Body mass index and risk of gastric cancer: A 30-year follow-up study in the Linxian general population trial cohort

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Although a number of previous studies have noted either positive or no association for body mass index (BMI) and gastric cancer risk, little evidence exists in the Chinese population. We prospectively examined the associations of BMI with risk of gastric cancer in the Linxian General Population Trial cohort, with 29 584 healthy adults enrolled in 1985 and followed through to the end of 2014. Body weight and height were measured during physical examination at baseline and BMI was calculated as weight in kilograms divided by height in meters squared. Body mass index from 138 subjects was missing, and a total of 29 446 participants were included in the final analysis. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals. During 30 years of follow-up, we confirmed 1716 newly diagnosed gastric cardia adenocarcinoma (GCA) cases and 626 new gastric non-cardia adenocarcinoma (GNCA) cases. Overall, compared to the lowest quartile (BMI <20.32 kg/m^2), subjects in the fourth quartile (BMI ≥23.31 kg/m^2) subjects had lower risk of developing GNCA (hazard ratio, 0.65; 95% confidence interval, 0.51–0.83). Age- and sex-specific analyses showed that this protective effect was only observed in men and older (52 + years) persons. No associations were observed for BMI with GCA incidence. Higher BMI was associated with decreased risk of GNCA in this population, particularly in men and older persons. Future studies are needed to confirm these findings. The trial is registered with ClinicalTrials.gov: NCT00342654.

Gastric cancer is a major health concern and ranked as the third leading cause of cancer death worldwide in 2012, causing an estimated 723 000 deaths.[1] Nearly 45% of the world's gastric cancers occur in China.[1] Within Lin County (Linxian) and the surrounding Taihang Mountain region in north central China, rates of upper gastrointestinal cancers are particularly high and account for over 20% of all deaths.

Over the past few decades, several risk factors for gastric cancer have been identified, including *Helicobacter pylori* infection,[2] smoking,[3] alcohol use,[4] and micronutrient deficiency.[5] Despite abundant epidemiological studies focused on the association between excess body weight and risk of gastric cancer, results have been inconclusive.[6–12] A number of studies showed increased risk for obesity[6–11] while others suggested no risk.[12] Prospective cohort[6,8] and case–control[9,13,14] studies found obesity was associated with risk of gastric cardia adenocarcinoma (GCA), but not with gastric non-cardia adenocarcinoma (GNCA). Most studies of body size and gastric cancer were undertaken in populations from Europe and North America where obesity is particularly common. It is still unknown whether the findings of these studies can be extrapolated to Asian populations.

The present study examined the associations between body mass index (BMI) and risk of GCA and GNCA in the Linxian general population trial cohort in China.

Materials and Methods

Study population. Detailed information on the Linxian general population trial cohort has been reported in previous studies.[15,16] Briefly, the general population trial enrolled individuals from the general population of four communes in northern Linxian. Potential participants were eligible if they were between the ages of 40 and 69 years, lived in one of the four communes, and provided written informed consent. A total of 29 584 healthy adults were randomized and received one of eight daily vitamin/mineral supplement combinations according to a one-half replicate of a 2^4 fractional factorial design for 5.25 years, beginning in March 1986.

Data collection. Data on demographic characteristics and lifestyle factors were obtained using a standard questionnaire at baseline. All participants had their weight and height measured by trained staff. Body weight and height were measured while subjects were not wearing shoes, using a standard protocol. Body mass index was then calculated as weight in kilograms divided by height in meters squared. Smoking (including ever or current smokers) was defined as regular cigarette or pipe use for at least 6 months, and alcohol use was defined as any alcohol consumption in the past 12 months. Family history of any cancer was considered positive if a cancer was reported in

at least one-first-degree relative. We also collected information on previous chronic disease at baseline including heart disease, stroke, cirrhosis, and diabetes mellitus.

Follow-up for cancer. During the trial period (1986–1991), village doctors visited all participants monthly, and all end-points were confirmed by an International End-points Review Committee consisting of American and Chinese experts in cytology, pathology, surgery, and radiology. During the post-trial follow-up periods (after 1991), village doctors continued to visit all participants monthly, and new cancer cases and deaths were verified by a panel of Chinese experts. All gastric cardia cancers were adenocarcinomas that occurred in the proximal 3 cm of the stomach and the gastroesophageal junction, and gastric non-cardia cancers were adenocarcinomas located more distally.

Statistical analysis. Body mass index was divided into four categories based on quartiles: <20.32, ≥20.32 to <21.76, ≥21.76 to <23.31, and ≥23.31. International standard categories for BMI (<18.5, 18.5–25.0, 25.0–30.0, and ≥30.0) were used in sensitivity analyses. Participants were censored at their last known follow-up date, date of death, or December 31, 2014, whichever occurred first. Frequency and percentage for demographic characteristics were calculated by BMI category. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for associations between baseline BMI and risk of GCA and GNCA. Crude and adjusted HRs were estimated using participants with a BMI <20.32 kg/m^2 as the reference group. Potential confounders included age at baseline (continuous variable), sex (male or female), smoking (yes or no), alcohol use (yes or no), education (never, less than 5 years, primary school, tertiary high school or higher education, others), and family history of cancer (positive defined as cancer in at least one-first-

degree relative or negative). Subgroup analyses were carried out by age at baseline (<52 or ≥52 years, based on the median age of members of the cohort at baseline), sex (male or female), smoking (yes or no), drinking (yes or no), and family history of cancer (yes or no).

Sensitivity analyses were also undertaken by excluding subjects who were smokers or drinkers or patients with pre-existing chronic disease or were followed up for less than 3 years. To address the possibility of residual confounding by measured variables, we further adjusted for a propensity score that reflected associations of BMI with the other variables in the Cox regression model.

The shape of the association between BMI and risk of gastric cancer was explored using BMI as a continuous variable in the Cox proportional hazards regression models. We also fit continuous models with the addition of a square term to investigate possible non-linear associations. All statistical analyses were carried out using SAS software (version 9.2; SAS Institute, Cary, NC, USA). All tests were two-sided and associations were considered significant for P-values less than 0.05.

Ethical approval. This study was approved by the Institutional Review Boards of the US NIH and the Chinese Academy of Medical Science. All participants gave written informed consent for the use of their blood samples and all data.

Results

A total of 29 446 individuals were included in the final analysis. During 583 070 person-years of follow-up, we identified 1716 incident GCA cases and 626 GNCA cases, and approximately 1% of participants were lost to follow-up. Compared with the lowest quartile (BMI <20.32), subjects with BMI

Table 1. Baseline demographic characteristics by body mass index (BMI) in the Linxian general population trial cohort

	BMI			
	Q1 (<20.32)	Q2 (≥20.32 to <21.76)	Q3 (≥21.76 to <23.31)	Q4 (≥23.31)
No. of participants, n (%)	7267 (24.68)	7530 (25.57)	7304 (24.80)	7345 (24.94)
Person-years	135 276.91	149 170.89	149 526.21	149 095.76
Age, years, mean ± SD	53.67 ± 8.81	51.74 ± 8.86	50.96 ± 8.78	51.09 ± 8.75
Sex, n (%)				
Men	3122 (42.96)	3876 (51.47)	3535 (48.40)	2594 (35.32)
Women	4145 (57.04)	3654 (48.53)	3769 (51.60)	4751 (64.68)
Education level, n (%)				
Never	3304 (45.47)	2734 (36.31)	2670 (36.56)	3098 (42.18)
Less than 5 years	2186 (30.08)	2530 (33.60)	2418 (33.11)	2054 (27.96)
Primary school	634 (8.72)	859 (11.41)	883 (12.09)	772 (10.51)
Tertiary high school or higher education	536 (7.38)	766 (10.17)	719 (9.84)	684 (9.31)
Others	607 (8.35)	641 (8.51)	614 (8.41)	737 (10.03)
Smoking, n (%)				
No	4977 (68.49)	4827 (64.10)	4958 (67.88)	5791 (78.84)
Yes	2290 (31.51)	2703 (35.90)	2346 (32.12)	1554 (21.16)
Alcohol drinking, n (%)				
No	5748 (79.10)	5614 (74.56)	5449 (74.60)	5721 (77.89)
Yes	1519 (20.90)	1916 (25.44)	1855 (25.40)	1624 (22.11)
Family history of cancer, n (%)				
No	4834 (66.52)	4988 (66.24)	4741 (64.91)	4748 (64.64)
Yes	2433 (33.48)	2542 (33.76)	2563 (35.09)	2597 (35.36)
BMI, kg/m^2, mean ± SD	19.13 ± 0.99	21.06 ± 0.41	22.48 ± 0.45	25.22 ± 1.81

Q, quartile.

Table 2. Crude and adjusted hazards ratios (HRs) and 95% confidence intervals (CIs) for the associations between body mass index (BMI) and gastric cardia adenocarcinoma (GCA) and gastric non-cardia adenocarcinoma (GNCA) in the Linxian general population trial cohort

	Body mass index, kg/m^2			
	Q1 (<20.32)	Q2 (≥20.32 to <21.76)	Q3 (≥21.76 to <23.31)	Q4 (≥23.31)
GCA				
No. of cases	403	481	442	390
Crude HR (95% CI)	1.00	1.08	0.99	0.87
		(0.95–1.23)	(0.86–1.13)	(0.76–1.00)
Age- and sex-adjusted HR (95% CI)	1.00	1.07	1.02	1.00
		(0.93–1.22)	(0.89–1.17)	(0.87–1.45)
Multivariate adjusted HR (95% CI)†	1.00	1.07	1.02	1.01
		(0.94–1.22)	(0.89–1.17)	(0.88–1.16)
GNCA				
No. of cases	170	199	154	103
Crude HR (95% CI)	1.00	1.07	0.82	0.55
		(0.87–1.31)	(0.66–1.02)	(0.43–0.70)
Age- and sex-adjusted HR (95% CI)	1.00	1.07	0.86	0.64
		(0.87–1.32)	(0.69–1.07)	(0.50–0.82)
Multivariate adjusted HR (95% CI)†	1.00	1.07	0.86	0.65
		(0.87–1.32)	(0.69–1.08)	(0.51–0.83)

†Adjusted for age at baseline, sex, smoking, drinking, family history of cancer, and education. Q, quartile.

≥23.31 were younger (51.1 *vs* 53.7 years), more often women (64.7% *vs* 57.0%), more educated (higher education, 9.3% *vs* 7.4%), more often alcohol users (22.1% *vs* 20.9%), and less commonly smokers (21.2% *vs* 31.5%). Among the variables examined, significant differences between quartiles of BMI were observed for age at baseline, sex, smoking, alcohol drinking, education, and family history of cancer (Table 1).

Table 2 presents associations between BMI and risk of GCA and GNCA. No associations were observed for BMI and risk of GCA. In contrast, persons with BMI ≥23.31 were at reduced risk of GNCA (HR, 0.65; 95% CI, 0.51–0.83) compared with the lowest quartile (BMI <20.32). No association with GNCA risk was seen for persons in the other two BMI categories. When we used the WHO/National Heart, Lung, and Blood Institute criteria, with a BMI of 18.5–25.0 as a reference, no associations were seen for GCA risk, but HRs for GNCA were 0.99 (95% CI, 0.68–1.42) for BMI <18.5, 0.66 (0.47–0.92) for BMI 25.0–30.0, and 0.43 (0.06–3.04) for BMI ≥30.0 (Table S1). Cumulative incidence rates of GCA and GNCA were significantly different by BMI categories using WHO/National Heart, Lung, and Blood Institute criteria (Figs. S1,S2).

In subgroup analyses (Table 3), no associations between BMI and GCA were observed in subgroups defined by either sex, age, smoking, drinking, or family history of cancer. However, risk of GNCA was reduced in men, older persons, non-smokers, non-drinkers, and individuals without family history of cancer. Compared with the lowest quartile, men with BMI ≥23.31 had an adjusted HR of 0.59 (95% CI, 0.42–0.82) for GNCA. Similarly, individuals aged ≥52 years with BMI ≥23.31 had an HR of 0.56 (95% CI, 0.38–0.83) compared with the lowest quartile. Results were similar across strata of smoking, drinking, and family history of cancer (all *P*-values for interaction >0.05).

Sensitivity analyses of exclusion subjects who were smokers or drinkers or had pre-existing chronic diseases did not alter our results. We also undertook lag analyses stratified by duration of follow-up, and results showed no effect on GCA risk,

but indicated that the reduced risk of GNCA was limited to cases diagnosed 3 or more years after entry into the trial cohort, suggesting that this reduced risk was not due to pre-existing disease. Further adjustment for propensity score for BMI in Cox models did not alter our findings (Table 4).

Discussion

This study prospectively examined the association between BMI categories and risk of gastric cancer in the Linxian general population trial cohort. In this prospective study, we found a significant association between higher BMI and lower risk of GNCA incidence. Compared with the lowest quartile, subjects with BMI ≥23.31 had a lower risk of GNCA, with an HR of 0.65 (95% CI, 0.51–0.83). Sensitivity analyses that excluded smokers or patients who had previous chronic disease did not affect our findings, and lag analyses did not suggest that pre-existing disease could explain our results. Finally, no associations were observed for BMI and risk of GCA.

Overweight and obesity are reportedly associated with risk of gastric cancer. However, it is still unclear whether overweight truly elevates the risk of gastric cancer. A number of meta-analyses have revealed a positive association of BMI and risk of gastric cancer.[10–12,17,18] The largest and most recent meta-analysis to date,[18] with a population of more than 10 million subjects from 24 prospective studies, showed that neither overweight nor obesity was associated with risk of total gastric cancer. Analyses restricted to Asian populations showed a borderline significant for overweight and risk of total gastric cancer. However, when gastric cancer was examined by anatomic subcategory, increased BMI was positively associated with risk of GCA (overweight: relative risk, 1.21; 95% CI, 1.03–1.42; obesity: relative risk, 1.82; 95% CI, 1.32–2.49), although no associations were seen with GNCA. Prospective cohort studies have suggested either a positive or no association for BMI and risk of gastric cancer.[6–8,19] The NIH-AARP study,[8] with a sample size of 218 854 participants, found a

Table 3. Subgroup analyses for the associations between body mass index (BMI) and risk of gastric cardia adenocarcinoma (GCA) and gastric non-cardia adenocarcinoma (GNCA) in the Linxian general population trial cohort

	GCA				GNCA			
	Q1 (<20.32)	Q2 (≥20.32 to <21.76)	Q3 (≥21.76 to <23.31)	Q4 (≥23.31)	Q1 (<20.32)	Q2 (≥20.32 to <21.76)	Q3 (≥21.76 to <23.31)	Q4 (≥23.31)
Sex†								
Men	1.00	1.04 (0.88–1.23)	1.04 (0.88–1.23)	1.01 (0.84–1.22)	1.00	1.00 (0.78–1.30)	0.78 (0.59–1.03)	**0.59 (0.42–0.82)**
Women	1.00	1.13 (0.91–1.41)	0.98 (0.79–1.23)	1.01 (0.81–1.24)	1.00	1.20 (0.85–1.70)	1.02 (0.71–1.46)	0.74 (0.51–1.08)
Age‡								
<52 years	1.00	1.21 (0.98–1.50)	1.17 (0.95–1.44)	1.16 (0.93–1.44)	1.00	1.23 (0.87–1.72)	1.02 (0.72–1.44)	0.87 (0.60–1.27)
≥52 years	1.00	1.00 (0.84–1.18)	1.00 (0.78–1.12)	0.92 (0.76–1.11)	1.00	1.01 (0.77–1.31)	0.78 (0.58–1.05)	**0.51 (0.36–0.72)**
Smoking§								
No	1.00	1.13 (0.95–1.36)	0.99 (0.83–1.19)	1.01 (0.84–1.21)	1.00	1.20 (0.91–1.60)	0.98 (0.73–1.31)	**0.68 (0.49–0.93)**
Yes	1.00	1.00 (0.82–1.22)	1.05 (0.86–1.29)	1.01 (0.80–1.27)	1.00	0.94 (0.70–1.27)	0.74 (0.53–1.03)	**0.63 (0.43–0.95)**
Drinking¶								
No	1.00	1.07 (0.91–1.24)	0.96 (0.82–1.13)	1.07 (0.91–1.26)	1.00	1.04 (0.82–1.32)	0.88 (0.68–1.31)	**0.61 (0.46–0.82)**
Yes	1.00	1.07 (0.83–1.39)	1.17 (0.90–1.52)	0.83 (0.61–1.11)	1.00	1.16 (0.77–1.76)	0.83 (0.53–1.30)	0.77 (0.47–1.26)
Family history of cancer††								
No	1.00	0.77 (0.56–1.06)	1.04 (0.87–1.23)	1.12 (0.68–1.83)	1.00	1.04 (0.81–1.34)	0.82 (0.62–1.07)	**0.56 (0.41–0.77)**
Yes	1.00	1.24 (0.89–1.73)	0.91 (0.73–1.14)	0.81 (0.40–1.63)	1.00	1.14 (0.80–1.63)	0.95 (0.66–1.38)	0.82 (0.55–1.23)

The bold entries are considered statistically significant. †Adjusted for age at baseline, smoking, drinking, family history of cancer, and education. ‡Adjusted for age at baseline, sex, smoking, drinking, family history of cancer, and education. §Adjusted for age at baseline, sex, drinking, family history of cancer, and education. ¶Adjusted for age at baseline, sex, smoking, family history of cancer, and education. ††Adjusted for age at baseline, sex, smoking, drinking, and education. Q, quartile.

strong positive association for obesity and risk of GCA (HR, 3.67; 95% CI, 2.00–6.71). However, a population-based cohort study in Norway with 73 133 participants showed no association for BMI and risk of gastric cancer.[19] In our study, we did not find excess risk associated with higher BMI; instead, higher BMI was protective for risk of GNCA and unrelated to risk of GCA, consistent with an earlier analysis in the Linxian trial cohort.[20] In this previous study, BMI was divided into four groups: <20 (reference), 20–21, 21–23, and ≥23, and an inverse association was observed for risk of GNCA among individuals with BMI ≥23 during 15 years of follow-up (HR, 0.68; 95% CI, 0.49–0.93). The lack of association between BMI and risk of GCA is at odds with results from several previous studies. Discrepancies between our study and these previous studies could be due to the BMI categories evaluated, the referent group used, population differences, and/or differences in variables adjusted for in the analyses.

Smoking or alcohol drinking is associated with BMI and an increased risk of gastric cancer, and can distort the association between BMI and risk of gastric cancer. We carefully adjusted our risk estimates for smoking and alcohol drinking, but model adjustment cannot fully address this confounding bias. Moreover, we excluded non-smokers or non-drinkers to perform a sensitivity analysis, and our results did not change. Additional adjustment of a propensity score that reflected associations of BMI with the other variables did not alter our findings.

Reverse causality may be a great concern in evaluating the association of BMI with risk of gastric cancer. Participants with severe chronic disease such as cancer lose weight over time.[21] In the current study, we collected information about cancer, heart disease, stroke, and diabetes at baseline, and excluded patients with these conditions as part of a sensitivity analysis, which did not alter our findings. We also carried out a lag analysis that showed that the protective effect of higher BMI was evident primarily, if not exclusively, in persons with three or more years of follow-up, which suggests that our findings were not a consequence of pre-existing disease.

A hypothesis links obesity and risk of cancer through the action of three hormonal systems, including the insulin and insulin-like growth factor axis, adipokines, and sex steroids.[22,23] These metabolic biomarkers are associated with obesity, and can help modulate cellular proliferation and apoptosis. Limited evidence from previous studies suggests that higher BMI seems to protect against the occurrence of GNCA. In our study, higher BMI had a protective effect on risk of GNCA. These findings could be explained by chance, and interpretations of our results should be very cautious.

This study has several strengths, including its prospective design, long duration of follow-up (30 years), measured (as opposed to self-reported) BMI, the ability to exclude participants with previous chronic diseases, and the availability of information on numerous potential confounders.

Table 4. Sensitivity analyses of the associations between body mass index (BMI) and risk of gastric cancer in the Linxian general population trial cohort

	GCA				GNCA			
	Q1 (<20.32)	Q2 (≥20.32 to <21.76)	Q3 (≥21.76 to <23.31)	Q4 (≥23.31)	Q1 (<20.32)	Q2 (≥20.32 to <21.76)	Q3 (≥21.76 to <23.31)	Q4 (≥23.31)
All subjects								
No. of cases	403	481	442	390	170	199	154	103
Multivariate HR (95% CI)†	1.00	1.07 (0.94–1.22)	1.02 (0.89–1.17)	1.01 (0.88–1.16)	1.00	1.07 (0.87–1.32)	0.86 (0.69–1.08)	0.65 (0.51–0.83)
Exclude ever smokers								
No. of cases	228	262	238	264	88	106	89	67
Multivariate HR (95% CI)‡	1.00	1.13 (0.95–1.36)	0.99 (0.83–1.19)	1.01 (0.84–1.21)	1.00	1.20 (0.91–1.60)	0.98 (0.73–1.31)	0.68 (0.49–0.93)
Exclude ever drinkers								
No. of cases	307	344	300	309	133	141	115	74
Multivariate HR (95% CI)§	1.00	1.07 (0.91–1.24)	0.96 (0.82–1.13)	1.07 (0.91–1.26)	1.00	1.04 (0.82–1.32)	0.88 (0.68–1.31)	0.61 (0.46–0.82)
Exclude previous chronic disease								
No. of cases	393	460	429	375	163	195	143	101
Multivariate HR (95% CI)†	1.00	1.04 (0.91–1.20)	1.01 (0.88–1.16)	1.01 (0.87–1.16)	1.00	1.10 (0.89–1.35)	0.83 (0.66–1.05)	0.67 (0.52–0.87)
Exclude the first 3 years of follow-up								
No. of cases	352	428	411	351	145	177	135	92
Multivariate HR (95% CI)†	1.00	1.07 (0.93–1.23)	1.06 (0.92–1.22)	1.02 (0.88–1.19)	1.00	1.09 (0.87–1.36)	0.86 (0.68–1.09)	0.66 (0.51–0.86)
Further adjust for intake of meat, eggs, vegetables and fruits								
Multivariate HR (95% CI)¶	1.00	1.07 (0.94–1.22)	1.02 (0.89–1.17)	1.01 (0.88–1.16)	1.00	1.07 (0.87–1.32)	0.86 (0.69–1.07)	0.65 (0.51–0.83)
Adjust for propensity score for BMI								
Multivariate HR (95% CI)††	1.00	1.07 (0.94–1.22)	1.02 (0.89–1.17)	1.01 (0.88–1.16)	1.00	1.07 (0.87–1.32)	0.86 (0.69–1.08)	0.65 (0.51–0.83)

†Adjusted for age at baseline, sex, smoking, drinking, family history of cancer, and education. ‡Adjusted for age at baseline, sex, drinking, family history of cancer, and education. §Adjusted for age at baseline, sex, smoking, family history of cancer, and education. ¶Additional adjustment for dietary intake of meat, eggs, vegetables and fruits. ††Adjusted for propensity score for BMI. CI, confidence interval; GCA, gastric cardia adenocarcinoma; GNCA, gastric non-cardia adenocarcinoma; HR, hazard ratio; Q, quartile.

Our study also has several limitations. We only had a single measurement for BMI at baseline, which may have contributed to misclassification and did not permit an assessment of the weight change or rate of change. Recent studies reported that weight gain during adulthood was positively associated with risk of total or gastric cancers.[7,24] Second, esophageal adenocarcinoma and GCA are adjacent tumors, which are difficult to separate clinically. Bias due to this type of misclassification is almost certain to occur.[25] However, the virtual absence of esophageal adenocarcinomas in Linxian makes this extremely unlikely.[26] Furthermore, although we adjusted for many potential confounders, we cannot exclude the possibility of residual confounding due to unknown and unmeasured factors, such as *H. pylori* infection. As shown in previous studies, *H. pylori* infection is positively associated with risk of gastric cardia and non-cardia cancers, but inversely associated with overweight/obesity. Our findings could be affected by the status of *H. pylori* infection, but we cannot assess this confounding bias due to lack of information at baseline. Finally, we cannot rule out the play of chance as an explanation for our results. Further studies are needed to address this issue.

In conclusion, we found a significant association of higher BMI with lower risk of GNCA, but not with risk of GCA, in the Linxian general population trial cohort, even among cases occurring ≥3 years after baseline investigation. Additional studies are needed to confirm these findings in other Chinese populations.

Acknowledgments

Disclosure Statement

The authors have no conflict of interest.

References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87–108.
2 Helicobacter and Cancer Collaborative Group. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; **49**: 347–353.
3 Praud D, Rota M, Pelucchi C *et al.* Cigarette smoking and gastric cancer in the Stomach Cancer Pooling (StoP) Project. *Eur J Cancer Prev* 2016;. https://doi.org/10.1097/CEJ.0000000000000290.
4 Sjödahl K, Lu Y, Nilsen TI *et al.* Smoking and alcohol drinking in relation to risk of gastric cancer: a population-based, prospective cohort study. *Int J Cancer* 2007; **120**: 128–132.
5 Abnet CC, Corley DA, Freedman ND, Kamangar F. Diet and upper gastrointestinal malignancies. *Gastroenterology* 2015; **148**: 1234–1243. e4
6 Abnet CC, Freedman ND, Hollenbeck AR, Fraumeni JF Jr, Leitzmann M, Schatzkin A. A prospective study of BMI and risk of oesophageal and gastric adenocarcinoma. *Eur J Cancer* 2008; **44**: 465–471.
7 Merry AH, Schouten LJ, Goldbohm RA, van den Brandt PA. Body mass index, height and risk of adenocarcinoma of the oesophagus and gastric cardia: a prospective cohort study. *Gut* 2007; **56**: 1503–1511.
8 O'Doherty MG, Freedman ND, Hollenbeck AR, Schatzkin A, Abnet CC. A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH-AARP Diet and Health Study. *Gut* 2012; **61**: 1261–1268.
9 Ji BT, Chow WH, Yang G *et al.* Body mass index and the risk of cancers of the gastric cardia and distal stomach in Shanghai, China. *Cancer Epidemiol Biomarkers Prev* 1997; **6**: 481–485.
10 Lin XJ, Wang CP, Liu XD *et al.* Body mass index and risk of gastric cancer: a meta-analysis. *Jpn J Clin Oncol* 2014; **44**: 783–791.
11 Yang P, Zhou Y, Chen B *et al.* Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. *Eur J Cancer* 2009; **45**: 2867–2873.
12 Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; **371**: 569–578.
13 Zhang J, Su XQ, Wu XJ *et al.* Effect of body mass index on adenocarcinoma of gastric cardia. *World J Gastroenterol* 2003; **9**: 2658–2661.
14 Chow WH, Blot WJ, Vaughan TL *et al.* Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998; **90**: 150–155.
15 Blot WJ, Li JY, Taylor PR *et al.* Nutrition intervention trials in Linxian, China-supplementation with specific vitamin mineral combinations, cancer incidence, and disease-specific mortality in the general-population. *J Natl Cancer Inst* 1993; **85**: 1483–1492.
16 Li B, Taylor PR, Li JY *et al.* Linxian nutrition intervention trials. Design, methods, participant characteristics, and compliance. *Ann Epidemiol* 1993; **3**: 577–585.
17 Turati F, Tramacere I, La Vecchia C, Negri E. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. *Ann Oncol* 2013; **24**: 609–617.
18 Chen Y, Liu L, Wang X *et al.* Body mass index and risk of gastric cancer: a meta-analysis of population with more than ten million from 24 prospective studies. *Cancer Epidemiol Biomarkers Prev* 2013; **22**: 1395–1408.
19 Sjödahl K, Jia C, Vatten L, Nilsen T, Hveem K, Lagergren J. Body mass and physical activity and risk of gastric cancer in a population-based cohort study in Norway. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 135–140.
20 Tran GD, Sun XD, Abnet CC *et al.* Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. *Int J Cancer* 2005; **113**: 456–463.
21 Martin L, Senesse P, Gioulbasanis I *et al.* Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol* 2015; **33**: 90–99.
22 McMillan DC, Sattar N, McArdle CS. ABC of obesity. Obesity and cancer. *BMJ* 2006; **333**: 1109–1111.
23 Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004; **4**: 579–591.
24 Liu Y, Warren Andersen S, Wen W *et al.* Prospective cohort study of general and central obesity, weight change trajectory and risk of major cancers among Chinese women. *Int J Cancer* 2016; **139**: 1461–1470.
25 Lindblad M, Ye W, Lindgren A, Lagergren J. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. *Ann Surg* 2006; **243**: 479–485.
26 Fan JH, Wang JB, Qu CX *et al.* Association between oral leukoplakia and upper gastrointestinal cancers: a 28-year follow-up study in the Linxian General Population Trial. *Oral Oncol* 2014; **50**: 971–975.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Associations between body mass index (BMI) and gastric cardia and non-cardia adenocarcinomas using WHO/National Heart, Lung, and Blood Institute criteria.

Fig. S1. Kaplan–Meier cumulative incidence for gastric cardia adenocarcinoma by body mass index (BMI) categories.

Fig. S2. Kaplan–Meier cumulative incidence for gastric non-cardia adenocarcinoma by body mass index (BMI) categories.