Body mass index, abdominal fatness and pancreatic cancer risk: A systematic review and nonlinear dose-response meta-analysis of prospective studies

D. Aune[1], D. C. Greenwood[2], D. S. M. Chan[1], R. Vieira[1], A.R. Vieira[1], D. A. Navarro Rosenblatt[1], J. E. Cade[3], V.J. Burley[3], T. Norat[1].

Affiliations

[1] Department of Epidemiology and Biostatistics, Imperial College, London, United Kingdom

[2] Biostatistics Unit, Centre for Epidemiology and Biostatistics, University of Leeds, Leeds, United Kingdom

[3] Nutritional Epidemiology Group, Centre for Epidemiology and Biostatistics, School of Food Science and Nutrition, University of Leeds, Leeds, UK

Correspondence to: Mr. Dagfinn Aune, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, St. Mary's Campus, Norfolk Place, Paddington, London W2 1PG, UK.

Telephone: +44 (0) 20 7594 8478

E-mail: d.aune@imperial.ac.uk

E-mail co-authors:

Darren C. Greenwood D.C.Greenwood@leeds.ac.uk

Doris S.M. Chan d.chan@imperial.ac.uk

Rui Vieira r.vieira@imperial.ac.uk

Ana Rita Vieira a.vieira@imperial.ac.uk

Deborah A. Navarro Rosenblatt d.navarro-rosenblatt@imperial.ac.uk

Janet Cade J.E.Cade@leeds.ac.uk

Victoria J. Burley V.J.Burley@leeds.ac.uk

Teresa Norat t.norat@imperial.ac.uk

Summary

Background: Questions remain about the shape of the dose-response relationship between body mass index (BMI) and pancreatic cancer risk, possible confounding by smoking, and differences by gender or geographic location. Whether abdominal obesity increases risk is unclear.

Methods: We conducted a systematic review and meta-analysis of prospective studies of the association between BMI, abdominal fatness and pancreatic cancer risk and searched PubMed and several other databases up to January 2011. Summary relative risks were calculated using a random effects model.

Results: Twenty-three prospective studies of BMI and pancreatic cancer risk with 9504 cases were included. The summary relative risk (RR) for a 5 unit increment was 1.10 (95% CI: 1.07-1.14, I^2=19%) and results were similar when stratified by gender and geographic location. There was evidence of a nonlinear association, $p_{nonlinearity}$=0.005, however, among non smokers there was increased risk even within the "normal" BMI range. The summary RR for a 10 cm increase in waist circumference was 1.11 (95% CI: 1.05-1.18, I^2=0%) and for a 0.1 unit increment in waist-to-hip ratio was 1.19 (95% CI: 1.09-1.31, I^2=11%).

Conclusions: Both general and abdominal fatness increases pancreatic cancer risk. Among non smokers risk increases even among persons within the "normal" BMI range.

Key words: Body mass index, waist circumference, waist-to-hip ratio, pancreatic cancer, systematic review, meta-analysis.

Introduction

Pancreatic cancer is the 9th most common cause of cancer with 277 000 new cases diagnosed in 2008 worldwide, accounting for about 2.2% of all cancer cases (1). Pancreatic cancer patients have a very low survival, on average only 6 months after diagnosis, because there are few early symptoms and the disease is usually diagnosed in the later stages. Currently there are no established methods of screening for early detection, thus, at present primary prevention by altering modifiable risk factors will probably be the most effective way of reducing the pancreatic cancer burden.

Epidemiological studies have suggested that overweight and obesity are associated with increased pancreatic cancer risk. The evidence that body fatness increases pancreatic cancer risk was considered conclusive in the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report from 2007 (2). However, more recent reviews of the evidence suggested an increased risk with higher body mass index (BMI, weight in kilograms divided by height squared in metres) among women, but not among men (3), and in addition, there were inconsistencies in the results by geographic location (3). The exact shape of the dose-response relationship between body mass index and pancreatic cancer risk has not been clearly defined. Smoking is an established risk factor for pancreatic cancer and a potentially important confounding factor of the association between BMI and pancreatic cancer risk. Smokers tend to have a lower BMI than non smokers and residual confounding by smoking may attenuate or distort the dose-response relationship between BMI and pancreatic cancer risk. The best way to avoid residual confounding by smoking is to restrict the analyses to non smokers or never smokers, however, because pancreatic cancer is a relatively uncommon type of cancer, individual studies may have had limited statistical power to examine the association among non smokers, thus combining results from several studies in a meta-analysis will increase statistical power to detect significant associations. Hence, we

explored whether smoking may have confounded the association between BMI and pancreatic cancer risk. Abdominal obesity may be more strongly associated with insulin resistance than peripheral obesity (4), but there have been relatively few studies of waist circumference and waist-to-hip ratio as measures of abdominal fatness in relation to pancreatic cancer risk. A number of additional large cohort studies have been published since the WCRF/AICR report from 2007 (5-17), thus, we conducted an updated meta-analysis of BMI, waist circumference and waist-to-hip ratio and pancreatic cancer risk with the aim to clarify whether body fatness is associated with pancreatic cancer in both men and women and in European and Asian populations as well. In addition, we wanted to clarify the dose-response relationship between BMI, waist circumference and waist-to-hip ratio and pancreatic cancer risk by conducting nonlinear dose-response analyses and by restricting the analysis to studies among non smokers or never smokers.

Methods

Search strategy

Initially relevant studies of anthropometric measures and pancreatic cancer risk were identified by searching several databases up to December 2005, including Pubmed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, LILACS, Cochrane library, CINAHL, AMED, National Research Register, and In Process Medline. However, because all the relevant studies were identified by the PubMed search, a change to the protocol was made and in the updated searches only Pubmed was searched from 1st January 2006 to 31st of January 2011. A prespecified protocol was followed for the review (http://www.dietandcancerreport.org/downloads/SLR_Manual.pdf) and we used standard criteria for meta-analyses of observational studies (18). In addition, we also searched the

reference lists of all the studies that were included in the analysis and the reference lists of published meta-analyses (3;19;20).

Study selection

Prospective cohort studies, case-cohort studies, or nested case-control studies of the association between BMI, waist circumference, or waist-to-hip ratio and pancreatic cancer risk incidence or mortality were included. Relative risk estimates (hazard ratio, risk ratio) had to be available with the 95% confidence intervals in the publication and for the dose-response analysis, a quantitative measure of intake and the total number of cases and person-years had to be available in the publication. We identified 48 potentially relevant full-text publications (5-17;21-56). We excluded fourteen duplicate publications (13;25;29;30;32;33;40;41;43;45-47;49;51;52) four publications which did not present risk estimates (23;24;26;39) and one publication using <3 categories for categorisation of BMI (27) leaving 29 publications for inclusion in the analysis (5-12;14-17;21;22;28;31;34-38;42;44;48;50;53-56). Results from two overlapping publications were included only in subgroup analyses stratified by sex (42) or smoking (44) but not in the overall analyses, because the superseding publications did not present sex-specific results (5) or results stratified by smoking in enough detail to be included (16).

Data extraction

We extracted from each study: The first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, gender, age, number of cases, assessment method of anthropometric factors (measured vs. self-reported), RRs and 95% CIs, and variables adjusted for in the analysis. Several reviewers at the University of Leeds conducted the search and data extraction of articles published up to December 2005,

during the systematic literature review for the WCRF/AICR report (http://www.dietandcancerreport.org/downloads/SLR/Pancreas_SLR.pdf). The search and data extraction from January 2006 and up to January 2011 was conducted by one author (D.A) and was checked for accuracy by one author (T. N).

Statistical analysis

Summary RRs and 95% CIs for a 5 unit increment in BMI, 10 cm increment in waist circumference and for a 0.1 unit increment in waist-to-hip ratio were estimated using a random effects model (57). The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted by the inverse of its variance. A two-tailed $p<0.05$ was considered statistically significant. If studies reported results separately for men and women we combined the sex-specific estimates using a fixed-effects model to generate an estimate for both genders combined. We conducted separate analyses for pancreatic cancer incidence and mortality.

The method described by Greenland and Longnecker (58) was used for the dose–response analysis and study-specific slopes (linear trends) and 95% CIs were computed from the natural logs of the RRs and CIs across categories of anthropometric measures. The method requires that the distribution of cases and person-years or non-cases and the RRs with the variance estimates for at least three quantitative exposure categories are known. We estimated the distribution of cases or person-years in studies that did not report these, but reported the total number of cases and person-years (Online supplement 1). The mean BMI, waist circumference of waist-to-hip ratio level in each category was assigned to the corresponding relative risk for each study and for studies that reported these measures by ranges we estimated the mean in each category using the method described by Chene and Thompson (59). A potential nonlinear dose-response relationship between BMI, waist circumference and

waist-to-hip ratio and pancreatic cancer was examined by using fractional polynomial models (60). We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity (60).

Subgroup and meta-regression analyses were conducted to investigate potential sources of heterogeneity and heterogeneity between studies was quantitatively assessed by the Q test and I^2 (61) Small study effects, such as publication bias, were assessed by inspecting the funnel plots for asymmetry and with Egger's test (62) and Begg's test (63), with the results considered to indicate small study effects when $p<0.10$. Sensitivity analyses excluding one study at a time were conducted to clarify whether the results were simply due to one large study or a study with an extreme result.

Role of the funding source

The funding source had no role in the study design, collection, analysis and interpretation of the data, in the writing of the report or in the decision to submit the paper for publication.

Results

We identified twenty-four prospective studies (23 publications) (5-12;14-17;21;22;28;31;34-38;42;44) that were included in the analyses of BMI and pancreatic cancer incidence (Supplementary Table 1, Figure 1). Two of these publications were only included in subgroup analyses of sex (42) and stratified by smoking (44) as they overlapped with two more recent publications (5;16). Seven cohort studies (16;48;50;53-56) were included in the analysis of pancreatic cancer mortality (Supplementary Table 2). Five cohort studies (four publications) (5;10;12;36) were included in the analysis of waist circumference and four cohort studies (5;10;12;37) were included in the analysis of waist-to-hip ratio and pancreatic

cancer incidence. Characteristics of the included studies are provided in Supplementary Table 1 and Supplementary Table 2. Most of the studies were from Europe and the US and used self-reported weight and height (Supplementary Table 1 and Supplementary Table 2).

BMI

Twenty three prospective studies (21 publications) (5-12;14-17;21;22;28;31;34-38) were included in the overall dose-response analysis of BMI and pancreatic cancer incidence and included a total of 9504 cases among 5,037,555 participants. Ten studies were from the US, ten were from Europe, and the remaining three were from Asia (Supplementary Table 1). The summary RR for a 5 unit increment in BMI was 1.10 (95% CI: 1.07-1.14), with no significant heterogeneity, I^2=19%, p=0.20 (Figure 2a). The summary RR was similar among men and women, summary RR= 1.10 (95% CI: 1.04-1.16, I^2=46%, $p_{heterogeneity}$=0.03) for women (7-12;16;17;28;34-38;42) and 1.13 (95% CI: 1.04-1.22, I^2=42%, $p_{heterogeneity}$=0.05) for men (6-11;14;17;28;34-38), respectively (Table 1). Although there was no statistically significant difference in the association between never or non smokers(5-7;10;44) and ever smokers (5-7;10) in stratified analyses the association was restricted to never and non smokers (Table 1). In sensitivity analyses excluding one study at a time, the summary RR in the overall analysis ranged from 1.09 (95% CI: 1.06-1.12) when the Cancer Prevention Study 2 Nutrition Cohort was excluded to 1.11 (95% CI: 1.08-1.14) when the Multiethnic Cohort Study was excluded. There was no evidence of small study effects with Egger's test, p=0.36, or with Begg's test, p=0.27 and when visually inspected the funnel plot showed no sign of asymmetry.

To address the question of reverse causality, e.g. whether prediagnostic disease may have influenced BMI, we restricted the analyses to the six studies (5;8;10;11;34;44) that provided results with exclusion of early follow-up (first 1-4 years of follow-up), but the

results were similar, summary RR=1.11 (95% CI: 1.05-1.18, I^2=35%, $p_{heterogeneity}$=0.18). Further restricting the analysis to the four studies (5;8;11;44) which excluded at least the first two years of follow-up did not materially change the results, summary RR=1.13 (95% CI: 1.05-1.21, I^2=26%, $p_{heterogeneity}$=0.25) (results not shown).

The results were in general consistent across subgroups of duration of follow-up, geographic location, number of cases, adjustment for most confounding factors and adjustment for diabetes (Table 1). Only in the subgroups of studies with and without adjustment for physical activity and red meat was there some evidence of heterogeneity ($p_{heterogeneity}$=0.03 for both comparisons), with a stronger association among studies that adjusted for physical activity (n=4), but no association among studies that adjusted for red meat (n=2), however, the number of studies in these subgroup analyses was very low. We also conducted further subgroup analyses within strata of gender to investigate potential sources for the observed heterogeneity for men and women when analyzed separately, but only in the analysis among women stratified by adjustment for meat intake was there some evidence of heterogeneity (p=0.009). An inverse association was found in the two studies that adjusted for meat intake (summary RR=0.86, 95% CI: 0.75-0.99), but a positive association was observed in studies that did not adjust for meat intake (summary RR=1.10, 95% CI: 1.06-1.15) (results not shown).

There was evidence of a nonlinear association between BMI and pancreatic cancer risk, $p_{nonlinearity}$=0.005 (Figure 2b), with the lowest risk among persons with a BMI around 21 and with the most pronounced increase in risk among persons with a BMI above 35. The association between BMI and pancreatic cancer risk appeared to be linear when we further restricted the nonlinear analysis to studies of never and non smokers (6;7;10), $p_{nonlinearity}$=0.61, however, the shape of the dose-response curve was steeper and there was evidence of an increase in risk even among persons with a BMI in the "normal" range (BMI 21<25) (Figure

3a). In contrast, there was no evidence of an association between BMI and increased pancreatic cancer risk when we restricted the nonlinear analysis to ever smokers (Figure 3b) (7;10).

Seven cohort studies (16;48;50;53-56) were included in the BMI and pancreatic cancer mortality analysis and included 8869 deaths among 2,537,564 participants. Three of the studies were from the US, two from Europe and two from Asia (Supplementary Table 2). The summary RR was 1.16 (95% CI: 0.98-1.36) and there was moderate heterogeneity, I^2=56%, $p_{heterogeneity}$=0.04 (Figure 4a). The summary RR ranged from 1.06 (95% CI: 1.01-1.11) when the Cancer Prevention Study 2 was excluded to 1.21 (95% CI: 0.97-1.49) when the Million Women's study was excluded. The Cancer Prevention Study 2 (55) also explained all the heterogeneity and when excluded, I^2=0%, $p_{heterogeneity}$=0.43. There was no evidence of small study effects with Egger's test, p=0.43, or with Begg's test, p=0.76. There was evidence that the association between BMI and pancreatic cancer mortality was nonlinear, $p_{nonlinearity}$=0.0001, and the risk was most pronounced above a BMI of 35 (Figure 4b).

Waist circumference

Five cohort studies (four publications) (5;10;12;36) were included in the analysis of waist circumference and pancreatic cancer risk and included 949 cases among 787,356 participants. Three studies were from Europe and two from the US (Supplementary Table 1). The summary RR for a 10 cm increase in waist circumference was 1.11 (95% CI: 1.05-1.18) with no evidence of heterogeneity, I^2=0%, p=0.74 (Figure 5a). The summary RR ranged from 1.11 (95% CI: 1.04-1.17) when the Cohort of Swedish Men was excluded to 1.14 (95% CI: 1.06-1.22) when the Women's Health Initiative was excluded. The summary estimate was similar among men (summary RR=1.13, 95% CI: 0.89-1.44, I^2=61%, p=0.11), and women (summary RR=1.14, 95% CI: 1.02-1.28, I^2=29%, p=0.24) p for heterogeneity=0.59 (results

not shown). There was no evidence of small study effects with Egger's test, p=0.11, or with Begg's test, p=0.22. There was no evidence of a nonlinear association between waist circumference and pancreatic cancer risk, $p_{nonlinearity}$=0.28 (Figure 3c).

Waist-to-hip ratio

Four cohort studies (5;10;12;37) were included in the analysis of waist-to-hip ratio and pancreatic cancer risk and included 1047 cases among 878,137 participants. Three were from the US and one from Europe (Supplementary Table 1). The summary RR for a 0.1 unit increment in waist-to-hip ratio was 1.19 (95% CI: 1.09-1.31) with no significant heterogeneity I^2=11%, p=0.34 (Figure 5b). The summary RR ranged from 1.15 (95% CI: 1.04-1.27) when the Women's Health Initiative was excluded to 1.24 (95% CI: 1.12-1.37) when the Iowa Women's Health Study was excluded. The summary estimate was similar among men (summary RR=1.20, 95% CI: 0.96-1.50, I^2=not calculable, n=1) and women (summary RR=1.17, 95% CI: 1.00-1.36, I^2=41%, p=0.18), p for heterogeneity=0.89 (results not shown). There was no evidence of small study effects with Egger's test, p=0.50, or with Begg's test, p=0.73. There was no evidence of a nonlinear association between waist circumference and pancreatic cancer risk, $p_{nonlinearity}$=0.29 (Figure 3d).

Discussion

In this meta-analysis we found evidence of an increased risk of pancreatic cancer with higher BMI and a similar association with measures of abdominal obesity, such as waist circumference and waist-to-hip ratio.

However, to our knowledge for the first time in a meta-analysis of BMI and pancreatic cancer, we have found a potential nonlinear association between BMI and pancreatic cancer

risk. The most pronounced increase in risk was observed at a BMI above 35, however, when we further restricted the analyses to studies among non and never smokers the shape of the curve became initially steeper and there was evidence of an increased risk even within the high "normal" range of BMI. In contrast, there was no association between BMI and pancreatic cancer risk among ever smokers. Thus, residual confounding from smoking may have distorted the dose-response relationship between BMI and pancreatic cancer risk in the overall analysis. The positive associations between waist circumference and waist-to-hip ratio and pancreatic cancer risk appeared to be linear. We found little evidence of heterogeneity in the overall analyses of BMI, waist circumference, and waist-to-hip ratio and pancreatic cancer incidence, while in the analysis of BMI and pancreatic cancer mortality the moderate heterogeneity that was present was explained by a large American study (55). Our analysis confirms the hypothesis that both overall body fatness and abdominal fatness are associated with increased risk of pancreatic cancer and provide further support for the findings from a recent meta-analysis (3) and the WCRF/AICR report from 2007 (2). However, with a larger number of studies, we also found significant associations among both men and women and among American, European and Asian studies and there was no evidence of a difference between the summary estimates for these subgroups, confirming the importance of body weight control for pancreatic cancer prevention in diverse populations and among both genders. Two pooled analyses (64;65) and a meta-analysis (3) have previously reported somewhat stronger associations among women than among men, while our meta-analysis and another pooled analysis (66) showed similar results in men and women. The difference between our findings and the previous analyses may relate to the larger number of studies now available and therefore more statistical power to detect an association also among men. In addition, a higher percentage of men than women were current or former smokers in one of the pooled analyses (65), thus residual confounding from smoking may have to a larger

degree obscured an existing association among men than among women. In another pooled analysis, the risk estimates for a BMI≥35 were similar for men and women when excluding current and former smokers (RR=1.65, 95% CI: 0.96-2.84 for men vs. RR=1.65, 95% CI: 1.13-2.40 for women) (64). In most of the studies data on smoking was collected only at baseline and it is possible that residual confounding from changes in smoking over time still may be present in the analysis of nonsmokers, however, this would most likely result in underestimation of the association between BMI and pancreatic cancer risk.

Our meta-analysis has some limitations which may affect the interpretation of the results. The main limitation is the low number of cohort studies available reporting on waist circumference and waist-to-hip ratio which limited our possibility to conduct subgroup and sensitivity analyses of these measures (including stratification by smoking status). In addition, we were not able to investigate whether the association between abdominal fatness and pancreatic cancer risk was independent of BMI because of the few studies that had explored this question. It is possible that the positive association between BMI or abdominal fatness and pancreatic cancer risk could be due to unmeasured or residual confounding by other lifestyle factors, such as lower physical activity or dietary factors. The results persisted when stratified by adjustment for physical activity, diabetes and smoking and also when restricted to never smokers. Diabetes may, however, also be considered an intermediate variable since BMI partly could increase pancreatic cancer risk through an effect on diabetes, but from our subgroup analyses it seems that there is still an association between higher BMI and increased pancreatic cancer risk which is independent of diabetes. Overweight and obesity is typically associated with unhealthy diets but very few studies adjusted for intake of alcohol, red meat, fruit and vegetables and energy intake, thus these subgroup analyses are difficult to interpret. Measurement errors in the assessment of height and weight may have influenced our results. Most of the studies relied on self-reported height and weight, and although there may be some

underreporting of weight and overreporting of height, most studies have found a high correlation between self-reported and measured height and weight (67;68). In addition, the results were very similar when studies were stratified by whether weight and height was measured or self-reported, lending further credibility to self-reported anthropometric measures. Weight was collected at baseline and not during follow-up in most of the studies, thus it is possible that these measures may not reflect usual adult weight so there may be some misclassification of long-term exposure. Pancreatic cancer is usually diagnosed in the later stages and is frequently associated with profound weightloss, thus it is also possible that use of baseline data in this case may provide more valid results than if the data were updated through follow-up because of less influence of prediagnostic weightloss. The subgroup analyses of BMI and pancreatic cancer among non and never and ever smokers were based on a limited number of studies and we can therefore not rule out the possibility that some degree of reporting bias may be present (e.g. more studies that found a difference between smokers and non smokers reported stratified results than studies which did not find a difference) and may have led to exaggerated findings in this subgroup. Nevertheless, a pooled analysis also reported stronger results among never smokers compared than among smokers (64), thus reporting bias is not likely to be the sole explanation for this finding. Although meta-analyses of published literature may be susceptible to small study effects, we found no evidence of small study effects with either Egger's test or with Begg's test or when visually inspecting the funnel plots.

Our meta-analysis also has several strengths. Because we based our analysis on prospective studies, recall bias and selection bias are not likely to explain our findings. In addition, prospective studies avoid the reliance on use of proxy respondents which have been used extensively in case-control studies of pancreatic cancer due to the poor survival rates. Our meta-analysis included a large number of cohort studies with relatively long follow-up

and included 9504 cases among 5037555 participants in the BMI analysis, so we had statistical power to detect moderate or weak associations. We also had statistical power to detect significant associations in various subgroups of populations including men and women, Asian, American and European studies, by duration of follow-up and number of cases. The results were generally robust to the influence of single studies. In addition, we investigated whether reverse causation (e.g. prediagnostic disease might have influenced BMI) could have biased the results by restricting the analyses to studies which excluded early follow-up, however, the risk estimates were similar in these analyses. Further, we explored, to our knowledge for the first time in a meta-analysis, a nonlinear association between BMI, waist circumference and waist-to-hip ratio and pancreatic cancer. Our results underscore the importance of body weight control in pancreatic cancer prevention in diverse populations and irrespective of gender, but they suggest that avoiding abdominal fatness also may be important. In addition, with decreasing prevalence of smoking in several populations it is important that future epidemiological studies report more detailed results (e.g. stratified by smoking status), both to avoid selective reporting of results and to avoid residual confounding which can result in underestimation of the impact of body fatness on pancreatic cancer risk.

In summary, our meta-analysis, which is the most up to date review of the evidence, confirms the hypothesis that increased BMI and abdominal obesity are associated with increased pancreatic cancer risk. The association between elevated BMI and increased pancreatic cancer risk is observed in both men and women and in North American, European and Asian studies. A nonlinear association is observed in the overall analysis with increased risk above a BMI of 25, but most pronounced above a BMI of 35, however, in analyses restricted to non smokers there is evidence of increased risk even among persons in the "normal" range of BMI (21<25). Thus, our results provide further support for previous

recommendations to be as lean as possible within the normal range of BMI, but also suggest that avoiding abdominal obesity is likely to be important in the prevention of pancreatic cancer.

Contributors

V.J. Burley, J. Cade, and the systematic literature review team at the University of Leeds conducted the search, data selection and data extraction up to December 2005. R. Vieira was responsible for developing and managing the database for the Continuous Update Project. D. Aune did the updated literature search, data extraction, study selection, statistical analyses and wrote the first draft of the original manuscript. DC Greenwood was expert statistical advisor and contributed towards the statistical analyses. All authors contributed to the revision of the manuscript. T. Norat is the PI of the Continuous Update Project.

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Conflict of interest: The authors declare that there are no conflicts of interest.

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Table 1: Subgroup analyses of BMI and pancreatic cancer

		BMI				
		n	RR (95% CI)	I^2 (%)	P_h [1]	P_h [2]
All studies		23	1.10 (1.07-1.14)	19.3	0.20	
Sex						
Men		14	1.13 (1.04-1.22)	45.6	0.03	0.76
Women		15	1.10 (1.04-1.16)	41.8	0.05	
Assessment of weight/height						
Measured		7	1.11 (1.07-1.15)	0	0.58	0.90
Self-reported		14	1.12 (1.05-1.20)	40.2	0.06	
Measured and self-reported		2	1.07 (0.95-1.21)	0	0.49	
Duration of follow-up						
<10 yrs follow-up		11	1.09 (1.03-1.15)	38.6	0.09	0.42
≥10 yrs follow-up		12	1.12 (1.08-1.17)	0	0.65	
Geographic location						
Europe		10	1.10 (1.06-1.15)	0	0.60	0.96
America		10	1.10 (1.03-1.17)	45.0	0.06	
Asia		3	1.15 (1.08-1.22)	0	0.55	
Number of cases						
Cases <299		14	1.15 (1.09-1.22)	0	0.59	0.14
Cases 300<500		5	1.07 (0.99-1.16)	45.5	0.12	
Cases ≥500		4	1.09 (1.04-1.14)	40.1	0.17	
Smoking status						0.16
Never/non smoker		5	1.11 (1.04-1.17)	0	0.55	
Ever smoker		4	1.03 (0.95-1.10)	0	0.93	
Adjustment for confounders						
Alcohol	Yes	4	1.14 (0.96-1.37)	0	0.56	0.70
	No	19	1.10 (1.06-1.14)	28.1	0.12	
Smoking	Yes	19	1.11 (1.06-1.17)	29.5	0.20	0.50
	No	4	1.09 (1.04-1.14)	0	0.76	
Diabetes	Yes	12	1.12 (1.05-1.20)	46.8	0.04	0.87
	No	11	1.11 (1.07-1.14)	0	0.78	
Physical activity	Yes	4	1.26 (1.09-1.46)	16.8	0.31	0.03
	No	19	1.09 (1.06-1.12)	0	0.48	
Red, processed meat	Yes	2	0.96 (0.86-1.07)	0	0.69	0.03

	No	21	1.11 (1.08-1.14)	4.7	0.40	
Fruit and vegetables	Yes	1	1.06 (0.65-1.70)			0.86
	No	22	1.10 (1.07-1.14)	22.9	0.16	
Energy intake	Yes	3	1.10 (0.89-1.36)	84.6	0.002	0.58
	No	20	1.10 (1.07-1.14)	0	0.81	

n denotes the number of risk estimates [1] P for heterogeneity within each subgroup,
[2] P for heterogeneity between subgroups with meta-regression analysis

Supplementary Table 1: Prospective studies of body mass index, waist circumference and waist-to-hip ratio and pancreatic cancer incidence

Author, publication year, country/ region	Study name	Follow-up period	Exclusion of early follow-up	Study size, gender, age, number of cases	Assessment of weight and height	Exposure	Description of quantiles of categories
Andreotti G et al, 2010, USA	Agricultural Health Study	1993/97 – 2005, 10 years follow-up	No	39628 men and 28319 women, age <40-70 years: 45/21 cases	Self-reported	BMI, men BMI, women	18.5-24.9 25-29.9 30-34.9 Per 1 unit 18.5-24.9 25-29.9 30-34.9 Per 1 unit
Stevens RJ et al, 2009, UK	The Million Women Study	1996/2001 - 2006/2007, 7.2 years follow-up	Yes, first 2 and first 4 years excluded in sensitivity analyses	1290000 women, age 50-64 years: 1338 cases	Self-reported	BMI BMI, all data BMI, excluding first 2 years of follow-up BMI, excluding first 4 years of follow-up	<22.5 22.5<25.0 25.0<27.5 27.5<30.0 30.0<32.5 ≥32.5 ≥25 vs. <25 ≥25 vs. <25 ≥25 vs. <25
Reeves GK et al, 2007, UK	The Million Women Study	1996/2001 – 2003/2004, 5.4 years follow-up	Yes, first 2 years excluded in sensitivity analyses	1222630 women, age 50-64 years: 305 cases (never smokers)	Self-reported	BMI, never smokers BMI, excluding first 2 years of follow-up	Per 10 units Per 10 units
Johansen D et al, 2009, Sweden	The Malmo Preventive Project	1974/1992 – 2004, 22.1 years follow-up	No	33346 men and women, mean age 50/44 years: 187 cases	Measured	BMI	<20 20<25 25<30 ≥30 Per 1 unit
Meinhold CL et al, 2009, Finland	ATBC Cancer Prevention Study	1985/88 – 2004, 19.4 years follow-up	Yes, first 5 years excluded in sensitivity analyses (not shown)	27035 smoking men, age 50-69 years: 305 cases	Measured	BMI	23.1 27.0 31.5 36.9 Continuous
Luo J et al, 2008, USA	Women's Health Initiative	1993/98-2005, 7.7 years follow-up	Yes, first 2 years excluded in senstivity analyses	138503 women, age 50-79 years: 251 cases	Measured	BMI Waist circumference	<22.0 22-24.9 25-29.9 30-34.9 ≥35.0 70.5 cm 78.0 85.0 92.4 105.0 Per 10 cm

						WHR WHR, excluding first 2 years	0.72 0.77 0.80 0.84 0.91 Per 0.1 units 0.91 vs. 0.72
Jee SH et al, 2008, Korea	National Health Insurance Corporation Study	1992/95 - , 10.8 years follow-up	Yes, first 2 years excluded in analyses, first 5 years excluded in sensitivity analyses (not shown)	1213829 men and women, age 30-95 years: 1860/791 cases	Measured	BMI, men BMI, women	<20.0 20-22.9 23.0-24.9 25.0-29.9 ≥30.0 <20.0 20-22.9 23.0-24.9 25.0-29.9 ≥30.0
Stolzenberg-Solomon R et al, 2008, USA	NIH-AARP Diet and Health Study	1995/96 – 2000, ~5 years follow-up	Yes, first year excluded in analysis	495035 men and women, age 50-71 years: 654 cases	Self-reported	BMI BMI, never smokers or former smoker quit 10+ yrs ago BMI, current or former smoker quit <10 yrs ago Waist, men WHR Waist, women WHR	18.5<25.0 25.0-29.9 30.0-34.9 ≥35 Per unit 18.5<25.0 25.0-29.9 30.0-34.9 ≥35 Per unit 18.5<25.0 25.0-29.9 30.0-34.9 ≥35 Per unit <88.9 cm 88.9<93.3 93.3<98.4 98.4<106.0 ≥106.0 <0.90 0.90<0.93 0.93<0.96 0.96<1.00 ≥1.00 <74.9 cm 74.9<83.2 83.2<92.1 ≥92.1 <0.76 0.76<0.81 0.81<0.86 ≥0.86
Luo J et al, 2007, Japan	Japan Public Health Center-based Prospective Study	1990 - 2003 1993 – 2003, 11.7 years follow-up	Yes, first 4 years excluded in sensitivity analyses	47499 men and 52171 women, age 40-69 years: 128/96 cases	Self-reported and measured in subset (32470 participants)	BMI, men BMI, men, excluding first 4 years BMI, women BMI, men, excluding	14-<21 21-<25 25-40 25-40 vs. 14-<21 14-<21 21-<25 25-40 25-40 vs. 14-<21

						first 4 years	
Nothlings U et al, 2007, USA	Multiethnic Cohort Study	1993/96 – 2002, 7.5 years follow-up	Yes, first 2 years excluded in sensitivity analyses (not shown), results reported to be similar	77255 men and 90175 women, age 45-75 years: 237/235 cases	Self-reported	BMI, men BMI, women BMI, men, never smokers BMI, women, never smokers BMI, men, ever smokers BMI, women, ever smokers	<25 25<30 ≥30 <25 25<30 ≥30 <25 25<30 ≥30 <25 25<30 ≥30 <25 25<30 ≥30
Verhage BA et al, 2007, Netherlands	Netherlands Cohort Study	1986-1999, 13.3 years follow-up	Yes, first 2 and 5 years excluded in sensitivity analyses (not shown), results reported to be similar	Case-cohort: 4774 men and women, age 55-69 years: 446 cases	Self-reported	BMI, men BMI, women	<23 23<25 25<27 27<30 ≥30 Per unit <23 23<25 25<27 27<30 ≥30 Per unit
Samanic C et al, 2006, Sweden	The Swedish Construction Worker's Study	1971-1999, 19 years follow-up	Yes, stratified analyses by <5, 5-9.9, 10-14.9 and ≥15 years follow-up (not shown), results reported to be similar	362552 men, age 18-67 years: 698 cases 147881 Never-smokers: 126 cases	Measured	BMI BMI, never smokers	25.0 25.0-29.9 ≥30.0 25.0 25.0-29.9 ≥30.0
Berrington de Gonzalez AB et al, 2006, Europe (EPIC)	European Prospective Investigation into Nutrition and Cancer	1991/2000 – 2004, 6.5 years follow-up	Yes, first 2 years excluded in sensitivity analyses	438405 men and women, age 19-84 years: 324 cases	Measured and self-reported	BMI BMI, excluding first 2 years of follow-up Waist circumference	<20 20-22.9 23-24.9 25-26.9 27-29.9 30-34.9 ≥35.0 per 5 kg/m^2 per 5 kg/m^2 <88/<73 cm m/w 88-94/73-79 94-101/79-88 ≥101/≥88

						Waist circumference, excluding first 2 years of follow-up WHR WHR, excluding first 2 years of follow-up	per 10 cm per 10 cm 0.90/0.75 m/w 0.90-0.94/0.75-0.79 0.94-0.98/0.79-0.84 ≥0.98/≥0.84 per 0.1 units per 0.1 units
Lukanova A et al, 2006, Sweden	Northern Sweden Health and Disease Cohort	1985-2003, 8.2 years follow-up	Yes, first year excluded in sensitivity analyses (not shown), results reported to be similar	33424 men and 35362 women, age 29-61 years: 24/41 cases	Measured	BMI, men BMI, women	18.5-23.4 23.5-25.3 25.4-27.6 18.5-22.1 22.2-24.2 24.3-27.0 ≥27.1
Patel AV et al, 2005, USA	Cancer Prevention Study 2 – Nutrition Cohort	1992-1999, 7 years follow-up	Yes, first 2 years excluded in sensitivity analyses (not shown)	145627 men and women, age 50-74 years: 242 cases	Self-reported	BMI	<25 25-30 ≥30
Sinner PJ et al, 2005, USA	Iowa Women's Health Study	1986-2001, 15 years follow-up	Yes, first 2 years excluded in sensitivity analyses (not shown)	38002 women, age 55-69 years: 209 cases	Self-reported	BMI WHR	<25.0 25.0-29.9 ≥30 0.335-0.7951 0.7952-0.8693 0.8694-2.8361
Larsson SC et al, 2005, Sweden	Swedish Mammography Cohort Study	1997-2004, 6.8 years follow-up	Yes, first year excluded in sensitivity analyses (not shown)	37147 women, mean age 62 years: 61 cases	Self-reported	BMI Waist circumference	<20.0 20.0-24.9 25.0-29.9 ≥30 Per 1 unit <76 cm 76-81 82-89 ≥90 Per 20 cm
Larsson SC et al, 2005, Sweden	Cohort of Swedish Men	1997-2004, 6.8 years follow-up	Yes, first year excluded in sensitivity analyses (not shown)	45906 men, mean age 60 years: 75 cases	Self-reported	BMI Waist circumference	<20.0 20.0-24.9 25.0-29.9 ≥30 Per 1 unit <90 90-94 95-101 ≥102 Per 20 cm
Kuriyama S et al, 2005, Japan	Miyagi Prefecture Cohort Study	1984 – 1992, 7.6 years follow-up	No	12485 men and 15054 women, age ≥40 years: 31/33	Self-reported	BMI, women BMI, men	18.5-24.9 25-27.4 27.5-29.9 18.5-24.9 25-27.4 27.5-29.9

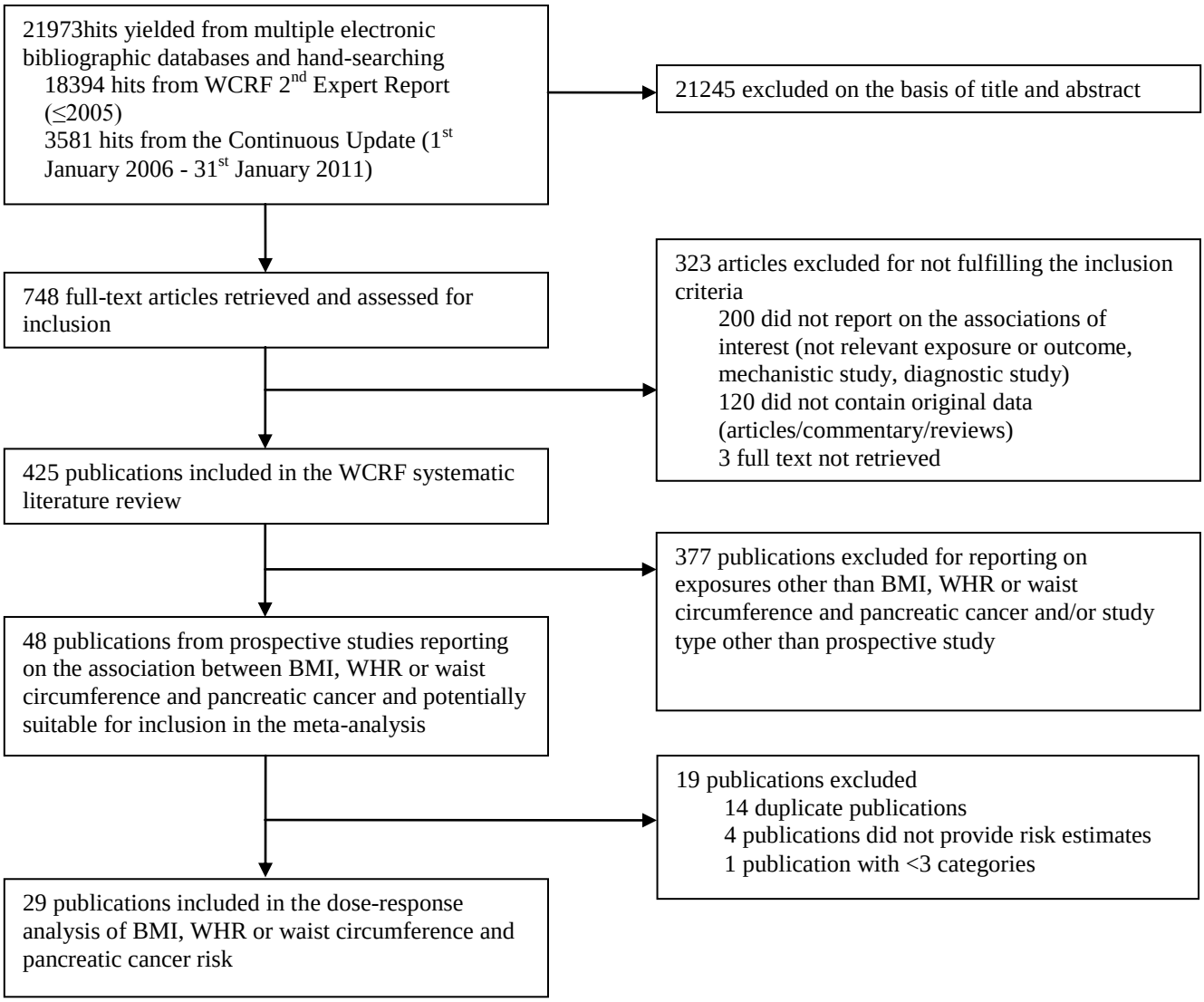
				cases			
Rapp K et al, 2005, Austria	The Vorarlberg Health Monitoring and Promotion Program	1985/2001 – 2002, 9.9 years follow-up	Yes, first year excluded in analysis	67447 men and 78484 women, mean age 42 years: 64/65 cases	Measured	BMI, men BMI, women	18.5-24.9 25.0-29.9 ≥30 18.5-24.9 25.0-29.9 ≥30
Isaksson B, 2002, Sweden	Cohort of Swedish Twins	1961/1967 – 1997, 16 years follow-up	No	21884, median age 56 years: 176 cases	Self-reported	BMI	18.5 18.5-24.99 25-30 ≥30
Michaud DS et al, 2001, USA	Nurses' Health Study	1976-1996, 20 years follow-up	Yes, first 4 years excluded in sensitivity analyses	117041 women, age 30-55 years: 210 cases	Self-reported	BMI BMI, excluding first 4 years of follow-up	<23.0 23.0-24.9 25.0-26.9 27.0-29.9 ≥30.0 ≥30.0 vs. <23.0
Michaud DS et al, 2001, USA	Health Professionals Follow-up Study	1986-1998, 12 years follow-up	Yes, first 4 years excluded in sensitivity analyses	46648 men, age 40-75 years: 140 cases	Self-reported	BMI BMI, excluding first 4 years of follow-up	<23.0 23.0-24.9 25.0-26.9 27.0-29.9 ≥30.0 ≥30.0 vs. <23.0
Shibata et al, 1994 California, USA	Leisure World Cohort Study	1981/1985 – 1990, 7.2 years follow-up	No	13979 elderly persons, mean age 75/74 years men/women: 65 cases	Self-reported	BMI	Low Medium High
Friedman et al, 1993, USA	Multiphase Check-up Study	1964-1988, ≈12 years follow-up	No	Nested case-control study: 452 cases 2687 controls Age 15-94 years	Measured	BMI	Per 1 unit

Supplementary Table 2: Prospective studies of body mass index and pancreatic cancer mortality

Author, publication year, country/ region	Study name	Follow-up period	Exclusion of early follow-up	Study size, gender, age, number of cases	Assessment of weight and height	Exposure	Description of quantiles of categories
Nakamura K et al, 2011, Japan	Takayama study	1992-1999, 6.9 years follow-up	No	30826, age ≥35 years: 33/19 m/f deaths	Self-reported	BMI, men BMI, women	21.3 >21.3-23.6 >23.6 20.7 >20.7-23.0 >23.0
Arnold LD et al, 2009, USA	Cancer Prevention Study 2	1984-2004, 20 yrs follow-up	Yes, first 2 years excluded	48525 blacks: 360 deaths 1011864 whites: 5883 deaths Age ≥45 yrs	Self-reported	BMI, blacks BMI, whites	<18.5 18.5<25.0 25.0<30.0 ≥30.0 <18.5 18.5<25.0 25.0<30.0 ≥30.0
Batty GD et al, 2009, UK	The Whitehall Study	1967/70 –, up to 38 yrs follow-up	No	17898 men, age 40-69 years: 163 deaths	Measured	BMI	1 2 3 Per 2.98 units
Stevens RJ et al, 2009, UK	The Million Women's Study	1996/2001 - 2006/2007, 8.9 years follow-up	No	1290000 women, age 50-64 years: 1710 deaths	Self-reported	BMI	<22.5 22.5<25.0 25.0<27.5 27.5<30.0 30.0<32.5 ≥32.5
Lin Y et al, 2007, Japan	Japanese Collaborative Cohort Study	1988/1990 – 2003, 12.8 years follow-up	Yes, first 3 years excluded in sensitivity analyses (not shown)	100932 men and women, age 40-79 years: 402 deaths	Self-reported	BMI, men BMI, women	<20.0 20.0-22.4 22.5-24.9 25.0-27.4 27.5-29.9 ≥30.0 <20.0 20.0-22.4 22.5-24.9 25.0-27.4 27.5-29.9

							≥30.0
Lee IM et al, 2003, USA	The College Alumni Health Study	1962 or 1966 – 1995, up to 34 years follow-up	No	32687: 212 deaths 1962-1995 men and women	Self-reported	BMI	<22.5 22.5<25.0 25.0<27.5 ≥27.5
Gapstur SM et al, 2000, USA	The Chicago Heart Association Detection Project in Industry Study	1967/73 – 1995, 25 years follow-up	Yes, first 5 years excluded in sensitivity analyses (not shown)	20475 men: 96 deaths 15183 women: 43 deaths Age 15-90 years (mean 40)	Measured	BMI BMI, men BMI, women	1 2 3 4 ≤24.128 24.129-26.292 26.293-28.630 ≥28.631 ≤20.977 20.978-23.240 23.241-26.156 ≥26.157

Figure 1. Flow-chart of study selection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3581 hits from the Continuous Update (1st January 2006 - 31st January 2011)
21245 excluded on the basis of title and abstract
748 full-text articles retrieved and assessed for inclusion
323 articles excluded for not fulfilling the inclusion criteria
200 did not report on the associations of interest (not relevant exposure or outcome, mechanistic study, diagnostic study)
120 did not contain original data (articles/commentary/reviews)
3 full text not retrieved
425 publications included in the WCRF systematic literature review
377 publications excluded for reporting on exposures other than BMI, WHR or waist circumference and pancreatic cancer and/or study type other than prospective study
48 publications from prospective studies reporting on the association between BMI, WHR or waist circumference and pancreatic cancer and potentially suitable for inclusion in the meta-analysis
19 publications excluded
14 duplicate publications
4 publications did not provide risk estimates
1 publication with <3 categories
29 publications included in the dose-response analysis of BMI, WHR or waist circumference and pancreatic cancer risk

Figure 2. BMI and pancreatic cancer incidence, linear (per 5 BMI units) and nonlinear dose-response analyses

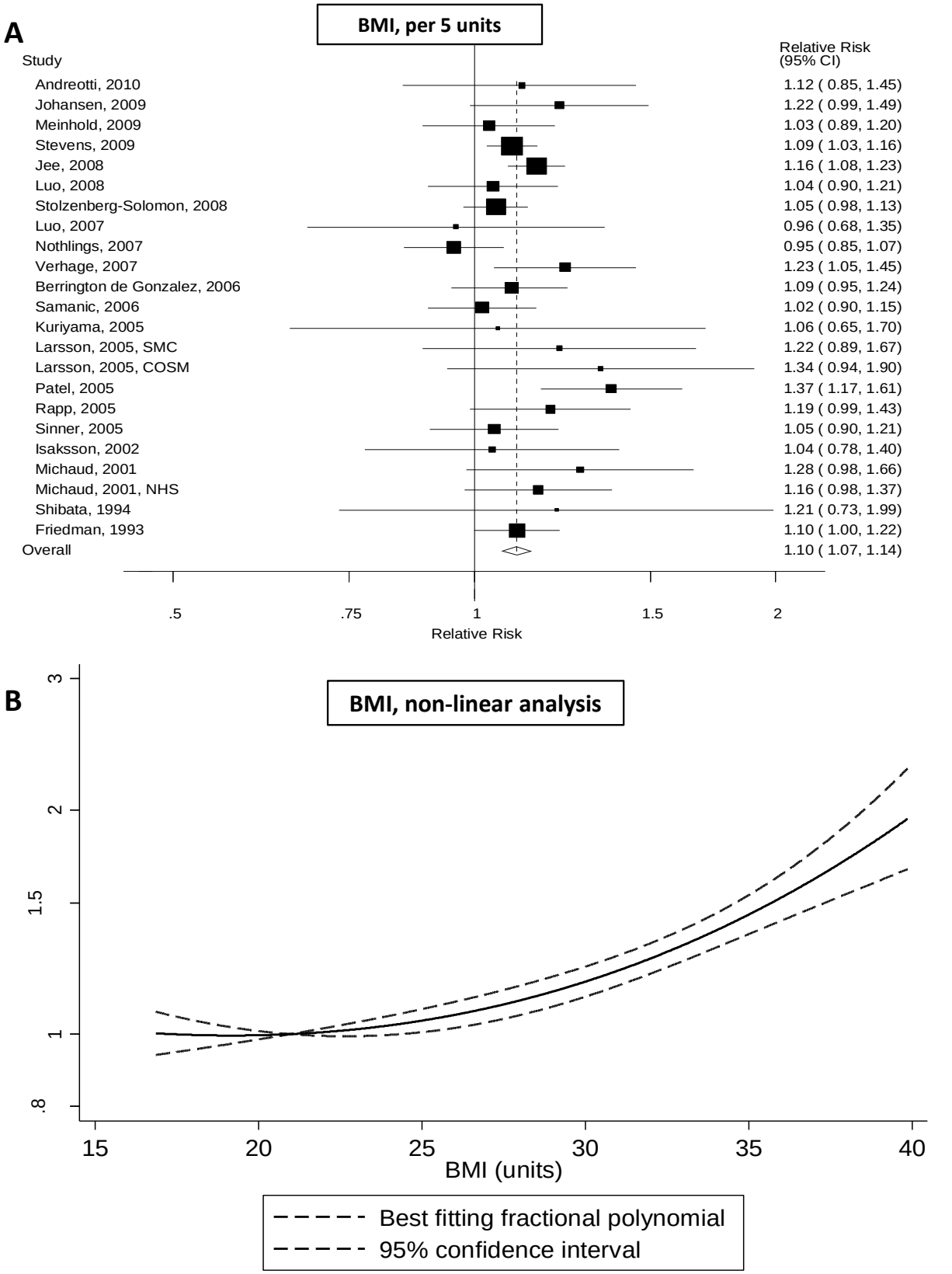

Figure 3: BMI stratified by smoking status, waist circumference and waist-to-hip ratio and pancreatic cancer incidence, nonlinear dose-response analysis

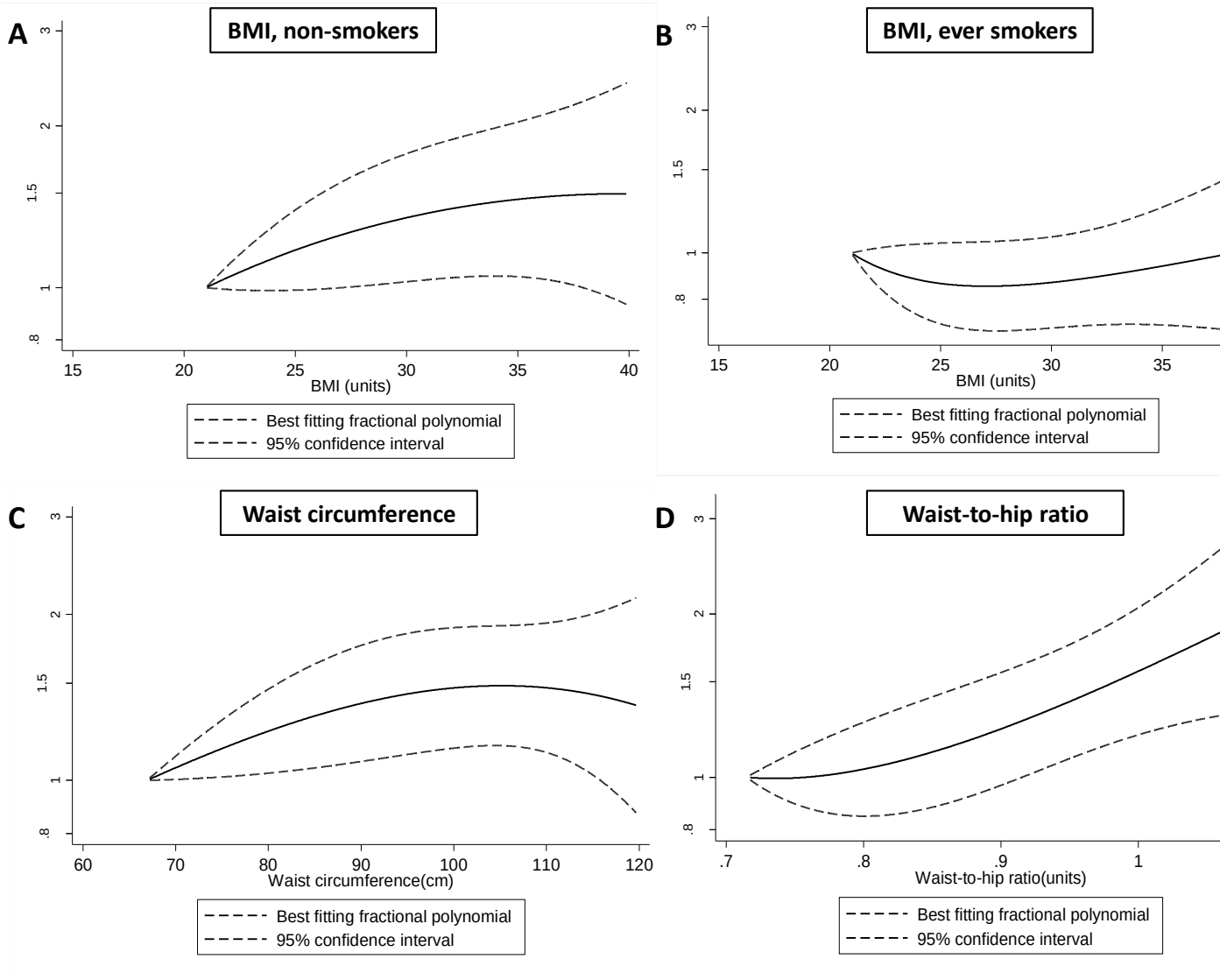

Figure 4: BMI and pancreatic cancer mortality, linear (per 5 units) and nonlinear dose-response analyses

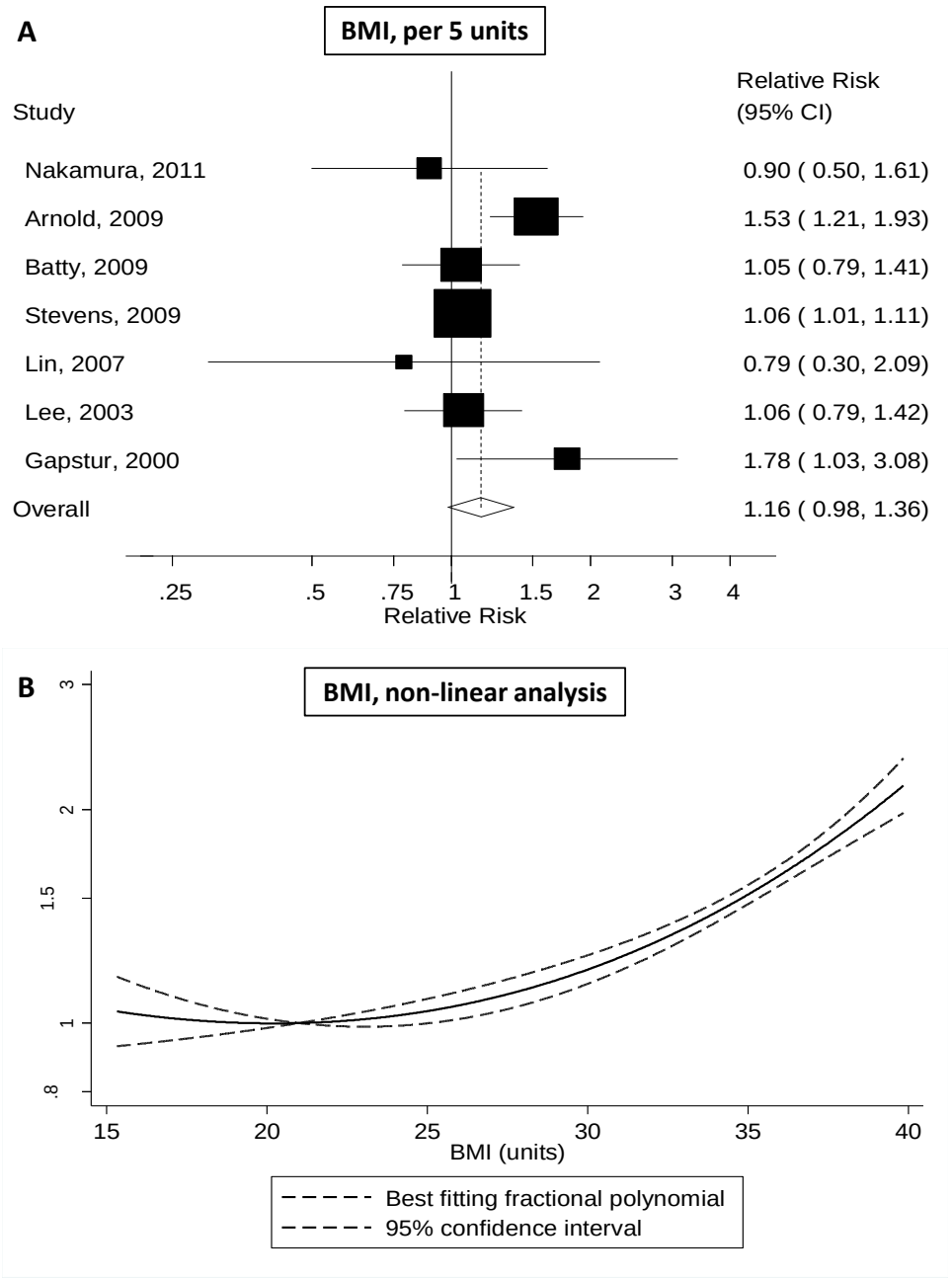

Figure 5: Waist circumference and waist-to hip ratio and pancreatic cancer incidence, linear dose-response analysis