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Measures of Adiposity Are Associated with Increased Risk of Peptic Ulcer

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Abstract

Background & Aims—Obesity is associated with systemic inflammation, alterations in the intestinal microbiome, and decreased epithelial integrity. The association between obesity and peptic ulcer has not been thoroughly investigated.

Methods—We conducted a prospective cohort study of 47,120 men enrolled in the Health Professionals Follow-up Study (mean age of 54 years at baseline). Biennially, we updated information on body mass index (BMI), physical activity, smoking, and use of non-steroidal anti-inflammatory drugs (NSAID) or aspirin. Self-reported waist and hip measurements were validated among a subsample of participants. Self-reported cases of gastric and duodenal ulcers were confirmed by medical record review. *Helicobacter pylori* status was determined from endoscopic biopsies, serum antibody measurements, and/or stool antigen assays documented in the medical record. We used Cox proportional hazards modeling to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results—We documented 272 gastric and 320 duodenal ulcers over 24 years of follow up. The multivariate-adjusted HR for gastric ulcer was 1.83 (95% CI, 1.20–2.78; P_{trend}<.01) for obese men (BMI ≥30.0 kg/m^2), compared to men with BMIs of 23.0–24.9 kg/m^2, and 1.88 (95% CI, 1.06–3.33; P_{trend}=.04) for men with waist-to-hip ratios (WHR) ≥1.00, compared to men with WHR of

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Author Contributions

HK and MRB conceived and designed the study. HK, ATC, ESH and MRB analyzed the data. ATC supervised the study. ATC, HK, ESH and MRB wrote and revised the manuscript.

0.85–0.89. Risk of duodenal ulcer was not associated with BMI (P_{trend}=.24) or WHR (P_{trend}=.68). In secondary analyses, increased BMI and WHR were each associated with increased risk of *H pylori*-negative, but not *H pylori*-positive, ulcers. The effect of BMI on ulcer risk did not change with use of aspirin or NSAID, alcohol consumption, physical activity, or smoking.

Conclusions—In a large prospective cohort of male health professionals, central and total obesity were associated with increased risk of peptic ulcer—particularly gastric and *H pylori*-negative ulcers.

Keywords

obesity; peptic ulcer disease; body mass index; waist-to-hip ratio

INTRODUCTION

Obesity is associated with increased chronic systemic inflammation, changes in gut microbiome composition[1–3], and disruption of normal epithelial barrier function in the gastrointestinal mucosa[4]. Although previous studies have identified obesity as a risk factor for gastroesophageal reflux disease (GERD) and gastric cancer[5–7], there is a paucity of data on the relationship between body mass index and peptic ulcer disease. Furthermore, prior studies are limited by small sample size, cross-sectional design, and a lack of information on important potential confounders, including aspirin and non-steroidal anti-inflammatory drug (NSAID) use[8–10].

We therefore sought to examine prospectively the association between obesity, as measured by body mass index (BMI) and waist-to-hip ratio (WHR), and the risk of gastric and duodenal ulcers, using the large, well-characterized Health Professionals Follow-Up Study (HPFS). With more than 20 years of detailed and updated information on BMI and lifestyle factors including physical activity, smoking, and aspirin and NSAID use, this cohort offered us a unique opportunity to examine the association between measures of adiposity and the risk of peptic ulcer in the context of other important risk factors.

METHODS

Study Population

The Health Professionals Follow-up Study (HPFS) is a prospective cohort of 51,529 U.S. male dentists (58%), veterinarians (20%), pharmacists (8%), optometrists (7%), osteopathic physicians (4%), and podiatrists (3%), aged 40 to 75 years at enrollment, who returned a mailed health questionnaire in 1986. Subsequently, participants returned biennial questionnaires with a follow-up rate exceeding 90%. Data on newly diagnosed medical conditions, including peptic ulcer, as well as lifestyle factors, including smoking, medication use, and physical activity, were obtained from follow-up questionnaires. The National Death Index was searched regularly for questionnaire non-respondents, which was found to have sensitivity of 98% in a comparable prospective cohort study[11].

Assessment of Measures of Adiposity

Body mass index (kg/m^2) was calculated from self-reported body weight (updated biennially) and height (reported at baseline in 1986). We used self-reported waist and hip measurements from 1987 to calculate waist-to-hip ratio and examined it according to previously defined categories (<0.85, 0.85–0.89, 0.90–0.94, 0.95–0.99, ≥1.00). The accuracies of self-reported weight and body measurements have been previously validated among a subsample of 123 men from this cohort[12]. Correlations between participant-reported values and measurements by a technician were 0.97 for weight, 0.95 for waist circumference, and 0.88 for hip circumference.

Assessment of Physical Activity

At baseline and every two years thereafter, participants were asked to report the average time per week they spent performing various physical activities, which included walking, jogging, running, cycling, swimming, tennis, squash or racquetball, yoga, yard work, and weight training. Potential responses for time spent on each activity ranged from zero to greater than 40 hours per week. Average daily stair climbing was also reported and incorporated as a measure of physical activity. Each reported activity was assigned a standardized Metabolic Equivalent (MET) score based on the energy expenditure of a 70-kilogram adult performing the activity. This value was multiplied by the duration of a participant's reported activity in hours and expressed in MET-hours per week. The MET-hours per week of all activities were then summed to derive the total amount of energy expended during physical activity for each 2-year follow-up period.

Because long-term physical activity is more likely to contribute to risk of a chronic disease like peptic ulcer, we used the cumulative average of MET-hour values across all follow-up periods for our assessment of physical activity. Consistent with a previous study[13], we categorized physical activity according to both quintiles and predefined categories (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 MET-hours/week). Within this cohort, self-reported physical activity measures have been validated among a subsample of 238 participants[14]. The correlation between past-week recall questionnaires and activity diaries were 0.42 for non-vigorous activity and 0.58 for vigorous activity.

Assessment of Aspirin/NSAID Use and Other Covariates

Assessment of aspirin and NSAID use has been previously described in this cohort[15,16]. In brief, at baseline and every two years thereafter, participants were asked to report if they used aspirin (eg. Anacin, Bufferin, Alka-Seltzer) and/or NSAIDs (eg. Advil, Motrin, Indocin, Naprosyn, Dolobid) regularly at least 2 or more times per week. This definition is consistent with prior analyses[17–21]. Beginning in 1992, aspirin assessment was expanded to include the average number of tablets used per week as well as more detailed intake frequency (in categories). Participants were instructed to convert intake of 4 baby aspirin to 1 standard tablet in their responses.

At baseline, participants reported any history of active liver disease or cirrhosis, chronic renal failure, and cardiovascular disease (myocardial infarction, coronary artery bypass grafting, stroke). Biennially, participants reported their smoking status and any new

diagnoses of periodontal disease with bone loss, which we have previously found to be associated with peptic ulcer[22]. Every four years, intake of alcohol was reported. The reproducibility and validity of alcohol consumption has been previously evaluated among 136 men from this cohort. Correlation between reported consumption on two FFQs and multiple 1-week diet records was 0.86[23]. Beginning in 1996 and updated biennially, participants reported regular use of warfarin, oral steroids, and selective serotonin reuptake inhibitors (SSRIs). Beginning in 2004, we asked participants to report if they had undergone an upper endoscopy procedure and the year of this procedure. Based on this information, we had the ability to restrict the cohort to individuals who underwent an upper endoscopy during follow-up.

Outcome Ascertainment

We have previously detailed our methods for confirming peptic ulcer[22]. In brief, participants were asked at baseline to report any prior history of peptic ulcer, including the type of ulcer (gastric or duodenal) and an approximate time of occurrence. Every two years thereafter, participants were asked to report new diagnoses of gastric or duodenal ulcer and the year of their diagnosis. Two study team members, blinded to exposure information, independently reviewed and extracted data from hospital notes, discharge summaries, endoscopy reports and pathology reports. A peptic ulcer was confirmed if an “ulcer” was explicitly stated in the medical record as being visualized in the stomach or duodenum by a treating physician during endoscopy or surgical procedure. For the participants with both a gastric and duodenal ulcer, the location of the primary ulcer was determined using ulcer size, number and/or stigmata. We further classified a peptic ulcer as complicated if it was associated with at least one of the following: (1) hospitalization for frank bleeding or anemia; (2) admission to the intensive care unit; (3) red blood cell transfusion; (4) surgery; or (5) ulcer stigmata of recent hemorrhage (active spurting, non-bleeding visible vessel, active oozing). In addition, an ulcer case was classified as *H. pylori* positive if it was associated with at least one positive *H. pylori* test on endoscopic biopsy, serum antibody measurement, and/or stool antigen assay. Participants who had at least one negative test for *H. pylori* (and no positive tests) were classified as *H. pylori* negative. If there was insufficient information in the medical record regarding *H. pylori* testing, participants were classified as having unknown *H. pylori* status. Over the 24-year follow-up period, we confirmed 632 incident ulcer cases that were located in the stomach or duodenum and documented by either endoscopy or surgery.

Statistical Analysis

At baseline, we excluded an additional 30 participants who had a history of cancer and 11 cases for whom we did not have data on BMI. Person-time for each participant was calculated from the date of return of the baseline questionnaire to the date of the first gastric or duodenal ulcer event, death from any cause, last returned questionnaire, or January 1, 2010, whichever came first. Because waist-to-hip measurements were obtained in 1987, we began this analysis with the next two-year questionnaire interval (1988). For analyses limited to cases with *H. pylori* data, we combined categories of BMI (<21, 21.0–22.9 kg/m^2) and WHR (<0.85, 0.85–0.89) due to limited sample size. We used Cox proportional hazards modeling, with time-varying variables containing the most updated information for BMI,

aspirin and NSAID use, and other covariates before each two-year interval, to compute hazard ratios (HRs) and 95% confidence intervals (CIs). We also tested for statistical heterogeneity within our analyses by calculating stratum-specific HRs and likelihood-ratios for other potential ulcer risk factors. All analyses in this study were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). All *P* values were two-sided, and $P<0.05$ was considered statistically significant.

RESULTS

Over 24 years, we documented 272 incident cases of gastric ulcer and 319 incident cases of duodenal ulcer among 47,120 men who contributed 927,223 person-years of follow-up. Based on medical record review, we categorized 82 ulcers as *H. pylori*-associated, among which 56 (68%) were also regular aspirin and/or NSAID users. For the 189 ulcers that tested negative for *H. pylori*, 137 (72%) were regular aspirin and/or NSAID users. Among the 320 ulcers with unknown *H. pylori* status, 199 (62%) were regular aspirin and/or NSAID users. At baseline, compared to men with a BMI of 23.0–24.9 k/m^2, obese men (BMI ≥30.0 m/kg^2) were more likely to have ever smoked, use aspirin and NSAIDs, have periodontal disease, and were less likely to consume alcohol (Table 1). As expected, compared to men with a BMI of 23.0–24.9 k/m^2, obese men were less physically active.

Compared to men with a BMI of 23.0–24.9 k/m^2, the age-adjusted HR of peptic ulcer was 1.46 (95% CI, 1.09–1.96; $P_{trend}<0.01$) for obese men (Table 2). This association remained unchanged even after adjustment for potential confounders including race, smoking, alcohol intake, periodontal disease, physical activity, and regular use of aspirin and NSAIDs (multivariate-adjusted HR=1.38; 95% CI, 1.03–1.86; $P_{trend}<0.01$). Obesity was more strongly associated with risk of gastric ulcer than duodenal ulcer. Compared to men with a BMI of 23.0–24.9 k/m^2, obese men had multivariate-adjusted HRs of 1.83 (95% CI, 1.20–2.78; $P_{trend}<0.01$) for gastric ulcer and 1.03 (95% CI, 0.67–1.59; $P_{trend}=0.24$) for duodenal ulcer. We observed similar results in analyses in which we examined BMI at baseline (1986) and subsequent risk of ulcer during follow-up (data not shown). In analyses restricted to the 271 cases with available *H. pylori* data, we observed that BMI was associated with *H. pylori* negative ulcer ($P_{trend}=0.01$), but not *H. pylori* positive ulcer ($P_{trend}=0.89$).

We next evaluated the relationship between obesity and risk of complicated ulcer, defined as an ulcer associated with hospitalization for frank bleeding or anemia, admission to an intensive care unit, requirement for red blood cell transfusion, surgery, or endoscopic stigmata of recent hemorrhage. Among the 591 peptic ulcers, we documented 251 that were complicated. Compared to men with a BMI of 23.0–24.9 k/m^2, the multivariate HR of a complicated peptic ulcer was 1.42 (95% CI, 0.91–2.22; $P_{trend}=0.08$)for obese men. The corresponding multivariate HRs associated with obesity of complicated ulcer were 2.03 (95% CI, 1.08–3.81; $P_{trend}=0.01$) for gastric ulcer and 1.00 (95% CI, 0.52–1.94; $P_{trend}=0.97$) for duodenal ulcer.

We also evaluated the potential confounding effect of concomitant drug use on our results. In an analysis of the cohort between 1996 and 2010, which additionally adjusted for use of warfarin, oral steroids, and SSRIs in addition to our other covariates, we found that

compared with men with a BMI of 23.0–24.9 k/m^2, obese men had a multivariate HR of 1.65 (95% CI, 1.06–2.57; P_{trend}=0.02) for any ulcer, 2.14 (95% CI, 1.12–4.09; P_{trend}=0.01) for gastric ulcer, and 1.33 (95% CI, 0.71–2.48; P_{trend}=0.38) for duodenal ulcer. Based on secular trends in medication use, we did not ask participants to report clopidogrel use until 2008, at which time only 4% of the cohort reported use. Thus, it is unlikely that concomitant clopidogrel use could explain our associations. Nevertheless, we also conducted a sensitivity analysis in which we restricted the analysis to follow-up between 1986 and 1996, which predated the approval of clopidogrel by the FDA. In this analysis, we found that the multivariate HR of peptic ulcer was 1.28 (95% CI, 0.84–1.94; P_{trend}=0.04) for obese men. For gastric and duodenal ulcer, these values were 1.79 (95% CI, 1.01–3.19; P_{trend}=0.08), and 0.88 (95% CI, 0.47–1.67; P_{trend}=0.23), respectively.

For our main analyses, we defined regular aspirin use as intake at least 2 or more times per week, consistent with the specific query on each biennial questionnaire during follow-up. Beginning in 1992, we provided a larger number of response categories for the frequency of use that allowed us to vary our categorization of regular aspirin use. In analyses in which we defined regular use as intake ≥1 times per month, we found that the multivariate HR of any peptic ulcer was 1.86 (95% CI, 1.30–2.65; P_{trend}<0.01) for obese men. For gastric and duodenal ulcer, these values were 1.95 (95% CI, 1.17–3.22; P_{trend}<0.01), and 1.73 (95% CI, 1.04–2.88; P_{trend}=0.01), respectively.

When we adjusted our models for comorbidities potentially associated with ulcer, including active liver disease or cirrhosis, chronic renal failure, and cardiovascular disease, we found that compared to men with a BMI of 23.0–24.9 k/m^2, the multivariate HR of peptic ulcer was 1.39 (95% CI, 1.03–1.86; P_{trend}<0.01) for obese men. For gastric and duodenal ulcer, these values were 1.83 (95% CI, 1.21–2.79; P_{trend}<0.01), and 1.03 (95% CI, 0.67–1.59; P_{trend}=0.24), respectively.

We considered the possibility that the association of obesity with ulcer disease may be due to a higher likelihood of undergoing an endoscopy during follow-up. Thus, we conducted a sensitivity analysis in which we limited the cohort to the 6,938 individuals who reported that they underwent an upper endoscopy during follow-up. Among these individuals, the multivariate HR of peptic ulcer was 1.86 (95% CI, 1.33–2.60; P_{trend}<0.01) for obese men compared to men with a BMI of 23.0–24.9 k/m^2. The corresponding HRs associated with obesity were 2.13 (95% CI, 1.34–3.37; P_{trend}<0.01) for gastric ulcer and 1.57 (95% CI, 0.95–2.59; P_{trend}=0.10) for duodenal ulcer.

We then evaluated the relationship between peptic ulcer and visceral adiposity as reflected by waist and hip circumference. Compared to men with a waist-to-hip ratio (WHR) of 0.85–0.89, the multivariate-adjusted HR of peptic ulcer was 1.46 (95% CI, 1.01–2.12; P_{trend}=0.08) for men with a WHR of 1.00 or greater (Table 3). The risk appeared to be specific for gastric ulcer (multivariate-adjusted HR=1.88; 95% CI, 1.06–3.33; P_{trend}=0.04), but not duodenal ulcer (multivariate-adjusted HR=1.19; 95% CI, 0.73–1.95; P_{trend}=0.68). We observed an association of WHR with *H. pylori* negative ulcer that approached statistical significance (P_{trend}=0.05). In contrast, WHR did not appear associated with *H. pylori* positive ulcers (P_{trend}=0.46).

We also examined the association of BMI with peptic ulcer within subgroups defined by known risk factors for peptic ulcer disease. We observed that the risk of peptic ulcer appeared greater in participants who did not regularly take aspirin or NSAIDs (multivariate-adjusted HR=1.91; 95% CI, 1.07–3.41) than in those who were regular users (multivariate-adjusted HR=1.12; 95% CI, 0.74–1.70; $P_{interaction}$=0.09) We did not observe significant differences in subgroups defined by physical activity ($P_{interaction}$=0.70), alcohol ($P_{interaction}$=0.45), or smoking ($P_{interaction}$=0.86).

Physical activity helps to maintain healthy energy balance and counteract the effects of obesity, so we also considered the possibility that physical activity may be independently associated with risk of peptic ulcer. After controlling for BMI and other potential risk factors, compared to men who averaged less than 3 MET-hours/week of physical activity, the multivariate-adjusted HR of peptic ulcer for men in the highest category of physical activity (≥27.0 MET-hours/week) approached statistical significance (HR=0.75; 95% CI, 0.54–1.03; P_{trend}=0.08) (Table 4). This association appeared similar for both gastric (P_{trend}=0.13) and duodenal (P_{trend}=0.34) ulcer. We observed similar results in analyses of physical activity according to quintiles (data not shown).

DISCUSSION

In this large prospective cohort of men, we found that obesity was associated with an increased risk of peptic ulcer, particularly gastric ulcer and *H. pylori* negative ulcers. We also observed an association between visceral adiposity, as measured by waist-to-hip ratio, and risk of gastric ulcer. These observed associations persisted even after adjusting for potential confounders including smoking and regular use of aspirin and NSAIDs. In secondary analyses, our findings persisted even after considering: (1) comorbidities, including active liver disease or cirrhosis, chronic renal failure, and cardiovascular disease; (2) an alternative definition of regular aspirin use; (3) use of other medications including warfarin, oral steroids, SSRIs, and clopidogrel; and (4) receipt of endoscopy over follow-up.

Our results are generally in agreement with two prior cross-sectional studies of smaller non-U.S. cohorts[8–9]. A Taiwanese study observed that BMI was higher in subjects with asymptomatic peptic ulcers incidentally found on endoscopy compared to subjects with no ulcers[8]; a Swedish study found that obesity at the time of endoscopic examination was associated with increased risk of gastric, but not duodenal ulcer[9]. In contrast, a U.S. mail survey observed an association between physical inactivity, but not BMI, and an increased risk of ulcer[10]. However, this study was limited by the lack of medical record confirmation of reported ulcers and collection of any information on aspirin and NSAID use.

Although the exact mechanism is unknown, the pathophysiology of peptic ulcer disease is likely related to mucosal breakdown and ulceration as the result of injury related to infection (e.g. *H. pylori*) and/or toxins (e.g. NSAIDs). Recent studies have also shown a link between obesity and susceptibility to mucosal injury. Obesity has been associated with promotion of inflammation in the gastrointestinal tract[24], alteration in the gut microbiome[1–3], and increased epithelial permeability due to disruption of structural cellular components such as occludin and myosin light-chain kinase[4,25]. Our observation that obesity was more strongly

associated with ulcers among non-aspirin or NSAID users and *H. pylori* negative ulcers suggests that the mechanism by which obesity influences ulcer disease may be independent of injury associated with anti-inflammatory drugs or *H. pylori* infection. Alternatively, the effect of obesity on ulcer disease may be less evident among aspirin or NSAID users or those with *H. pylori* infection since these are particularly strong risk factors for ulcer disease and may overwhelm other environmental influences. Our observation that physical activity had an inverse, but non-significant, relationship with risk of peptic ulcer suggests that physical activity may reduce ulcer risk, although the effect may be in part mediated by lower BMI.

The strengths of our study include long-term follow-up, confirmation of self-reported cases by medical record review, prospective assessments of obesity and physical activity, and detailed and biennially updated information on potential confounders including smoking and aspirin and NSAID use. In our study, we were also able to examine the association of visceral adiposity on risk of peptic ulcer. Because our cohort is comprised of male health professionals, confounding by education and socioeconomic status was also minimized.

We acknowledge several limitations of our study. First, data on body measurements was self-reported. However, a previous validation study found that self-reported body measurements were highly representative of actual measurements within a subsample of our cohort[12]. Second, our cohort is comprised of predominantly white, middle-aged, U.S. males working in the health professions, which may limit the generalizability of our findings to other populations. Third, peptic ulcer cases required confirmation via endoscopy or surgery, and our findings may not be generalizable to patients with less severe ulcer disease. Fourth, some ulcers are caused by acute exposures to aspirin and NSAIDs, opposed to chronic use of these drugs. However, we did not have data available on use of aspirin and NSAIDs in the immediate days prior to ulcer diagnosis. Thus, we were only able to consider the potential influence of long-term, regular use of these medications in relation to ulcer risk. Lastly, our study is observational and we cannot rule out the possibility of residual confounding.

In conclusion, we showed that obesity is associated with an increased risk of gastric, but not duodenal, ulcer. In contrast, physical activity may be associated with a lower risk of ulcer. Our findings are consistent with emerging data suggesting that obesity and physical activity may influence gastrointestinal mucosal integrity.

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Table 1

Baseline characteristics of participants in the Health Professionals Follow-up Study, according to body mass index (BMI)

	Baseline BMI (kg/m^2)					
	<21.0	**21.0–22.9**	**23.0–24.9**	**25.0–26.9**	**27.0–29.9**	**≥30.0**
N (participants)	**1,750**	**6,807**	**13,280**	**12,756**	**8,645**	**3,882**
Mean age, years	54.2	53.7	54.1	54.7	54.8	54.2
SD[†]	10.6	10.1	9.9	9.6	9.4	9.0
Non-white race, %	8	6	5	5	5	5
Regular user of Aspirin[‡], %	25	27	29	30	31	32
Regular user of NSAID[‡], %	3	5	5	5	6	8
Periodontal disease, %	15	15	15	16	16	17
Physical Activity (MET-hours/week), %						
<3.0	20	16	16	20	24	32
3.0–8.9	21	19	21	23	26	29
9.0–17.9	19	20	20	20	19	16
18.0–26.9	14	13	14	13	13	10
≥27.0	27	31	29	24	19	13
Smoking, %						
Never	50	51	47	43	42	40
Past	32	36	41	44	44	47
Current	13	10	9	10	10	9
Missing	4	3	4	4	4	4
Alcohol intake (g/day), %						
0.0	29	24	21	22	24	28
0.1–4.9	23	23	23	24	24	25
5.0–14.9	27	29	31	30	28	27
≥15.0	21	24	25	25	24	20

[†]Standard Deviation

[‡]Defined as intake ≥2 times/week.

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Table 2

Body mass index (BMI) and risk of peptic ulcer

	BMI (kg/m^2)						
	<21.0	**21.0–22.9**	**23.0–24.9**	**25.0–26.9**	**27.0–29.9**	**≥30.0**	**P_{trend}**
All Peptic Ulcer							
Person-Years	35,899	120,697	232,397	236,655	194,637	106,938	
Cases	23	74	125	151	143	75	
Age-Adjusted HR (95% CI)	1.10 (0.70–1.73)	1.13 (0.85–1.52)	1.00	1.21 (0.95–1.54)	1.46 (1.14–1.86)	1.46 (1.09–1.96)	<0.01
Multivariate HR (95% CI)*	1.14 (0.73–1.79)	1.15 (0.86–1.54)	1.00	1.20 (0.94–1.53)	1.43 (1.12–1.82)	1.38 (1.03–1.86)	<0.01
Gastric Ulcer							
Cases	8	33	53	66	68	44	
Age-Adjusted HR (95% CI)	0.91 (0.43–1.92)	1.18 (0.76–1.83)	1.00	1.20 (0.83–1.74)	1.57 (1.09–2.26)	1.96 (1.30–2.95)	<0.01
Multivariate HR (95% CI)*	0.96 (0.45–2.03)	1.22 (0.79–1.90)	1.00	1.19 (0.83–1.72)	1.52 (1.05–2.19)	1.83 (1.20–2.78)	<0.01
Duodenal Ulcer							
Cases	15	41	72	85	75	31	
Age-Adjusted HR (95% CI)	1.25 (0.71–2.20)	1.10 (0.75–1.62)	1.00	1.22 (0.89–1.68)	1.37 (0.99–1.90)	1.08 (0.70–1.65)	0.17
Multivariate HR (95% CI)*	1.27 (0.72–2.24)	1.11 (0.75–1.64)	1.00	1.22 (0.89–1.67)	1.36 (0.98–1.90)	1.03 (0.67–1.59)	0.24

*Models adjusted for age (months), race (white, non-white), alcohol intake (0–4.9, 5–14.9, ≥15 g/day), periodontal disease (no, yes), physical activity (<3, 3–9, 9–18, 18–27, ≥27 MET-hours/week), smoking status (never, past, current), regular aspirin use (<2, ≥2 times/week), and regular NSAID use (<2, ≥2 times/week).

Table 3

Waist-to-hip ratio (WHR) and risk of peptic ulcer

	Baseline WHR†					
	<0.85	**0.85–0.89**	**0.90–0.94**	**0.95–0.99**	**≥1.00**	**P_{trend}**
All Peptic Ulcer						
Person-Years	17,644	112,867	211,513	164,045	79,346	
Cases	12	53	154	125	72	
Age-Adjusted HR (95% CI)	1.58 (0.84–2.98)	1.00	1.42 (1.04–1.95)	1.40 (1.01–1.94)	1.57 (1.09–2.25)	0.03
Multivariate HR (95% CI)*	1.59 (0.84–2.99)	1.00	1.39 (1.01–1.91)	1.33 (0.96–1.86)	1.46 (1.01–2.12)	0.08
Gastric Ulcer						
Cases	6	20	68	61	36	
Age-Adjusted HR (95% CI)	2.18 (0.86–5.49)	1.00	1.69 (1.02–2.80)	1.91 (1.14–3.21)	2.16 (1.23–3.79)	<0.01
Multivariate HR (95% CI)*	2.22 (0.88–5.61)	1.00	1.62 (0.98–2.70)	1.78 (1.06–3.00)	1.88 (1.06–3.33)	0.04
Duodenal Ulcer						
Cases	6	33	86	64	36	
Age-Adjusted HR (95% CI)	1.24 (0.52–2.99)	1.00	1.26 (0.84–1.89)	1.10 (0.72–1.69)	1.22 (0.75–1.98)	0.60
Multivariate HR (95% CI)*	1.21 (0.50–2.92)	1.00	1.26 (0.84–1.90)	1.09 (0.70–1.67)	1.19 (0.73–1.95)	0.68

*Models adjusted for age (months), race (white, non-white), alcohol intake (0–4.9, 5–14.9, ≥15 g/day), periodontal disease (no, yes), physical activity (<3, 3–9, 9–18, 18–27, ≥27 MET-hours/week), smoking status (never, past, current), regular aspirin use (<2, ≥2 times/week), and regular NSAID use (<2, ≥2 times/week).

†WHR data collected in a supplemental 1987 questionnaire. Analysis based on follow-up from 1988–2010.

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Table 4

Physical activity[†] and risk of peptic ulcer

	Physical Activity (MET-hours/week)					
	<3.0	**3.0–8.9**	**9.0–17.9**	**18.0–26.9**	**≥27.0**	**P_{trend}**
All Peptic Ulcer						
Person-Years	65,359	132,200	185,081	155,866	388,718	
Cases	52	90	126	98	225	
Age-Adjusted HR (95% CI)	1.00	0.85 (0.60–1.20)	0.88 (0.63–1.23)	0.81 (0.57–1.14)	0.75 (0.55–1.03)	0.06
Multivariate HR (95% CI)[*]	1.00	0.83 (0.59–1.18)	0.86 (0.61–1.20)	0.80 (0.56–1.13)	0.75 (0.54–1.03)	0.08
Gastric Ulcer						
Cases	18	46	61	48	99	
Age-Adjusted HR (95% CI)	1.00	1.24 (0.71–2.15)	1.17 (0.68–2.01)	1.08 (0.62–1.89)	0.88 (0.52–1.48)	0.09
Multivariate HR (95% CI)[*]	1.00	1.21 (0.69–2.10)	1.12 (0.65–1.93)	1.05 (0.60–1.85)	0.88 (0.52–1.50)	0.13
Duodenal Ulcer						
Cases	34	44	65	50	126	
Age-Adjusted HR (95% CI)	1.00	0.64 (0.40–1.00)	0.72 (0.47–1.10)	0.66 (0.42–1.03)	0.69 (0.46–1.02)	0.32
Multivariate HR (95% CI)[*]	1.00	0.63 (0.40–1.00)	0.72 (0.47–1.10)	0.65 (0.41–1.02)	0.69 (0.46–1.03)	0.34

[†]Physical activity based upon cumulative average of activity from all available questionnaires, prior to each two-year interval.

[*]Models adjusted for age (months), body mass index (<21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, ≥30.0 kg/m^2), race (white, non-white), alcohol intake (0–4.9, 5–14.9, ≥15 g/day), periodontal disease (no, yes), smoking status (never, past, current), regular aspirin use (<2, ≥2 times/week), and regular NSAID use (<2, ≥2 times/week).