study with the reference category and summarized these estimates. However, there were minor differences in reported categories of obesity in individual studies; hence, for standardized interpretation, we calculated mortality risk in obese patients (BMI 30 kg/m²) and overweight patients (BMI 25.0–29.9 kg/m²), compared with normal BMI patients. For this analysis, we pooled effects for all BMI categories of BMI 30 kg/m² into a single summary estimate for obese patients and likewise pooled effects of all BMI categories for BMI 25.0–29.9 kg/m² into a single summary estimate for

overweight patients. This analysis also helped assess for the presence of a dose-response relationship (deemed to be present if the summary estimates for overweight and obese patients had an incremental association, compared with referent normal BMI). Finally, we estimated change in mortality per unit BMI by using linear trend meta-analytic statistical methodology (Supplementary Materials).¹⁶

Subgroup and Sensitivity Analyses

A priori hypotheses to assess robustness of the analysis and explain potential heterogeneity in the direction and magnitude of effect among different observational studies were assessed by using subgroup analyses. These subgroups were based on location (Western vs Asia-Pacific), design (pooled cohorts vs individual studies), and study setting (hospital-based vs population-based); during the review process, additional subgroup analyses were proposed on the basis of method of exposure ascertainment (self-reported vs measured weight and height) and time period over which study was conducted (defined on the basis of period of cohort recruitment: before 1980s vs 1980s–2000 vs beyond 2000 vs a category from 1980s to current). Because it is possible that the association between obesity and mortality in pancreatic cancer may be confounded by diabetes and stage, treatment response (especially surgical resection), and performance status, we performed subgroup analysis comparing studies that did and did not account for these variables.

We also performed a sensitivity analysis restricted only to studies reporting the association between obesity and mortality in a cohort of patients with established pancreatic cancer (excluding studies that included cancer-free individuals at inception). In addition, we performed sensitivity analysis by excluding one study at a time to assess whether a particular study significantly influenced the summary estimate and/or heterogeneity.

Statistical Analysis

We used random-effects model described by DerSimonian and Laird to calculate summary HR and 95% CI.¹⁷ Maximally adjusted HR (aHR), when reported in studies, was used for analysis to account for confounding variables. To estimate what proportion of total variation across studies was due to heterogeneity rather than chance, inconsistency index (I² statistic) was calculated; values of <30%, 30%–59%, 60%–75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.¹⁸ Subgroup analyses was performed by stratifying original estimates according to study characteristics (as described above). In this analysis, a *P* value < .10 for differences between subgroups was considered statistically significant.

We assessed for publication bias quantitatively by using the Egger regression test (publication bias considered present if $P_{...10}$) and qualitatively by visual inspection of funnel plots.^{19,20} All *P* values were 2-tailed. All calculations and graphs were performed by using Comprehensive Meta-Analysis (CMA) version 2 (Biostat, Englewood, NJ).

Results

Of 795 unique studies identified by using our search strategy, we reviewed full texts of 61 studies, and 13 studies fulfilled our inclusion criteria and were included in the meta-analysis

(10 independent cohorts and 3 studies reporting pooled data from multiple cohorts).^{12,13,21–31} There were no randomized controlled trials evaluating the association between obesity and mortality in patients with pancreatic cancer. Five studies^{32–36} from overlapping cohorts, 1 study that reported alternative measures of obesity³⁷ (intra-abdominal fat via preoperative computed tomography imaging), and 1 study with insufficient data for estimation of statistical association were excluded.³⁸

Characteristics and Quality of Included Studies

Thirteen studies were included that reported on 3,434,737 participants, of whom 11,626 patients with pancreatic cancer died.^{12,13,21–31} For the purposes of data abstraction, all studies were cohort by design (with subjects being followed over time after exposure [obesity], for development of outcome [mortality]), although some studies inherently were reported as case-control studies.^{12,24,25} Although 5 studies^{12,21,23-25} included a cohort of patients with established pancreatic cancer and reported the association between premorbid obesity and all-cause mortality, 8 studies were large cohorts of cancer-free participants at inception and followed them for development of pancreatic cancer-related mortality through record linkage with national death indices. The characteristics of the included studies are shown in Table 1. Eleven studies were based in North America or Europe, ^{12,21–25,27–31} including 1 pooled study of 7 cohorts of black participants.²⁷ Two studies were conducted in the Asia-Pacific region, both pooled analysis of multiple individual cohorts (30 cohorts from the Asia-Pacific Cohort Studies Collaboration²⁶ and 16 cohorts from the Asia Cohort Consortium¹³). Study size ranged from 475 patients with pancreatic cancer to 1,222,630 participants (of which 8 studies had an unclear proportion of pancreatic cancer), and total number of deaths in patients with pancreatic cancer ranged from 139 to 3558. All of the included studies had an average follow-up of at least 3 years. BMI was assessed as primary measure of obesity in all studies, with premorbid evaluation performed at least 1 year before pancreatic cancer diagnosis. The association between central adiposity (using waist circumference) and mortality was assessed in only 1 study.²⁶ The baseline characteristics of the participants in individual studies are reported in Table 2. Patients with obesity expectedly had higher rates of diabetes in included studies.

Supplementary Table 1 depicts the methodological quality of all studies. The overall risk of bias was low to moderate. Ten studies relied on self-reported weight (4 studies using self-reported "usual" body weight and height and 6 studies using self-reported "current" body weight and height at time of enrollment in cohort), and 2 studies relied on weight and height measured by research staff at enrollment; 1 study relied partly on self-reported values and partly on measured values. Mortality in most studies was assessed through record linkage with the national death index and/or other sources to obtain death certificates, and some studies complemented this with mailed inquiries to the family. In the Asia-Pacific Cohort Studies Collection, BMI was measured at enrollment; however, the study had an acknowledged limitation of non-standardization of data collection. Most studies adjusted for the following confounders: age (12 of 13), sex (8 of 13), race (4 of 13), diabetes mellitus (9 of 13), smoking (11 of 13), and stage (5 of 13).

Body Mass Index and All-cause Mortality in Patients With Pancreatic Cancer

Of 13 studies, 9 studies observed higher mortality in patients with higher premorbid BMI, and this was statistically significant in 5 studies. On meta-analysis, when comparing patients in the highest category of BMI with the lowest category, we observed that patients with high BMI had 33% higher mortality (aHR, 1.33; 95% CI, 1.19–1.49), with moderate heterogeneity ($I^2 = 35\%$) (Figure 2A).

Dose-response Relationship

On comparing 9 studies that allowed estimation of a summary estimate for obese and overweight patients, we observed an incremental and significant increase in mortality in both overweight patients (aHR, 1.06; 95% CI, 1.02–1.11; $I^2 = 0\%$) and obese patients with pancreatic cancer (aHR, 1.31; 95% CI, 1.20–1.42; $I^2 = 43\%$), as compared with normal BMI pancreatic cancer patients (Figure 2B); 4 studies were excluded from this analysis because they provided data only as tertiles, quartiles, or nonconventional BMI categories (without conventional World Health Organization–defined categories for overweight and obesity). There was significant difference between summary estimates for overweight and obese patients, suggesting a dose-response relationship (*P* value for trend, < .001).

On inputing mortality risk per unit BMI, we again observed a dose-response relationship, with each unit increase in BMI above normal associated with a 10% increase in mortality (aHR, 1.10, 95% CI, 1.05–1.15) with minimal heterogeneity (Figure 2C).

Subgroup Analysis

To assess robustness of the association between BMI and mortality in patients with pancreatic cancer, we performed several pre-planned subgroup analyses. For these analyses, we used World Health Organization-defined categories for overweight and obesity for studies where such data were available; when these data were not available, available BMI categories were transformed into 3 categories, and lowest BMI category was used as reference, middle category was regarded as overweight, and highest category was regarded as obese. We observed that incremental and significant increase in mortality in both overweight and obese patients with pancreatic cancer was seen only in Western studies (11 studies; overweight vs normal BMI: aHR, 1.07; 95% CI, 1.02-1.12; obese vs normal BMI: aHR, 1.32; 95% CI, 1.22–1.42) but not in studies performed in the Asia-Pacific region (2 studies; overweight vs normal BMI: aHR, 0.98; 95% CI, 0.87–1.11; obese vs normal BMI: aHR, 0.98; 95% CI, 0.76–1.27) (Table 3). The association between obesity and mortality was stronger in individual studies as compared with pooled cohorts, although 2 out of 3 pooled cohorts were performed in Asia-Pacific regions. Both population-based and hospitalbased subgroups reported increase in mortality to a similar degree. There was no differences in summary estimates that were based on subgroups defined by method of exposure ascertainment and time period in which the study was conducted (ie, the association between obesity and mortality was stable over time).

To evaluate for potential confounding by presence of diabetes and differences in treatment and/or performance status between obese and normal BMI patients, we performed stratified analysis of studies that did and did not adjust for these variables in their analysis. Higher

mortality in overweight and obese patients persisted after adjusting for diabetes, suggesting a diabetes independent effect (Table 3). Similarly, no difference was observed in the association between obesity and mortality outcome in studies that did or did not adjust for pancreatic cancer stage, treatment, or performance status. Because obesity increases risk of surgical mortality in patients with pancreatic cancer, we analyzed the association between obesity and mortality in patients who underwent resection and those who did not. Obese patients (vs normal BMI) had increased mortality in both patients who underwent surgical resection (2 studies; aHR, 2.29; 95% CI, 1.13–4.67) and those who did not undergo resection of primary tumor (2 studies; aHR, 1.53; 95% CI, 1.17–2.01), with comparable summary estimates (*P* value for difference between groups, .30).^{12,24}

Sensitivity Analysis and Publication Bias

The results were stable on restricting analysis to studies performed in patients with established pancreatic cancer^{12,21,23–25} (overweight vs normal BMI: aHR, 1.07; 95% CI, 0.98–1.16; $I^2 = 0$; obese vs normal BMI: aHR, 1.35; 95% CI, 1.21–1.51; $I^2 = 21\%$).

To assess whether any one study had a dominant effect on the meta-analytic HR, we excluded each study at a time and analyzed its effect on the main summary estimate. On this analysis, the overall summary estimate for the comparison between obesity and mortality in pancreatic cancer patients ranged from 1.26 to 1.32, with no single study significantly affecting summary estimate. On the basis of the visual inspection of the funnel plot (Supplementary Figure 1) as well as on quantitative measurement by using the Egger regression test, there was no evidence of publication bias (P = .67).

Discussion

Although obesity has been associated with increased risk of developing pancreatic cancer, in this systematic review we made several key observations on the association between premorbid obesity and pancreatic cancer-related mortality. First, we observed that obesity (present before diagnosis of pancreatic cancer) is associated with increased pancreatic cancer-related mortality both in patients with established pancreatic cancer and in cancerfree individuals at baseline in a dose-dependent and consistent manner. Both overweight (BMI 25.0–29.9 kg/m²) and obese patients (BMI 30 kg/m²) had 6% and 31% higher mortality, respectively, as compared with patients with normal BMI, without significant heterogeneity. Second, this association between obesity and increased mortality is observed only in the Western regions but not in patients with pancreatic cancer diagnosed in the Asia-Pacific regions. Third, the association is independent of diabetes and pancreatic cancer stage and treatment and is observed regardless of whether patients underwent surgical resection. Because of the very poor prognosis of patients with pancreatic cancer even with aggressive intervention, this observation mandates further research into the role of obesity-associated proinflammatory state in the progression of pancreatic cancer and merits evaluation of obesity as an effect modifier in treatment trials of pancreatic cancer.

Several observational and preclinical interventional studies have demonstrated an association between obesity and pancreatic cancer. The underlying mechanism of how obesity drives pancreatic tumorigenesis is related to complex interplay between obesity/high-fat diet,

associated altered metabolism including insulin resistance, chronic inflammation, and oncogenic *KRAS* signaling. Metabolically active visceral fat exerts systemic proinflammatory effects that may promote, independently or synergistically, pancreatic carcinogenesis.^{39–42} Recent evidence suggests that obesity is associated with intrapancreatic fatty infiltration, which is associated with pancreatic intraepithelial neoplasia, a precursor of pancreatic cancer, thus suggesting a paracrine effect of these mediators. Obesity-induced insulin resistance and peripheral hyperinsulinemia have also been associated with increased risk of developing pancreatic cancer. Insulin-like growth factor-1 and insulin-like growth factor-1 mediated signalling promotes proliferation, invasion, and expression of angiogenic factors and decreases apoptosis in these cell lines. Hence, obesity may induce a more aggressive phenotype of pancreatic cancer.

We observed that obesity, as measured by BMI, was associated with increased mortality only in the Western population but not in the Asia-Pacific regions. This may be related to underlying differences in the pathophysiology and progression of pancreatic cancer in these different populations or may be a reflection of the failure of overall obesity to capture underlying metabolic syndrome. It is well-known that Asians, in particular South Asians, may have higher rates of metabolic syndrome even with apparently normal BMI; hence, Asians may be experiencing similar effects of adiposity-associated chronic inflammation and insulin resistance at seemingly normal levels of BMI. In their pooled analysis of the Asia-Pacific Cohort Studies Collaboration, Ansary-Moghaddam et al²⁶ did not observe any significant association between premorbid BMI and pancreatic cancer mortality but observed that each 2-cm increase in waist circumference was associated with 8% increase in mortality (aHR, 1.08; 95% CI, 1.02–1.14). Additional studies evaluating ethnicity as an effect modifier of obesity in pancreatic cancer mortality are warranted.

Obesity also creates unique challenges in delivering appropriate therapy that may lead to worse survival outcomes for obese patients. It can limit the extent of a cancer operation and increase surgical morbidity and mortality. Obesity also complicates the planning or delivery of radiation therapy and is associated with inadequate dosing of chemotherapeutic agents. Despite guidelines recommending dosing that is based on actual body weight, practice pattern studies demonstrate that up to 40% of obese patients receive limited chemotherapy doses that are not based on actual body weight because of concerns about toxicity or overdosing.⁴³ Hence, one of the factors linking obesity and worse survival could be inadequate chemotherapy dosing in obese patients.

Strengths and Limitations

The strengths of this systematic review include (1) comprehensive and systematic literature search with well-defined inclusion criteria, carefully excluding redundant studies and studies in which BMI was assessed at time of pancreatic cancer diagnosis; (2) rigorous evaluation of study quality by using a validated tool for prognostic studies; (3) subgroup and sensitivity analyses to evaluate the stability of findings, regardless of presence or absence of heterogeneity; and (4) rigorous assessment of a dose-response relationship by using 2 approaches, adding biological credibility to findings.

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There are several limitations in our study. First, the meta-analysis included only observational studies with inherent biases and suboptimal control of confounders. Second, not all studies were restricted to patients with established pancreatic cancer; several studies were large cohort studies that enrolled cancer-free individuals at baseline and followed them for development of several outcomes including pancreatic cancer-related mortality; however, our results were stable on restricting analysis to the former group of studies. Third, all studies did not consistently account for relevant covariates, including pancreatic cancer stage and treatment, and despite adjusting for several covariates, it is not possible to eliminate the potential of residual confounding, especially with regard to factors that go into determining treatment choice for patients with medically complicated obesity. However, subgroup analyses that are based on adjustment for diabetes and pancreatic cancer stage and treatment did not suggest significant impact of these factors. Fourth, we did not specifically analyze all-cause and cancer-related mortality separately because of paucity of such data in the included studies. However, competing risk for mortality is unlikely to play a significant part in pancreatic cancer because of high mortality associated with this disease. The included studies had inherent limitations, including variability in method and timing of exposure ascertainment and outcome assessment.

In conclusion, we observed that premorbid obesity adversely influences pancreatic cancerrelated mortality in a dose-dependent manner, independent of presence or absence of diabetes or type of treatment. This increased risk is observed primarily in the Western population but not in Asia-Pacific regions. Premorbid obesity and its underlying metabolic alterations and associated chronic inflammation may be a potential therapeutic target in improving mortality in this highly lethal cancer. In current treatment schemes, premorbid obesity should be considered as a marker of poor prognosis, with a focus on more aggressive intervention, and may be used as a stratification variable in interventional studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

aHR	adjusted hazard ratio
BMI	body mass index
CI	confidence interval
HR	hazard ratio



Figure 1.

Flow sheet summarizing study identification and selection. OR, short of odds ratio; PaC, pancreatic cancer; RR, relative risk.

Study or Subgroup Log [hazard ratio] SE Weight N. random, 95% CI V. random, 95% CI V				Hazard ratio	Hazard ratio
Araby-Magadami 2000 0 0 0 160 0 200 0 0 0 160 0 1701 18 0 0 0 0 160 0 1701 18 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Study or Subgroup Log [ha	zard ratio] SI	E Weight	IV, random, 95% C	IV, random, 95% CI
Lang 2001 Lang 2001 Lang 2002 Lang 2002	Insary-Moghaddam 2006	0 0.189	3 6.7%	1.00 [0.69, 1.45]	
Here 2014 2020 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	seny 2009	0.1655 0.204	7 6.0%	1.18 [0.79, 1.76]	
Attack 2030 0.3886 0.000 0.388 0.000 0.388 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000	Bethea 2014	-0.0408 0.223	1 5.2%	0.96 [0.62, 1.49]	
Additional space of the second space of the	Calle 2003	0.3988 0.208	6 5.8%	1.49 [0.99, 2.24]	
Dardy 2012 0.2690 0.1480 7.0% 1.28 0.19 1.88 1.28 0.19 1.88 0.19 1.88 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19	Gapetur 2000	0.6152 0.280	3 3.6%	1.85 [1.07, 3.20]	
$\frac{1}{2} \frac{1}{2} \frac{1}$	Uong 2012	0.2469 0.174	1 7.6%	1.28 [0.91, 1.80]	
$\frac{142001}{122} = 0000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 100000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 10000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 100000 + 10$	Lee 2003	-0.0101 0.255	0 4.2%	0.99 [0.60, 1.63]	
La 2013 Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Development Developm	Li 2009	0.6206 0.163	5 8.3%	1.86 [1.35, 2.56]	
Advances 2010 0 0 277 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Jin 2013	-0.0408 0.183	5 7.0%	0.96 [0.67, 1.38]	
Adding July (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)	McWilliams 2010	0.47 0.121	9 11.7%	1.60 [1.26, 2.03]	
Carters 2007 0.278 0.029 18.78 1.22 [15, 1.30] Theory (SK) (C) 100.00 1.33 [15, 1.40] 0.00 0.00 1.33 [15, 1.40] Theory (SK) (C) 100.00 1.33 [15, 1.40] 0.00 0.00 1.33 [15, 1.40] Theory (SK) (C) 100.00 1.33 [15, 1.40] 0.00 0.00 1.33 [15, 1.40] Study or Subgroup Log (hazard ratio) SE Weight M. Xrandom, 95%; CI Hazard ratio Hazard ratio C12 (Derevestor involution in the state of the stat	Olson 2010	0.3577 0.187	0 0.0%	1.43 [0.99, 2.07]	
Take (16% C) the interconnexity: Take * 0.01; Chi * 18.3.4, df = 12 (P = 11); P = 30% the for overall effect 2 + 4.3.6 (P = 0.0001) 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.3 3.5 3.5 3.5 3.5 3.5 3.5 3.5 3.5 3.5 3.5 3.5 3.5 3.5	Reeves 2007 Yuan 2013	0.4253 0.163	9 18.7% 7 8.2%	1.32 [1.16, 1.50] 1.53 [1.11, 2.11]	<u> </u>
Heterogenety: Tar ² = 0.01; Ch ² + 18.34, df = 12 (P + 11); P = 30% Test for overall effect 2 + 3.68 (P + .0001)	fotal (95% CI)		100.0%	1.33 [1.19, 1.49]	•
Burdy of Subgroup Log [hazard ratio] SE Weigh H zard ratio W, random 55% CI Hazard ratio W, random 55% CI 121 Octoverspit is normal BM 0.005 0.0756 0.3% 0.0710 0.3% 0.0710 0.4% of the formation 55% CI 121 Octoverspit is normal BM 0.005 0.0716 0.3% 0.0710 0.055 0.117	feterogeneity: Tau ^a = 0.01; Chi ^a = 18.3 fest for overall effect: $Z = 4.98$ ($P < .00$	34, df = 12 (P = .11); 1 2001)	*= 35%	02	0.5 1 2 Decreased motality
Study or Subgroup Log hazard ratio SE Weight M: Aradom, 55%, C1 Hazard ratio M: random, 55%, C1 221 Occurrence Date 2001 0.0055 0.0756 0.3% 0.9715 0.3% 0.9715 221 Occurrence Date 2001 0.0055 0.0756 0.3% 0.9715 0.3% 0.9715 221 Occurrence Date 2001 0.0055 0.0756 0.3% 0.9715 0.3% 0.9715 2005 0.0221 0.1485 3.4% 1.2015 1.00 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 1.01 <td< td=""><td>2</td><td></td><td></td><td></td><td></td></td<>	2				
Study or Subgroup Log [hazard ratio] SE Weight (V, random, 95% CI V, random, 95% CI	5			Hazard ratio	Hazard ratio
Interest 2014 -0.005 0.013 0.0216 0.013 0.0216 0.013 0.0216 0.013 0.0216 0.013 0.0216 0.013 0.0216 0.013 0.0216 0.013 0.0216 0.013 0.0216 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.016 0.01	Study or Subgroup Log [ha	zard ratio] SI	E Weight	IV, random, 95% C	IV, random, 95% CI
The solo 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 0013 <td>lethes 2014</td> <td>0.0305 0.020</td> <td>6 6.94</td> <td>0 97 10 83 1 130</td> <td></td>	lethes 2014	0.0305 0.020	6 6.94	0 97 10 83 1 130	
Story Strip Story St	ale 2003	0 1133 0.037	8 8.6%	1 12 11 04 1 211	
10001 0011 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.00000 0.0000 0.0000	2000 2012	0.0392 0.115	1 4.6%	1 04 10 83 1 301	
Answer Original Original <thoriginal< th=""> Original <</thoriginal<>	12000	0.2311 0 140	5 3.4%	1 26 10 94 1 691	
Answer Sound Dial O Order Sound O Order Sound <tho order="" sound<="" th=""> O Order Sound</tho>	in 2013	-0.0305 0.067	4 7.0%	0.97 10.85 1.171	
Discussion Original Operation Operation Num 2010 Operation Operation Operation Operation Num 2017 Operation Operation Operation Operation Operation Num 2013 Operation Operation Operation Operation Operation Operation Num 2013 Operation Operat	ALL AND AND ADDA	0.0198 0.065	6 6.9%	1 02 10 89 1 171	
Additional State (1997) 00000 00000 00000 00000 00000 00000 0000	Acvinants 2010	0.0392 0.123	6 2.8%	1 04 10 74 1 451	
Name 2013/ Lobols (05K C) teterography: Tar ≠ 0.00; Chr ≠ 6.96; df ≠ 6 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 6.96; df ≠ 6 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 6.96; df ≠ 6 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 6.96; df ≠ 6 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 6.96; df ≠ 6 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 4.96; df = 12 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 4.96; df = 12 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 4.96; df = 12 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 4.96; df = 12 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 4.96; df = 12 (P = 54); P = 0N; teterography: Tar ≠ 0.00; Chr ≠ 4.96; df = 12 (P = 06); P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 06]; P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 06]; P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 06]; P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 06]; P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 06]; P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 06]; P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 06]; P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 06]; P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 07; teterography: Tar ≠ 0.00; Chr ≠ 4.40; df = 8 (P = 06); P = 06; P	Alson 2010	0.0488 0.051	1 7.9%	1.05 (0.95, 1.16)	
Lan 2013 Lan 2013 Standbord (Pilon, Tar.) Standbord (Pilon, Tar.)	teeves 2007	0.0862 0.064	8 7.1%	1 09 10 96 1 243	T_
Name (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)	Juan 2013		54.7%	1.06 [1.02, 1.11]	-
The for ownail effect 2 + 2.77 (/P + 0.06) 2.22 Observe xn. normal BMA Behna 2014 0 1133 0.0786 6.4% 1.12 (0.96, 1.31) Calle 2003 0.3267 0.057 7.6% 1.42 (1.27, 1.58) UL 2013 0.0046 0.171 2.2% 1.28 (0.91, 1.56) UL 2013 0.0046 0.1735 2.6% 1.42 (1.27, 1.58) UL 2013 0.0046 0.1735 2.6% 1.42 (1.27, 1.58) UL 2013 0.0046 0.1355 2.6% 0.98 (0.67, 1.38) UL 2013 0.0276 0.050 5.1% 1.32 (1.10, 1.58) Studeut (65/C C) Study or Subgroup Log [hazard ratio] Study or Subgroup Log (hazard ratio) Study (hazard ratio) St	Subtotal (90% CI) Heterogeneity: Tau ^a = 0.00; Chi ^a = 6.9	9. df = 8 (P = .54); P =	0%		r
2.2.2 Observes no. normal BMI Bethes 2014 0.3020 0.3020 0.057 7.66 4.44 112 [0.96, 1.31] Calle 2003 0.3020 0.057 7.66 1.42 [1.27, 1.59] 0.420 0.0500 0.057 7.66 1.42 [1.27, 1.59] 0.420 0.0500 0.050 7.76 1.42 [1.27, 1.59] 0.420 0.0500 0.050 0.050 3.06 1.86 [1.53, 2.86] 0.420 0.0500 0.057 0.050 7.76 1.27 [1.54, 1.47] 0.420 0.0500 0.057 0.050 7.76 1.32 [1.10, 1.58] 0.420 0.0500 0.0270 0.050 5.66 1.32 [1.10, 1.58] 0.420 0.0500 0.0270 0.0500 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26 0.050 1.26	Test for overall effect: Z = 2.77 (P = .00	96)			
Befma 2014 0.1133 0.0786 6.44, 12 [0.86, 13] Befma 2010 0.0135 0.0786 6.44, 12 [0.86, 13] L020 0.0000 0.0135 3.04, 18[127, 158] L020 0.0000 0.0135 3.04, 18[125, 2.86] L020 0.0000 0.035 2.04, 0.96 [0.7, 18] McMilana 2010 0.0276 0.059 7.14, 12[1.4, 14] Decreased motality Reverse 207 0.2776 0.059 7.14, 132[1.40, 180] Budusta (BCK-CI) Reverse 207 0.2776 0.059 7.14, 132[1.40, 180] Budusta (BCK-CI) Reverse 207 0.2776 0.059 7.14, 132[1.40, 180] Budusta (BCK-CI) Reverse 207 0.2776 0.059 7.14, 132[1.10, 180] Budusta (BCK-CI) Reverse 207 0.1614 0.062 6.45, 131[1.20, 142] Percented motality Reverse 2014 0.0714 0.0756 0.1638 1.971 1.071, 142] Reverse 2014 0.0714 0.0767 0.1630 1.971 1.071, 142] Reverse 2015 0.00170 0.0023 0.1636 1.971 1.071, 142] Reverse 2016 0.0714 0.0775 0.170 1.000, 132] Reverse 2016 0.0714 0.0775 0.170 1.000, 132] Reverse 2017 0.00171 0.0757 0.1000 1.10[0.5, 113] Reverse 2017 0.00171 0.0757 0.421 1.000, 132] Reverse 2010 0.0714 0.0775 0.421 1.000, 132] Reverse 2010 0.0714 0.0756 0.055 0.110 1.000, 132] Reverse 2010 0.0714 0.0756 0.055 0.110 1.000, 132] Reverse 2010 0.0714 0.0756 0.054 0.0551 0.000, 138] Reverse 2010 0.0714 0.0756 0.054 0.0551 0.000, 138] Reverse 2010 0.0013 0.0656 0.054 0.054, 120, 1000, 138] Reverse 2000, Chi# 4.455, df = 12 (P= .050	2.2.2 Obese vs. normal BMI				
Lale 2003 0 3000 0.009 7 0% 142[127.158] 0.000 0.01201 0.0206 0.173 2.26% 128[10.168] 0.000 0.0200 0.020 0.000 7.7% 127[14.141] 0.000 0.010 0.0377 0.0176 2.0% 1.43[0.09.207] 0.000 0.0377 0.0176 2.0% 1.43[0.09.207] 0.000 0.02776 0.003 5 0% 1.32[1.10.158] 0.000 0.02776 0.003 5 0% 1.32[1.10.158] 0.000 0.0276 0.003 5 0% 1.32[1.10.158] 0.000 0.017 0.0008 4.5% 1.31[1.20.142] 0.000 0.0171 0.0008 4.5% 1.10[10.7, 148] 0.000 0.0174 0.0175 1.22] 0.000 0.0174 0.0175 1.22] 0.000 0.0174 0.0175 1.22] 0.000 0.0174 0.0175 1.52] 0.000 0.0174 0.0175 1.52] 0.000 0.0161 0.0176 1.23] 0.000 0.0161 0.0176 1.23] 0.000 0.0161 0.0176 1.23[0.000 0.100 0.0174 0.0175 1.52] 0.000 0.0161 0.0176 0.0181 0.0176 1.23] 0.000 0.0161 0.0176 0.000 1.207 0.000 0.100 0.000 0.0174 0.0005 1.207 0.000 0.100 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.0000 0.000 0.000 0.000 0.0000 0.000 0.0000 0.0000 0	Bethea 2014	0.1133 0.078	6 6.4%	1.12 [0.96, 1.31]	
Sing 2012 0 2469 01/41 2 2/8 1 28 (0.9) 18.0 12000 0.0200 0.053 2 0/6 06(0.9) 18.0 an 2013 0.0000 0.053 2 0/6 06(0.7) 1.38 Sing 2010 0.02776 0.059 7 1/8 1.32 (1.6) 1.58 Sing 2010 0.01 Chr = 4.0 0.01 H = 6/P - 08] (P = 43% Test for overall effect 2 = 6.44 (P < 0.0001) Sing 2010 0.01 Chr = 4.0 0.000 1.527 Sing 2006 0.01 H = 6/P - 08] (P = 4.3% Test for overall effect 2 = 6.44 (P < 0.0001) Sing 2012 0.01 Chr = 4.00 Chr = 6.000 1.527 Sing 2006 0.01 H = 1.57 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.37 1.02 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.38 1.12 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.38 1.12 (D.7) 1.47 Sing 2006 0.01 H = 0.197 1.38 1.12 (D.7) 1.47 Sing 2001 0.01 H = 0.197 1.38 1.12 (D.7) 1.47 Sing 2001 0.01 H = 0.197 1.48 1.12 (D.7) 1.47 Sing 2001 0.01 H = 0.197 1.48 1.12 (D.7) 1.47 Sing 2001 0.01 H = 0.197 1.48 1.12 (D.7) 1.47 Sing 2013 0.01 H = 0.197 1.48 1.12 (D.7) 1.47 Sing 2013 0.01 H = 0.197 1.48 1.12 (D.7) 1.47 Sing 2013 0.01 H = 0.000 Chr = 0.198 1.10 H = 0.197 1.44 1.12 (D.7) 1.47 Sing 2013 0.01 H = 0.000 Chr = 0.000 1.10 1.10 (D.1) 1.11 Sing 2013 0.01 H = 0.000 Chr = 0.000 1.10 1.10 (D.1) 1.11 (D.1, 1.18) Sing 2013 0.00 Chr = 4.450, dr = 12 (P = 0.00 H = 0.000 H	Calle 2003	0.3507 0.05	7 7.6%	1.42 [1.27, 1.59]	
Li 2003 0.6806 0.4835 3.0° 1.68[15, 2.58] Microllina 2010 0.270 0.665 2.56 1.48[16, 2.58] Microllina 2010 0.2776 0.665 7.18 1.40[16, 9, 207] Max 2013 0.2776 0.665 7.18 1.40[16, 9, 207] Max 2013 0.2776 0.665 4.56 1.32[1.10, 1.58] Microllina 2010 0.2776 0.683 5.66 1.32[1.10, 1.58] Microllina 2010 0.2776 0.68] P = 43% Hazard ratio V random, 55% CI Hazard ratio V random, 55% CI Hazard ratio Microllina 2010 0.0114 0.162 1.58] Microllina 2010 0.0114 0.162 1.58] Microllina 2010 0.0114 0.162 1.58] Microllina 2010 0.0114 0.162 1.58] Jacobi Microllina 2010 0.0116 0.058 1.021 0.158 Jacobi Microllina 2010 0.0116 0.058 1.021 0.051 1.59] Jacobi Microllina 2010 0.0116 0.0576 8.2% 1.18[1.02, 1.58] Jacobi Microllina 2010 0.01016 0.0576 8.2% 1.18[1.02, 1.58] Jacobi Microllina 2	Gong 2012	0.2469 0.174	1 2.8%	1.28 [0.91, 1.80]	
Lin 2013 Lin 2013 Lin 2013 December 2010 December 2010 Decemb	Li 2009	0.6206 0.163	5 3.0%	1.86 [1.35, 2.56]	
McMilliama 2010 McMilliama 2010 McMilliama 2010 Memory 2007 Memory	Lin 2013	-0.0408 0.183	5 2.6%	0.96 [0.67, 1.38]	
Steen 2010 Steen	McWilliams 2010	0.239 0.055	1 7.7%	1.27 [1.14, 1.41]	
Steves 2007 0.276 0.0659 7.1% 1.2(1:6.1.58) Lanca2015 0.0276 0.025 5.5% 1.32(1:0.1.58) Lanca2015 0.0276 0.025 4.5% 1.31(1:0.1.58) Lanca2015 0.0276 0.025 4.5% 1.31(1:0.1.58) Lanca2016 0.0276 0.055 5.5% 1.31(1:0.1.58) Lanca2016 0.0174 0.075 5.5% 1.31(1:0.1.58) Lanca2016 0.0168 0.0564 1.05% 1.02(0:06, 1:07) Lanca2016 0.0168 0.0575 6.2% 1.11(0:07, 1:48] Lanca2016 0.0176 0.0175 1.02(0:06, 1:7) Lanca2017 0.0176 0.0176 0.0575 6.2% 1.11(0:07, 1:48] Lanca2016 0.0176 0.0176 0.0575 6.2% 1.11(0:07, 1:48] Lanca2016 0.0176 0.0176 0.0575 6.2% 1.11(0:07, 1:48] Lanca2016 0.0176 0.0176 0.0175 1.02(0:06, 1:7) Lanca2016 0.0176 0.0176 0.0575 6.2% 1.11(0:07, 1:48] Lanca2016 0.0176 0.0176 0.0575 6.2% 1.11(0:07, 1:48] Lanca2016 0.0176 0.0176 0.0175 0.0075 0.055 1.2% 1.00075 1.000 1.10(1:05, 1:18] Lanca2016 0.0176 0.0176 0.0176 0.0176 0.0176 0.0075 0.0575 1.02 0.0176 0.0176 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.0075 0.	Olson 2010	0.3577 0.187	6 2.5%	1.43 [0.99, 2.07]	
Viam 2013 0.2776 0.093 5 Mr 1.2(11.0) 1.80 Subular (6%, C1) 4.01, C1* = 1.01, c1 = 8 (P = 08); P = 43% 4.33% 1.31 (12.0, 1.42) 4.33% 1.31 (12.0, 1.42) Mare 2005 C.0* = 1.4.01, c1 = 8 (P = 08); P = 43% 1.31 (12.0, 1.42) 4.33% 1.31 (12.0, 1.42) Mare 2005 C.0 Mare and table Mare and table Mare and table Mare and table Subdy or Subgroup Log [hazard ratio] SE Weinh Mare and table	Reeves 2007	0.2776 0.065	9 7.1%	1.32 [1.16, 1.50]	
Substatut (6% C) 43.35 1.31 (1.20, 1.42) Substatut (6% C) 43.05 1.31 (1.20, 1.42) Substatut (6% C) 43.05 1.31 (1.20, 1.42) Substatut (6% C) 43.05 1.31 (1.20, 1.42) Substatut (6% C) 5.05 1.2 Statut (6% C) 5.05 1.2 Statut (6% C) 0.053 1.05 Statut (7% C) 0.056 1.05 Statut (7% C) 0.056 1.05 Statut (7% C) 0.056 1.05 Statut (7% C) 0.057 1.05<	Yuan 2013	0.2776 0.09	3 5.6%	1.32 [1.10, 1.58]	
Heat-organisty: Tax* = 0.01; C.Pr = 14.01, d1 = 6 (P = .08); P = .43% Test for overall effect 2 = 8.44 (P < .00001) Macro 1 = .0000000000000000000000000000000000	Subtotal (95% CI)		45.3%	1.31 [1.20, 1.42]	•
Aussyndhysissen Aussyndhysin Aussyndhysissen Aussyndhysiss	Heterogeneity: Tau ^a = 0.01; Chi ^a = 14. Test for overall effect: $Z = 6.44$ ($P < .0$	01, df = 8 (P = .08); P 0001)	= 43%		
Jos Jos <thjos< th=""> <thjos< th=""> <thjos< th=""></thjos<></thjos<></thjos<>					•
Study or Subgroup Log [hazard ratio] SE Weight Winay Hazard ratio (X random, 55%, CI Hazard ratio (X random, 55%, CI Hazard ratio (X random, 55%, CI Study or Subgroup Log [hazard ratio] 0.063 0.063 1.9% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0% 1.0				02	0.5 1 2
Study or Subgroup Log [hazard ratio] SE Weight (M random, 55%, Cl) Hazard ratio (M random, 55%, Cl) Hazard ratio (M random, 55%, Cl) Armay Mogladdam 2006 0.053 0.1628 1.91 1.07 (1.07) 1.01 Barg 2000 0.0196 0.1957 1.31 1.02 (0.70, 1.67) 1.01 1.02 (0.70, 1.67) Barg 2000 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 Garaka 2000 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191 0.0191					Decreased mortality Increased mortality
Study or Subgroup Log [hazard ratio] SE Weight V. random, 95% CI IV. random, 95% CI Name Mogladamia 2008 0.005 0.458 1.9% 107 (0.77, 147) Bang 2008 0.0168 0.1567 1.3% 102 [0.70, 16.0] Bang 2008 0.0174 0.0054 6.458 6.6% 1.3% 1.02 [0.70, 15.0] Gale 2003 0.0174 0.0028 4.5% 1.11 [1.04, 1.18] • Gauphiz 2000 0.0279 0.154 1.4% 1.28 [0.70, 15.0] • Gauphiz 2000 0.0174 0.0128 4.5% 1.11 [1.04, 1.18] • Gauphiz 2000 0.0174 0.175 1.5% 1.010 [0.71, 152] • Lin 2013 0.0176 0.15% 1.010 [0.61, 153] • • News 2007 0.1160 0.0706 0.057 1.05% 1.10 [0.61, 127] • News 2007 0.1006 0.0707 8.2% 1.18 [1.02, 1.38] • • Gauphiz 2005 0.1681 0.0776 8.2% 1.18 [1.02,	•			Hazard ratio	Hazard ratio
Visup: Monipuladami 2006 0.053 0.1528 1.071 (0.77, 1.47) Jernes 2014 0.0714 0.0662 6.04, 1.071 (0.91, 1.27)	Study or Subgroup Log [ha	zard ratio] S	E Weight	IV, random, 95% C	I IV, random, 95% CI
Barky 2009 0 01968 0.1967 1 33% 102 [0.70, 1.50] Barky 2009 0 01918 0.1967 1 33% 102 [0.70, 1.50] Calle 2003 0 0171 0 00328 45.0% 1.11 [1.04, 1.18] Barky 2003 0 02796 0.1554 1.4% 1.32 [0.20, 1.60] Barky 2003 0 0174 0.1758 1.4% 1.20 [0.56, 1.52] L2009 0 0.1630 0.1186 3.5% 1.20 [0.56, 1.52] L2009 0 0.1630 0.1186 3.5% 1.20 [0.56, 1.52] L2009 0 0.1630 0.1186 3.5% 1.20 [0.56, 1.52] Deno 2010 0 0.0750 0.1055 1.0% 1.20 [0.56, 1.52] Deno 2010 0 0.0710 0.1056 1.05% 1.01 [0.56, 1.52] That [0.57, 1.44] Total (0.57, 1.42] Total (0.57, 1.42] 0 0.05, 1.5% 0 0.100 0.118] Dotal 0.0776 0.2% 1.18 [1.00, 1.38] Data (0.57, 1.42) 0 0.5% 0 0.2% 0 0.5% 0 0.2% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5% 0 0.5\% 0	Ansary-Moghaddam 2006	0.063 0.162	8 1.9%	1.07 [0.77, 1.47]	
Befnes 2014 0.0714 0.0862 6.061 1.07 [0.91, 1.27] Gapster 2000 0.2796 0.454 1.411 1.20 [0.92, 1.60] Gapster 2000 0.2796 0.454 1.441 1.20 [0.92, 1.60] Gapster 2000 0.2796 0.454 1.441 1.20 [0.92, 1.60] Lee 2003 0.0714 0.178 1.541 1.07 [0.56, 1.52] Lee 2003 0.0714 0.1189 3.541 1.07 [0.65, 1.52] Lin 2013 0.0110 0.0575 0.166, 1.075 1.441 Oleva 2010 0.00730 0.165 1.054 1.066, 1.27] General 2010 0.00730 0.165 1.061 1.066, 1.27] Gapster 2010 0.00730 0.165 1.061 1.061, 1.27] Gapster 2010 0.00730 0.165 1.061, 1.061, 1.27] 1.001/0 Gapster 2010 0.00730 0.1641 0.0776 6.274 1.161(1.06, 1.18] Gapster 2010 0.1681 0.0776 6.201 1.000/0 0.2 0.5 1 <td>Batty 2009</td> <td>0.0198 0.195</td> <td>7 1.3%</td> <td>1.02 [0.70, 1.50]</td> <td><u> </u></td>	Batty 2009	0.0198 0.195	7 1.3%	1.02 [0.70, 1.50]	<u> </u>
Calle 2003 0 1017 00228 45 84 1.11 [1.04, 1.18] Geng 2010 0 22196 0.154 1.44 1.32 (202, 160) Geng 2012 0 0073 0.104 40% 1.04 [0.64, 1.28] L2009 0 1240 0.175 1.52 L2009 0 1280 1.55 1.57 L2009 0 1280 1.55 1.57 L2009 0 1281 2.57 1.44 Oten 2010 0 0.019 0.084 1.57 1.44 Denn 2010 0 0.019 0.084 1.57 1.44 Denn 2010 0 0.019 0.084 1.18 [1.06, 1.28] Tuan 2013 0 1661 0.0776 8.2% 1.18 [1.06, 1.28] Tuan 2013 0 1661 0.0776 8.2% 1.18 [1.06, 1.28] Tuan 2013 0 0.00 Chi ⁰ 4.455, df = 12 (P = J68), IP 0.0% 1.00 [1.05, 1.18] Double 1.00 Chi ⁰ 4.455, df = 12 (P = J68), IP 0.0%	Bethea 2014	0.0714 0.086	2 6.6%	1.07 [0.91, 1.27]	
Jappshur 2000 0.2799 0.8554 1.4% 1.2(0.92, 1.60) Jong 2012 0.0773 0.1074 4.0% 1.64(0.64, 1.28) cee 2003 0.0714 0.1785 1.5% 1.0% 1.07(0.76, 1.52) jun 2013 0.0140 0.1589 3.5% 1.01(0.66, 1.52) 1.0% Jewes 2007 0.0198 0.0554 1.05% 1.02(0.66, 1.27) 1.0% Jewes 2007 0.0190 0.0573 0.1641 0.0575, 1.44 1.60(0.61, 1.27) 1.10(1.06, 1.27) Jun 2013 0.1641 0.0776 6.2% 1.10(1.06, 1.15) 1.00(0.12, 1.15) 1.00(0.12, 1.15) 1.00(0.12, 1.15) 1.00(0.12, 1.15) 1.02(0.12, 1.15) 0.2 0.5 1 2	Calle 2003	0.1017 0.032	8 45.8%	1.11 [1.04, 1.18]	-
Gorg 2012 0.0073 0.1104 4/04 1.04 (0.84, 1.28) L2008 0.1120 1.541 1.29 1.2008 1.521 L2008 0.1220 3.0112 3.041 1.20 (0.61, 5.22) L2008 0.0120 3.0112 3.041 1.20 (0.61, 5.22) L2008 0.0120 1.000 1.010 1.20 (0.128) L2008 0.0120 1.000 1.010 1.010 1.101 L2008 0.000 1.010 0.000 1.010 1.010 1.101 L2008 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.0000 0.0000 0.	Gapstur 2000	0.2799 0.185	4 1.4%	1.32 [0.92, 1.90]	
Lee 2003 0 0714 0.1785 15% 107 [0.78, 152] 12009 0 0.1823 0.1123 35% 120 [0.6, 152] Le 2013 0 01 0.1169 35% 101 [0.6, 152] Diece 2010 0.0179 0.065 16% 105% 120 [0.6, 127] Diece 2010 0.0179 0.0655 16% 1.06% 1.07 [0.6, 127] Diece 2013 0.1661 0.0776 8.2% 1.16 [1.0, 1.38] Polal (85% C1) Polal (85% C1) Polal (95%	3ong 2012	0.0373 0.110	4 4.0%	1.04 [0.84, 1.29]	
22006 0.1622 0.1192 3.5% 1.20[0.6%,1.52] 4cV/Wiama2010 0.0148 0.0664 10.5% 1.20[0.6%,1.52] 4cV/Wiama2010 0.0148 0.0664 10.5% 1.20[0.6%,1.7] 4cW/Wiama2010 0.0173 0.465 11% 10.4(0.75,1.44] 4cW/Wiama2013 0.01691 0.0776 4.6% 10.11(10.6%,1.18] 4cW/Wiama2013 0.01691 0.0776 4.2% 114[10.6%, 1.18] 4cW/Wiama2013 0.01691 0.0776 4.2% 114[10.6%, 1.18] 4cW/Wiama2010 0.01691 0.01691 0.01691 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681 0.01681	.ee 2003	0.0714 0.178	5 1.5%	1.07 [0.76, 1.52]	
Lin 2013 001 1189 35% 101 [0.00, 1.28] MeWilliama 2010 00198 0056% 116% 102 [0.06, 1.37] Diece 2010 00198 0056% 116% 104 [0.75, 1.44] Herews 2007 0.01070 00710 100% 1.11 [0.66, 1.27] Tutan 2013 0.1681 00776 8.2% 1.16 [1.02, 1.38] Foldal (85% C1) Foldal (85% C1) C100 (51, 10) C100 (J 2009	0.1823 0.119	2 3.5%	1.20 [0.95, 1.52]	
McV/Mamar 2010 0.0164 0.0684 10.5% 102 [0.69, 1.17] McV/Mamar 2010 0.0173 0.1652 1.8% 1.64 [0.57, 1.44] Reverse 2007 0.1007 0.1007 0.0751 1.44 Nuan 2013 0.1681 0.0756 8.2% 1.18 [1.02, 1.38] Total (M5% C) 100 Chi ⁰ = 0.00, Chi ⁰ = 4.85, df = 12 (P = .96); IP = 0% 0.00 1.10 [1.05, 1.15] 0.2 0.5 1 2	Lin 2013	0.01 0.118	9 3.5%	1.01 [0.80, 1.28]	
Oteon 2010 0 0073 0.655 18% 104 [0.75, 1.44] Herews 2007 0 1006, 127] Tuan 2013 0 1661 0.0776 8.2% 1.18 [1.00, 1.38] Total (65%, C1) Total (65%, C1) 0.0, Chi ⁰ = 4.65, df = 12 (P = .68), P = 0%. 1.0 [1.06, 1.15] 0.2 0.5 1 2	McWilliams 2010	0.0198 0.068	4 10.5%	1.02 [0.89, 1.17]	
Reverse 2007 0.1007 0.0701 10.0% 1.11 [0.66, 1.27] Yuan 2013 0.1661 0.0776 6.2% 1.16 [1.02, 1.36] Total (M5% CI) 0.000 1.10 [1.05, 1.15] 0.2 0.5 1	Olson 2010	0.0373 0.165	5 1.8%	1.04 [0.75, 1.44]	
Yuan 2013 0.1681 0.0776 8.2% 1.18 [1.02, 1.38] Total (65%, CI) 1000 0.00% 1.00 [1.06, 1.16] 0.00% Total (65%, CI) 0.00% 1.00 [1.06, 1.16] 0.00% 0.00% 0.00%	Reeves 2007	0.1007 0.070	1 10.0%	1.11 [0.96, 1.27]	
Total (95% C1) 100.0% 1.10 (1.05, 1.15) 100.0% 1.10 (1.05, 1.15) 02 0.5 1 2	ruan 2013	0.1681 0.077	5 8.2%	1.18 [1.02, 1.38]	
Heterogenety: tau" = 0.00, Chi" = 4.05, df = 12 (P = .95); P = 0% 0.2 0.5 1 2	Total (95% CI)		100.0%	1.10 [1.05, 1.15]	•
	Heterogeneity: Tau ² = 0.00; Chi ² = 4.8	5, df = 12 (P = .96); P	* 0%	0.2	0.5 1 2

Figure 2.

(*A*) Summary of maximally adjusted HR for association between premorbid BMI and pancreatic cancer-related mortality, comparing patients in the highest category of BMI with the lowest category. The *size of the box* corresponds to the weight of the given study. (*B*) Summary of maximally adjusted HR for association between premorbid BMI and pancreatic cancer-related mortality, comparing overweight (BMI 25.0–29.9 kg/m²) and obese (BMI 30 kg/m²) patients with normal BMI patients. The size of the box corresponds to the weight of the given study. (*C*) Summary of maximally adjusted HR for evaluation of dose-

weight of the given study. (*C*) Summary of maximally adjusted HR for evaluation of doseresponse relationship between premorbid BMI and pancreatic cancer–related mortality. The estimate represents mortality increase per 1 kg/m² increase in BMI. SE, standard error.

First author, year of publication	Location; study design	Time period; follow-up	Patients/participants	Deaths; method of outcome assessment	BMI; % obese (BMI >30 kg/ m ²); timing and method of BMI ascertainment	Association between BMI categories and mortality (95% CI)	Covariates adjusted for
Ansary-Moghaddam, 2006 ²⁶	Asia-Pacific; pooled cohort of 30 sites; population-based	1961–1999; 7 y	182,173 (all cancer-free at inception): unclear what proportion developed pancreatic cancer	324; record linkage with death certificates	Range of mean BMI in individual cohorts: 21.2- 26.9 kg/m ² ; NR, but 24.2% with BMI >26 kg/m ² ; premorbid BMI assessed at inception (measured)	Terriles of BMI; Reference: BMI <23 kg/m ² 23-26 vs reference: 1.07 (0.76–1.49) 26 vs reference: 1.00 (0.69–1.45)	1, 2, 4, 6, 7
Olson, 2010 ²⁴	United States; single center; hospital-based	2004–2008; 4 y	475 (all pancreatic cancer patients)	472; record linkage with manual chart review	NR; 23%; BMI assessed on basis of usual premorbid height and weight (self- reported)	Reference: BMI ~25 kg/m ² Resected: 25-30 vs reference: 1.02 (0.56-1.88) 30 vs reference: 1.62 (0.76-3.44) Unresected: 25-30 vs reference: 1.05 (0.70-1.57) 30 vs reference: 1.38 (0.90-2.11)	1, 2, 4, 6, 9, 10, 11, 12
McWilliams, 2010 ²¹	United States; single cohort, hospital-based	2000–2009; 3 y	1861 (all pancreatic cancer patients)	1527: record linkage with death indices, and periodic mailings, manual chart treview and tumor registry	28.5 ± 5.8 kg/m ² ; 31.9%; BMI assessed on basis of usual height and weight (66.2%) or weight at enrollment plus reported weight loss (33.8%) (combination of measured and self-reported)	Reference: BMI 18.5–24.9 kg/m ² ~18.5 vs reference: 1.42 (0.76–2.68) 25–29.9 vs reference: 1.03 (0.89–1.18) 30–34.9 vs reference: 1.16 (0.98–1.37) 33–39.9 vs reference: 1.16 (0.98–1.37) 33–39.9 vs reference: 1.16 (0.98–1.37) 33–39.9 vs reference: 1.16 (0.98–1.37) 33–39.9 vs reference: 1.16 (0.98–1.37) 33–39.9 vs reference: 1.16 (0.98–1.37) 33–39.9 vs reference: 1.16 (0.98–1.37) 33–39.0 vs reference: 1.16 (0.98–1.37) 33–39.0 vs reference: 1.16 (0.98–1.37) 33–39.0 vs reference: 1.16 (0.98–1.37) 33–39.0 vs reference: 1.16 (0.98–1.37) 33–39.0 vs reference: 1.16 (0.98–1.37) 33–30.0 vs reference: 1.16 (0.98–1.37) 33–30.0 vs reference: 1.16 (0.98–1.36) 33–30.0 vs reference: 1.16 (0.98–1.18) 30–34.0 vs reference: 1.16 (0.98–1.18) 30–34.0 vs reference: 1.16 (0.98–1.18) 31–34.0 vs reference: 1.16 (0.98–1.36) 31–34.0 vs reference: 1.16 (0.98–1.36) 33–34.0 vs reference: 1.16 (0.98–1.36) 33–34.0 vs reference: 1.16 (0.98–1.37) 33–34.0 vs reference: 1.16 (0.98–1.36) 33–34.0 vs reference: 1.16 (0.98–1.36) 33–34.0 vs reference: 1.16 (0.98–1.36) 33–34.0 vs reference: 1.16 (0.98–1.36) 33–34.0 vs reference: 1.16 (0.98–1.37) 33–34.0 vs reference: 1.16 (0.98–1.36) 35–34.0 vs reference: 1.16 (0.98–1.36) 35–34.0 vs reference: 1.16 (0.98–1.36) 35–34.0 vs reference: 1.16 (0.98–1.36) 36–34.0 vs reference: 1.16 (0.98–1.36) 36–34.0 vs reference: 1.16 (0.98–1.36) 36–34.0 vs reference: 1.16 (0.98–1.36) 36–34.0 vs reference: 1.16 (0.98–1.36) 37–34.0 vs reference: 1.16 (0.98–1.36) 36–34.0 vs reference: 1.16 (0.98–1.37) 37–34.0 vs reference: 1.16 (0.98–1.36) 36–34.0 vs reference: 1.16 (0.98–1.36) 36–34.0 vs reference: 1.16 (0.98–1.36) 36–34.0 vs reference: 1.16 (0.98–1.36) 36–34.0 vs reference: 1.16 (0.96–1.36) 36–34.0 vs reference: 1.16 (0.96–1.06) 36–34.0 vs reference: 1.16	1, 2, 6, 9
Yuan, 2013 ²³	United States; pooled analysis of 2 cohorts; population-based	1988–2010; 4 y	902 (all pancreatic cancer patients)	868; record linkage with national	25.9 ± 4.5 kg/m²; 15.1%; premorbid BMI assessed at	Reference: BMI <25 kg/m ²	1, 2, 3, 4, 9, 13

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Table 1

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Characteristics of Included Studies

First author, year of publication	Location; study design	Lime period; follow-up	Patients/participants	Deaths; method of outcome assessment	BMI; %0 obese (BMI >30 kg/ m ²); timing and method of BMI ascertainment	Association between BMI categories and mortality (95% CI)	Covariates adjusted for
				death index, and postal contact with next of kin	inception (self- reported)	25-26.99 vs reference: 0.88 (0.73-1.06) (0.73-1.06) (0.72-9.9 vs reference: 1.04 (0.86-1.26) 30-34.9 vs reference: 1.21 (0.96-1.53) 35 vs reference: 1.45 (1.05-1.99)	
Gong, 2012 ²⁵	United States; single cohort; population-based	1995-1999; 10 y	510 (all pancreatic cancer patients)	495; record linkage with Social Security Death Index and California Death Records databases	NR; 10%; BMI assessed on basis of usual premorbid height and weight (self- reported)	Reference: BMI ~25 kg/m ² 25-29.9 vs reference: 1.04 (0.83-1.28) 30 vs reference: 1.28 (0.91-1.81)	1, 2, 3, 4, 6, 8, 9, 14, 15, 16
Li, 2009 ¹²	United States; single center; hospital-based	2004–2008; 2 <i>y</i>	841 (all pancreatic cancer patients); 609 assessable patients with at least 1 y of follow-up	352; record linkage with Social Security Death Index Death Index and local tumor registry, manual chart review	$24.7 \pm 3.8 \text{ kg/m}^2$; 26.7% ; BMI assessed on basis of usual premorbid height and weight (self-reported)	Reference: BMI ~25 kg/m ² 25-29.9 vs reference: 1.26 (0.94-1.69) 30 vs reference: 1.86 (1.35-2.56)	6, 9, 15
Reeves, 2007 ²²	United Kingdom; single cohort; population-based	1996-2001; >1 y	1,222,630 (all cancer- free at inception); unclear what proportion developed pancreatic cancer	1130; record linkage with National Health Service central registry	Median BMI: 25.4 (IQR, 23– 28.6); NA; BMI assessed on basis of usual premorbid height and weight (self- reported)	Reference: 22.5– 24.9 kg/m ² ~22.5 vs reference: 1.11 (0.97–1.27) (0.97–1.27) (0.97–1.27) (0.97–1.16) (0.97–1.16) 25–27.4 vs reference: 1.12 (0.96–1.31) 30 vs reference: 1.32 (1.16–1.51)	1, 4, 5, 17, 18, 19, 20, 21, 22
Calle, 2003 ²⁸	United States; single cohort; population-based	1982–1998, 16 y	900,053 (all cancer-free at inception); unclear what proportion	3558; record linkage with national death index,	NR; NR; BMI assessed on basis of usual premorbid height	Reference: 18.5– 24.9 kg/m ² Men:	Men: 1, 3, 4, 5, 8, 20, 23, 24, 25, 26

First author, year of publication	Location; study design	Time period; follow-up	Patients/participants	Deaths; method of outcome assessment	BMI; % obese (BMI >30 kg/ m ²); timing and method of BMI ascertainment	Association between BMI categories and mortality (95% CI)	Covariates adjusted for
			developed pancreatic cancer	and personal inquiries by volunteers	and weight (self- reported)	25-29.9 vs reference: 1.13 (1.03-1.25) 30-34.9 vs reference: 1.41 (1.19-1.66) 35-39.9 vs reference: 1.49 (0.99-2.22) Women: 25-29.9 vs reference: 1.11 (1.00-1.24) 30-34.9 vs reference: 1.28 (1.07-1.52) 37-39.9 vs reference: 1.41 (1.01-1.99) 40 vs reference: 1.41 (1.01-1.99) 40 vs reference: 1.41 (1.01-1.99) 40 vs reference: 1.41 (1.01-1.99)	Women: 1, 3, 4, 5, 8, 20, 22, 23, 24, 25, 26
Lin, 2013 ¹³	Asia; pooled cohorts of 16 sites; population- based	1990–2002; range of follow-up: 3–22 y	799,452 (all cancer-free at inception); unclear what proportion developed pancreatic cancer	1489; record linkage with death certificates	Range of mean BMI in individual cohorts: 19.9– 23.7 kg/m ² ; NR; BMI assessed on basis of usual premorbid height and weight at inception (self- reported)	Reference: 22.5– 24.9 kg/m ² <18.5 vs reference: 1.04 (0.84–1.30) 18.5–19.9 vs reference: 0.82 (0.67–1.00) 20–22.4 vs reference: 0.91 (0.80–1.05) 25–27.4 vs reference: 0.95 (0.80–1.10) 27.5–29.9 vs reference: 1.01 (0.80–1.29) 30 vs reference: 1.01 (0.80–1.20) 30 vs reference:	1, 2, 4, 6, 7
Bethea, 2014 ²⁷	United States; pooled cohorts of 7 sites; population-based	1982–2008; 12 y	239,597 (all cancer-free at inception); unclear what proportion developed pancreatic cancer	897: record linkage with national death index	NR; 33%; BMI assessed on basis of usual premorbid height and weight at inception (self- reported)	Reference: 18.5– 24.9 kg/m ² 25–29.9 vs reference: 1.08 (0.90–1.31) 30-34.9 vs reference: 1.25 (0.99–1.57)	1, 2, 4, 5, 8, 20, 26

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First author, year of publication	Location; study design	Time period; follow-up	Patients/participants	Deaths; method of outcome assessment	BMI; % obese (BMI > 30 kg/ m ²); timing and method of BMI ascertainment	Association between BMI categories and mortality (95% CI)	Covariates adjusted for
						35 vs reference: 1.31 (0.97–1.33)	
Batty, 2009 ²⁹	United Kingdom; single cohort; population-based	1967–1970; 38 y	17,898 (all cancer-free at inception); unclear what proportion developed pancreatic cancer	163; record linkage with National Health Service central registry	NR; 33%; BMI assessed on basis of usual premorbid height and weight at inception (self- reported)	Reference: 18.5– 24.5 kg/m ² 25–29.9 vs reference: 1.02 (0.69–1.50) 30–34.9 vs reference: 1.18 (0.79–1.75)	1, 4, 6, 18, 20, 26, 27, 28, 29, 30
Gatspur, 2000 ³⁰	United States; single cohort; population-based	1967–1973; 25 y	35,658 (all cancer-free at inception); unclear what proportion developed pancreatic cancer cancer	139; record linkage with national add bidex and Social Security and postal inquiries	Men: 26.6 ± 3.7 Women: 24.0 ± 4.4; NR; premorbid BMI assessed at inception (measured)	Quartiles of BMI; Men: Reference: <24.3 kg/m ² 24.2-26.3 vs reference: 1.84 (0.87-3.92) 56.3-28.6 vs reference: 1.71 (0.81-3.61) >28.6 vs reference: 3.07 (1.53-6.15) Women: Reference: 0.50 (0.18-1.41) 23.2-26.2 vs reference: 0.79 (0.32-1.95) (0.32-1.95) (0.32-1.95)	1, 3, 4, 6
Lee, 2003 ³¹	United States: single cohort; population-based	1962–1966; 27–31 y	32,687 (all cancer-free at inception); unclear what proportion developed pancreatic cancer	212; record linkage with death certificates	NR; 10.2% with BMI 27.5 kg/m ² ; BMI assessed on basis of usual bremotid height and weight at inception (self- reported)	Reference: <22.5 kg/m ² 22.5-24.9 vs reference: 0.84 (0.58.1.22) (5.8.1.22) (0.58.1.22) (0.58.1.22) (0.58.1.22) (0.58.1.22) (0.74.1.57) 27.5 vs (0.60.1.62) (0.60.1.62)	1, 2, 4, 6, 20

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NOTE. Variables adjusted for: 1, age; 2, sex; 3, race; 4, smoking; 5, alcohol use; 6, diabetes; 7, study (pooled cohorts); 8, education; 9, stage; 10, allergies; 11, chemo; 12, performance status; 13, year of diagnosis; 14, tumor grade; 15, primary treatment; 16, tumor site; 17, geographical region; 18, socioeconomic status; 19, reproductive history; 20, physical activity; 21, time since menopause; 22, use of hormone replacement therapy; 23, aspirin use; 24, fat consumption; 25, vegetable consumption; 26, marital status; 27, plasma cholesterol; 28, forced expiratory volume in 1 second; 29, height; 30, blood pressure. IQR, interquartile range; NR, not reported.

First author, reference	Age at pancreatic cancer diagnosis or enrollment (y)	Sex (% male)	Race (% white)	Smoking	Diabetes	Stage at diagnosis of pancreatic cancer – stage 1/2/3/4	Cancer-related therapy (proportion of patients undergoing surgery, chemotherapy, radiation)
Ansary-Moghaddam ²⁶	47	65	NR	23	6%	NR	NR
Olson ²⁴	64	52	88	53	10	Resected: 9% (T1/T2), 91% (T3/T4)	Resected (34%): 89% received chemotherapy as well;
						Unresected cohort: 56% M1	Unresected (66%): 88% received chemotherapy
McWilliams ²¹	66	56	NR	NR	31	Resectable (stage I/II): 30% Locally advanced: 35% Metastatic: 35%	NR
Yuan ²³	71	ΥN	95	60	ν.	Localized: 15% Locally advanced: 11% Metastatic: 49% Unknown: 25%	NR
Gong ²⁵	BMI <25: 66 BMI 25-29: 63 BMI 30: 62	55	83	BMI <25: 69% BMI 25-<30: 72% BMI 30: 57%	BMI <25: 9% BMI 25-29: 14% BMI 30: 39%	Local: 12% Regional: 43% Distant: 30% Unknown: 15%	Resection: 31% Chemo/radiation: 29% Bypass/stent: 9% Other treatment: 9% Unknown: 23%
Li ¹²	61	59	86	54	26	NR	Resection: 16%
Reeves ²²	56	0	NR	19	NR	NR	NR
Calle ²⁸	57	45	NR	57	NR	NR	NR
Lin ¹³	Range: 37–60	50	0	34	NR	NR	NR
Bethea ²⁷	52	29	0	NR	NR	NR	NR
Batty ²⁹	NA	100	NR	NR	NR	NR	NR
Gatspur ³⁰	40	57	88	39	NR	NR	NR
Lee ³¹	47	93	NR	48	1.8	NR	NR

NR, not reported.

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Table 2

Baseline Characteristics of Participants in Individual Studies

Table 3

Subgroup Analysis

Subgroups	Categories	No. of studies	Overweight	Obese
Location	Asia-Pacific	2	$0.98 (0.87 - 1.11), I^2 = 0$	$0.98 (0.76 - 1.27), I^2 = 0$
	Western	11	1.07 (1.02–1.12), $I^2 = 0$	1.32 (1.22–1.42), $I^2 = 30$
Study type	Pooled cohort	3	$0.98 (0.89 - 1.08), I^2 = 0$	1.08 (0.95–1.23), $I^2 = 3$
	Individual site	10	1.08 (1.03–1.13), $I^2 = 0$	1.35 (1.27–1.43), $I^2 = 5$
Study setting	Population-based	10	1.06 (1.01–1.11), $I^2 = 0$	1.26 (1.15–1.37), $I^2 = 60$
	Hospital-based	3	1.06 (0.94–1.18), $I^2 = 0$	1.45 (1.14–1.84), $I^2 = 60$
Adjusted for diabetes	Yes	9	1.03 (0.95–1.10), $I^2 = 0$	1.27 (1.11–1.46), I ² = 37
	No	4	1.08 (1.02–1.14), $I^2 = 2$	1.30 (1.18–1.44), $I^2 = 50$
Whether primary tumor underwent	Yes	2	_	2.29 (1.13–4.67), I ² = 39
surgical resection	No	2	_	1.53 (1.17–2.01), $I^2 = 0$ (<i>P</i> value for difference, .30)
Adjusted for stage and/or treatment of	Yes	5	1.07 (0.98–1.16), $I^2 = 0$	1.35 (1.21–1.51), $I^2 = 21$
status	No	8	1.06 (1.01–1.12), $I^2 = 0$	1.23 (1.09–1.38), $I^2 = 49$ (<i>P</i> value for difference between groups, . 26)
Ascertainment of exposure	Self-reported	3	1.05 (0.93–1.18), $I^2 = 0$	1.26 (1.00–1.58), I ² = 41
	Measured	10	1.06 (1.02–1.11), $I^2 = 0$	1.30 (1.18–1.42), $I^2 = 41$ (<i>P</i> value for difference between groups, . 83)
Time period of recruitment of patients	Before 1980s	3	1.04 (0.85–1.26), $I^2 = 0$	1.26 (0.90–1.75), I ² = 32
	1980-2000	5	1.07 (1.02–1.13), $I^2 = 0$	1.28 (1.13–1.45), $I^2 = 42$
	2001-2010	3	1.06 (0.94–1.18), $I^2 = 0$	1.45 (1.14–1.84), $I^2 = 60$
	Across 1980-2010	2	1.04 (0.93–1.16), I ² = 21	1.21 (1.03–1.42), $I^2 = 43$ (<i>P</i> value for difference between groups = . 66)