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Composite protective lifestyle factors and risk of developing gastric adenocarcinoma: the Singapore Chinese Health Study

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Background: Incidence of gastric cancer is the highest in Eastern Asia. Multiple modifiable lifestyle factors have been identified as risk factors for gastric cancer. However, their aggregated effect on the risk of gastric cancer has not been examined among populations with high prevalence of *Helicobacter pylori*.

Methods: A study was conducted to examine the association between multiple lifestyle factors together and the risk of developing gastric adenocarcinoma in the Singapore Chinese Health Study, a prospective cohort of 63 257 men and women between 45 and 74 years enroled during 1993–1998. Composite score of cigarette smoking, alcohol consumption, obesity, dietary pattern, and sodium intake at baseline was assessed with hazard ratio (HR) and 95% confidence interval (CI) of gastric adenocarcinoma using Cox regression method.

Results: Higher healthy composite lifestyle scores were significantly associated with reduced risk of gastric adenocarcinoma in a dose-dependent manner. Hazard ratios (95% CIs) for total, cardia, and non-cardia gastric adenocarcinoma for the highest (score 5) vs lowest composite score (score 0/1/2) were 0.42 (0.31–0.57), 0.22 (0.10–0.47), and 0.55 (0.39–0.78), respectively (all $P_{trend} < 0.001$). These lifestyles together accounted for 48% of total gastric adenocarcinoma cases in the study population. The inverse association was observed in both genders, and remained after exclusion of first 5 years of follow-up.

Conclusions: The inverse association between the aggregated healthy lifestyle factors and the risk of gastric adenocarcinoma is in dose-dependent manner in this highly *H. pylori*-exposed population. These lifestyle factors together may account for up to half of disease burden in this study population.

Globally, gastric cancer is the fifth most common malignancy. Geographically the highest incidence rate is recorded in Eastern Asia such as China, Japan, and South Korea whereas the lowest in Western Europe and North America (Ferlay *et al*, 2014). Infection with *Helicobacter pylori* is an established underlying, but insufficient causal factor for gastric cancer (de Martel *et al*, 2012).

The prevalence of *H. pylori* infection varies substantially world-wide. The highest infection rate is observed at more than 80% of the entire population in Eastern Asian countries where high incidence rates of gastric cancer are reported. However, < 2% of infected people eventually develop gastric cancer over their lifetime (Conteduca *et al*, 2013), strongly suggesting that

other environmental exposures and genetic factors must play an important contributing role to the variation of individual's risk of developing gastric cancer.

Several modifiable lifestyle factors have been identified as risk factors for gastric cancer in various populations. The risk factors include cigarette smoking (Ladeiras-Lopes *et al*, 2008), heavy alcohol consumption (Tramacere *et al*, 2012), obesity (Yang *et al*, 2009), high sodium intake (D'Elia *et al*, 2012), low physical activity (Abioye *et al*, 2015), low vegetable and fruit intake (Lunet *et al*, 2007), and high red meat intake (Zhu *et al*, 2013). These lifestyle factors usually go hand in hand with each other such as cigarette smoking and alcohol consumption on an individual subject level. We hypothesised that people with multiple healthy lifestyle factors would have lower risk of gastric cancer than those with no or fewer healthy lifestyle factors, and the beneficial effect would be incremental, that is, the healthier lifestyle factors one has, the greater risk reduction one would derive from. Thus it would be more informative for studies that simultaneously examine multiple lifestyle factors together in relation to risk of gastric cancer in populations with different background risk of gastric cancer, especially in population with different prevalence of *H. pylori*.

Two prospective cohort studies examined the association between combined lifestyle factors and risk of gastric cancer. Both were conducted in the European countries where both the prevalence of *H. pylori* and the incidence rate of gastric cancer are lower (9.4 per 100 000) than the world average (12.1 per 100 000; Conteduca *et al*, 2013; Ferlay *et al*, 2013). In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, a composite score of three healthy lifestyle factors was significantly associated with reduced risk of gastric adenocarcinoma (Buckland *et al*, 2015). The other study in France, a part of EPIC, reported a similar association between a composite score of five lifestyle habits and reduced risk of cancers of the oesophagus, stomach, biliary tract, small bowel, and pancreas combined (Dartois *et al*, 2014).

To our knowledge, there has been no study that prospectively assesses the composite score of multiple lifestyle factors together in relation to risk of gastric cancer in any Asian population that have a higher prevalence of *H. pylori* infection than western population, where the findings may not be directly applicable to Asian populations. These modifiable lifestyle factors including cigarette smoking, alcohol consumption, obesity, dietary pattern, and sodium intake together may have different impact on the risk of developing gastric adenocarcinoma in a high-risk population. The results of this study can provide important evidence in the development of gastric cancer prevention strategy that promotes healthy lifestyle in populations with high prevalence of *H. pylori* infection.

MATERIALS AND METHODS

Study population. The details about the Singapore Chinese Health Study (SCHS) had been described previously (Hankin *et al*, 2001). Briefly, 63 257 Singapore Chinese men and women aged 45–74 years old who were citizens or permanent residents of Singapore and belonged to one of the two major dialect groups (Hokkien or Cantonese) were recruited between 1993 and 1998. After excluding 1936 subjects who had a history of cancer at baseline, the present analysis included 61 321 participants. The SCHS was approved by the Institutional Review Boards at the National University of Singapore and the University of Pittsburgh (Pittsburgh, PA).

Assessment of lifestyle factors. Baseline in-person interviews were conducted using a structured questionnaire for each participant to obtain demographics, body weight and height, tobacco smoking, alcohol consumption, physical activity, diet, medical history, and family history of cancer. Information on dietary consumption was obtained using a structured semi-quantitative food frequency questionnaire (FFQ) with 165 listed dietary items representing majority of food and beverage items commonly consumed by the study population in Singapore. For each dietary item, an individual subject was asked to choose a consumption frequency among eight pre-defined categories from 'never or hardly ever' to 'two or more times a day' along with pre-determined portion sizes illustrated in a companion food photo album. This FFQ was validated subsequently in a sub-cohort of our study population (Hankin *et al*, 2001).

As height and body weight were self-reported, for subjects with missing body weight ($N = 9971$) or height ($N = 289$), a linear regression equation (Weight $= \alpha + \beta *$ Height) derived from known weight and height of the entire cohort was used to estimate the missing value. Body mass index (BMI) was calculated as weight in kg divided by squared height in m ($\mathrm{kg\,m}^{-2}$).

For cigarette smoking, a subject who reported smoking at least one cigarette per day for a year or longer (a smoker) was asked the average number of cigarettes smoked per day and the total number of years of smoking on a regular basis. Ex-smokers were asked how many years ago since quitting smoking. Total number of pack-years of smoking was calculated as the number of packs (20 cigarettes per pack) smoked per day multiplied by the number of years of smoking.

For daily ethanol consumption, participants were asked the frequency of drinking type of alcoholic beverages during the past year by the usual serving size. Daily consumption of each type of alcoholic beverage was calculated by frequency multiplied by the serving size, and daily total ethanol was the sum of ethanol over all types of alcoholic beverages consumed. The average ethanol content is 13.5 g in one drink (375 ml) of beer, 10.85 g in one drink (30 ml) of rice wine or hard liquor, and 11.68 g in one glass (118 ml) of grape wine (USDA, 1975).

Daily sodium intake was derived from validated FFQ and the Singapore Food Composition Table that also provides sodium content for each of 165 dietary items (mg per 100 g). The final value of sodium intake was adjusted for total energy intake (mg per 1000 kcal).

Dietary pattern was determined using the principal component analysis as described previously (Butler *et al*, 2006). Briefly, we identified two dietary patterns among SCHS participants: vegetable-fruit-soy (VFS) and meat-dim-sum (MDS). Vegetable-fruit-soy was characterised by high intake of fruits, vegetables, and soy foods whereas MDS by high intake of pork, chicken, dim-sum foods, and noodle dishes, respectively (Butler *et al*, 2006). For each subject, the average of the two VFS (ascending order) and MDS (descending order) ranking scores (range 1–100) was calculated for the present analysis, a high score was indicative of a high intake of VFS and a low intake of MDS (Supplementary Table S1).

Case ascertainment. Gastric cancer cases among the SCHS participants were identified through the linkage analysis with The Singapore Cancer Registry under the National Registry of Diseases Offices (NRDO) of Singapore. This nationwide registry has collected information on individual cancer patients and national cancer trends and patterns since 1968 (Lee, 2015) and has been shown to be complete in recording incident cancer cases (Forman *et al.*, 2014). Gastric cancer was defined using the International Classification of Disease Oncology, 3rd edition (ICD-O-3) as C16.0-C16.9.

Construction of composite protective lifestyle score. Our literature search identified six modifiable risk factors for gastric cancer. They were cigarette smoking, alcohol consumption, obesity, physical inactivity, high intake of sodium, and diet with low fruits/vegetables and high meat. In our study population, we did not find physical inactivity to be a risk factor for gastric adenocarcinoma

($P = 0.243$), hence we excluded it from the composition of final lifestyle score.

Two sets of algorithm were applied for construction of composite protective lifestyle score based on dichotomised cutoff and Z-score of each factor. In the first algorithm, each lifestyle factor was dichotomised and final cut-off value was chosen to reflect the strongest effect size for its univariate association with gastric adenocarcinoma risk. Pack-years of smoking was categorised at median (i.e., 21.9) among ever smokers (low-risk/protective lifestyle score $1 = <21.9$, $0 = \geqslant 21.9$). Daily ethanol consumption was categorised at 8.1 g (the third tertile) among ever drinkers ($1 = <8.1$, $0 = \geqslant 8.1$). Dietary pattern score was categorised at 62 (the fourth quartile) of the entire cohort ($1 = \geqslant 62$, $0 = <62$). Daily sodium intake was categorised at 782 mg per 1000 kcal (the third tertile; $1 = <782$, $0 = \geqslant 782$). BMI was categorised at $\geqslant 27.5 \, \text{kg m}^{-2}$ for obesity recommended by the World Health Organisation for Asian populations (WHO, 2004; $1 = <27.5$, $0 = \geqslant 27.5 \, \text{kg m}^{-2}$). The percentages of the study population in high or low score of these five individual lifestyle factors are presented in Supplementary Table S2. The final composite protective lifestyle score was the sum of five individual lifestyle factors: 0 represented the lowest and 5 the highest protective lifestyle score.

The second algorithm was to generate sex-specific Z-score for each lifestyle factor to avoid overfitting the model based on dichotomised values of individual lifestyle factors. In the study population, ~70% of participants were never smokers and 81% never consumed alcoholic beverages. Thus the Z-scores for pack-years of smoking and daily ethanol consumption were derived from ever smokers and ever alcoholic drinkers, respectively. We assigned half of the lowest Z-score for pack-years of smoking and daily ethanol to never smokers and never drinkers, respectively. The composite healthy lifestyle Z-score was the sum of Z-score for all five individual factors for each study subject as follows:

$$\text{Composite Z score} = Z_{\text{diet}} - \left(Z_{\text{smoking}} + Z_{\text{drinking}} + Z_{\text{BMI}} + Z_{\text{sodium}} \right).$$

A higher composite Z-score stands for higher score presenting healthier dietary pattern, lower pack-years of smoking, lower ethanol consumption, lower BMI, and lower sodium consumption. The distribution of single lifestyle factor by quartile of composite Z-score was shown in Supplementary Table S3.

H. pylori infection status testing. To further examine the association of composite protective lifestyle score in combination with H. pylori infection status in relation to gastric adenocarcinoma risk, a nested case–control study was conducted involving 522 subjects (133 gastric adenocarcinoma cases and 389 individually matched controls) whose serological H. pylori infection status was determined by the presence or absence of CagA 116 kDa in serum. The details of this case–control study have been previously reported (Ainslie-Waldman et al, 2014).

Statistical analysis. Person-years at risk for each of 61 321 eligible subjects were computed from the date of enrolment to the date of gastric cancer diagnosis, death, migration out of Singapore, or 31 December 2014, whichever occurred first. Cox proportional hazard regression method was employed for calculation of hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) of gastric adenocarcinoma associated with individual lifestyle factors and both the composite protective lifestyle scores derived from dichotomised cutoff and Z-score of these lifestyle factors together. Test for linear trends was conducted by treating the composite lifestyle score as a continuous variable in the Cox model. The proportional hazards assumption was examined by testing the significance of Pearson's correlation coefficient between Schoenfeld residuals of the composite lifestyle score and ranked survival time

(Harrell and Lee, 1986). We found no violation of proportional hazards assumption.

To adjust for potential confounding, age, sex, dialect group, year of recruitment, and level of education were included in all regression models. Further adjustment for other covariates such as intake of individual vegetables and fruit, family history of cancer, and history of gastric/duodenal ulcer did not meaningfully alter the association between the composite lifestyle score and gastric adenocarcinoma risk. Thus the results presented were not adjusted for these variables.

Population attributable risk (PAR) estimate was computed for the proportion of gastric adenocarcinoma cases that would be avoided on a population level attributable to higher composite lifestyle category. On the basis of the HRs from Cox proportional hazard regression model and their variance–covariance matrix and the prevalence of each unique combinations of the covariates in the model, an algorithm developed by Spiegelman et al (2007) was applied to calculate partial PAR along with its 95% CIs while age, sex, dialect group, year of recruitment, and level of education remain unchanged.

To examine the potential modifying effect of subclinical symptoms of gastric cancer on the association between composite protective lifestyle score and gastric adenocarcinoma risk, we conducted sensitivity analyses on subset of data set divided by the length of follow-up, for example, $\leqslant 5$ years and >5 years. To investigate the association between composite lifestyle score and gastric adenocarcinoma risk with adjustment of H. pylori infection status, conditional logistic regression model was performed in the nested case–control study for all subjects and for subjects with positive H. pylori infection status defined by positive CagA test results. Stratified analyses were performed by anatomical sites such as cardia and non-cardia of the stomach.

All statistical analysis was performed in SAS 9.4 software package (SAS Institute, Inc., Cary, NC, USA). All P-values reported are two-sided. P-values <0.05 were considered to be statistically significant.

RESULTS

With increasing composite lifestyle score, there was an increase in proportion of women and a decrease in BMI. A higher composite lifestyle score was also characterised by fewer current smokers, lower pack-years of smoking, and lower daily intake of ethanol, sodium, and red meat (Table 1). The distributions of individual lifestyle factors across different composite score of protective lifestyle factors are shown in Supplementary Table S4. These individual lifestyle factors were not or moderately correlated each other (all correlation coefficients <0.23).

After more than 1 million cumulative person-years of follow-up (mean 16.9 years per subject), as of 31 December 2014, a total of 801 incident cases of gastric cancer were identified among all participants of SCHS. Among them, 32 were sarcomas, 29 lymphomas, and 49 malignancies with unspecified histology; all of them were excluded from the present analysis. Thus the present study included 691 cases of gastric adenocarcinoma; among them, 118 were cardia, 491 were non-cardia, and 82 were unspecified subsite of the stomach. The mean duration between baseline interview and the diagnosis of all gastric adenocarcinoma cases was 6.9 years (s.d. = 3.9).

Individual scores of all five protective lifestyle factors separately were significantly associated with a 18–34% reduction in HR of gastric adenocarcinoma (Table 2). The association was stronger for BMI with risk of cardia than non-cardia cancer (Table 2). HRs (95% CIs) of gastric adenocarcinoma for individual risk factor (before dichotomised) are presented in Supplementary Table S5.

Table 1. Distribution of selected baseline characteristics of all participants by composite lifestyle scores (five factors), the Singapore Chinese Health Study, 1993–2014

Characteristics	Composite lifestyle scores			
	0/1/2	3	4	5
N	6223	20 017	24 799	10 282
Age in years, mean (s.d.)	56.4 (7.7)	55.9 (7.9)	56.6 (8.1)	56.9 (7.9)
BMI (kg m^{-2}), mean (s.d.)	24.8 (4.5)	23.3 (3.5)	22.8 (2.8)	22.5 (2.4)
Female, %	21.8	50.5	61.5	71.2
Education level, %				
No formal education	20.2	24.7	30.0	30.0
Primary school	52.8	44.8	43.0	41.5
⩾Secondary level	27.0	30.5	27.0	28.5
Smoking status, %				
Never smoker	25.4	63.5	78.2	87.0
Former smoker	21.3	12.8	8.6	6.3
Current smoker	53.3	23.7	13.2	6.7
Smoking amount among ever smokers, mean (s.d.)				
Number of cigarettes per day	24.1 (11.2)	18.1 (11.1)	12.3 (9.0)	9.2 (6.2)
Number of years of smoking	36.4 (8.8)	33.6 (11.4)	30.5 (12.7)	28.2 (13.6)
Pack-years of smoking	43.8 (21.9)	31.2 (22.4)	18.5 (16.4)	11.8 (7.4)
Alcohol consumption status, %				
Non-drinkers	58.9	77.9	86.4	91.4
Drinkers	41.1	22.1	13.6	8.6
Ethanol intake (g per day) among drinkers, mean (s.d.)	20.6 (22.3)	8.4 (14.2)	3.3 (5.9)	2.0 (1.8)
Daily sodium intake (mg), mean (s.d.)	1607.9 (784.4)	1361.0 (663.3)	915.1 (414.8)	816.9 (319.4)
Food consumption in grams, mean (s.d.)				
Total vegetables	113.5 (67.9)	110.2 (62.3)	99.2 (58.3)	137.3 (67.0)
Total fruits	183.9 (174.5)	194.7 (161.9)	191.1 (160.3)	256.8 (189.9)
Total red meat	46.9 (32.0)	37.7 (26.0)	25.6 (19.2)	18.7 (15.2)

Abbreviation: BMI = body mass index.

The cut-off value of each lifestyle factors was chosen based on their risk association with gastric adenocarcinoma for the creation of composite score. High composite score of protective lifestyle factors was significantly associated with reduced HR of gastric adenocarcinoma in a dose-dependent manner (Table 2). Compared with the lowest composite scores using dichotomous cutoff (0–2), HRs (95% CIs) of gastric adenocarcinoma for composite scores of 3, 4, and 5 protective lifestyle factors were 0.68 (0.52–0.88), 0.51 (0.40–0.66), and 0.42 (0.31–0.57), respectively ($P_{\text{trend}} < 0.001$). This association was stronger for cardia than non-cardia cancer. (Table 2). On the basis of the distribution of the composite score, we estimated that 48% of total gastric adenocarcinoma, including 72% in cardia and 43% in non-cardia, could be attributable to these five risk factors combined.

We also examined the association between Z-score of single lifestyle factor and gastric adenocarcinoma risk (Supplementary Table S6). High Z-score for all individual lifestyle factors except for dietary pattern was associated with significantly increased risk of gastric cancer

When these Z-scores were summed up after reversing the Z-scores of risk lifestyle factors (see Materials and Methods section), high composite Z-score representing healthier lifestyle factors was associated with statistically significant, reduced risk of gastric adenocarcinoma (Table 2). Although weaker than the composite score of the dichotomised lifestyle protective factors, the inverse association was strong and in dose-dependent manner, and present for both cardia and non-cardia cancers. (Table 2). This inverse association between composite score of protective lifestyle factors, either derived from dichotomised categories or Z-scores, and gastric adenocarcinoma risk was present in both men and women (Table 3), and for both short (⩽5 years) and long (>5 years) duration of follow-up of the entire cohort (Table 4).

To take into account the impact of H. pylori infection on the observed risk association, we conducted similar analysis in a nested case–control study within the SCHS whose serological status of

H. pylori infection was determined by the presence or absence of CagA in serum. There was a statistically significant inverse association between composite score of dichotomised lifestyle factors and gastric adenocarcinoma risk among all subjects of the case–control study after adjustment for H. pylori infection status as well as among subjects with positive CagA status only. A similar inverse association was observed for both cardia and non-cardia cancer. For composite Z-score, the association slightly attenuated after adjustment for H. pylori infection status and among subjects with positive CagA status, especially for non-cardia cases, given the small sample size (Table 5).

DISCUSSION

The present study demonstrates that a high composite score of five healthier lifestyle factors including smoking, alcohol consumption, BMI, a diet high in vegetables/fruit and low in red meat, and low intake of dietary sodium is significantly associated with reduced risk of developing gastric adenocarcinoma in an Asian population with high prevalence of H. pylroi. The highest composite score was associated with a statistically significant 58% decreased risk of gastric adenocarcinoma compared with the lowest composite score. These lifestyle factors together can account for up to half of the disease burden in this study population, of which ∼85% had a history of infection with H. pylori.

To our knowledge, the present study is the first prospective study to examine the association between combined lifestyle factors and gastric adenocarcinoma risk in an Asian population with high H. pylori prevalence. There are only two previous reports, both in low-risk European populations, on the composite lifestyle factors and gastric cancer risk. In the EPIC study with 11.4 years of follow-up, highest score of three lifestyle factors (cigarette smoking, alcohol consumption, and adherence to a Mediterranean diet) was

Table 2. Lifestyle factors and gastric adenocarcinoma risk among all participants ($n = 61\,321$), the Singapore Chinese Health Study, 1993–2014

Characteristics	Person-years	All cases Cases	All cases HR (95% CI)[a]	Cardia Cases	Cardia HR (95% CI)[a]	Non-cardia Cases	Non-cardia HR (95% CI)[a]
Smoking							
Pack-years of smoking >21.9	132 949	187	1.00 (reference)	37	1.00 (reference)	128	1.00 (reference)
Pack-years of smoking $\leqslant 21.9$	906 112	504	0.66 (0.55–0.83)	81	0.54 (0.35–0.84)	363	0.66 (0.53–0.83)
Alcohol							
Daily ethanol intake >8.1 g	62 238	70	1.00 (reference)	11	1.00 (reference)	51	1.00 (reference)
Daily ethanol intake $\leqslant 8.1$ g	976 823	621	0.69 (0.53–0.89)	107	0.86 (0.45–1.63)	440	0.66 (0.49–0.89)
BMI							
$\geqslant 27.5$ kg m^{-2}	89 879	66	1.00 (reference)	16	1.00 (reference)	47	1.00 (reference)
<27.5 kg m^{-2}	949 182	635	0.80 (0.62–1.03)	102	0.54 (0.32–0.93)	444	0.79 (0.58–1.07)
Dietary pattern score							
1st–3rd Quartile (<62)	774 142	549	1.00 (reference)	101	1.00 (reference)	383	1.00 (reference)
4th Quartile ($\geqslant 62$)	264 919	142	0.82 (0.68–0.99)	17	0.60 (0.35–1.01)	108	0.89 (0.71–1.11)
Sodium intake							
$\geqslant 782$ mg per 1000 kcal energy	340 708	242	1.00 (reference)	48	1.00 (reference)	161	1.00 (reference)
<782 mg per 1000 kcal energy	698 353	449	0.80 (0.68–0.94)	70	0.64 (0.44–0.93)	330	0.87 (0.72–1.05)
Composite scores (five factors)[b]							
0/1/2	97 712	123	1.00 (reference)	30	1.00 (reference)	77	1.00 (reference)
3	334 135	246	0.68 (0.52–0.88)	41	0.49 (0.30–0.79)	179	0.80 (0.61–1.04)
4	427 141	237	0.51 (0.40–0.66)	38	0.36 (0.22–0.60)	169	0.57 (0.43–0.76)
5	180 074	85	0.42 (0.31–0.57)	9	0.22 (0.10–0.47)	66	0.55 (0.39–0.78)
P_{trend}			<0.001		<0.001		<0.001
PAR (95% CI)			0.48 (0.36–0.59)		0.72 (0.51–0.84)		0.43 (0.27–0.57)
Composite Z-score (five factors)							
1st Quartile	251 028	212	1.00 (reference)	44	1.00 (reference)	140	1.00 (reference)
2nd Quartile	258 747	167	0.76 (0.62–0.93)	29	0.64 (0.40–1.02)	129	0.88 (0.70–1.12)
3rd Quartile	263 404	162	0.72 (0.58–0.88)	25	0.54 (0.33–0.88)	109	0.72 (0.56–0.92)
4th Quartile	265 881	150	0.64 (0.51–0.78)	20	0.42 (0.25–0.71)	113	0.71 (0.55–0.91)
P_{trend}			<0.001		0.001		0.002

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio; PAR = population attributable risk.
[a] For single lifestyle factor, model included all factors simultaneously and adjusted age at baseline interview (in years), baseline interview year (1993–1995, 1996–1998), father's dialect (Cantonese, Hokkien), gender, and education (no formal education, primary education, $\geqslant$ secondary education).
[b] Model adjusted for age at baseline interview (in years), baseline interview year (1993–1995, 1996–1998), father's dialect (Cantonese, Hokkien), gender, and education (no formal/primary, $\geqslant$ secondary education).

associated with a significant 50% decrease in risk of gastric adenocarcinoma and a PAR of 19% if all subjects were in the healthiest lifestyle score category (Buckland *et al*, 2015). The E3N (*Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale*) study in French women with 15 years of follow-up, a part of EPIC study, showed similar results; the highest score of protective lifestyle factors, including abstinence from smoking, low to moderate alcohol drinking (<2 drinks per day), normal range of BMI (18.5–25 kg m^{-2}), high recreational physical activity, and high vegetable and fruit intake, was associated with a statistically significant 40% decrease in risk of cancer in the digestive system excluding large bowel and a PAR of 12% (Dartois *et al*, 2014). The relative risk findings of the present study are consistent with those in low-risk populations. Compared with previous studies, we found a higher PAR of 48%. Possible explanations include (1) more lifestyle factors included (five for present study; three factors for EPIC study); (2) stronger association for certain lifestyle factors (e.g., HR for low alcohol intake $= 0.69$ in present study *vs* 0.83 in EPIC study); and (3) higher prevalence of risk factors in our study population.

Epidemiological evidence and biological plausibility lend support for the observed association between each of the lifestyle factors studied and gastric cancer risk. For tobacco smoking, a meta-analysis of 27 cohort studies showed a 62% increased relative risk (RR) of gastric cancer for current *vs* never smokers among males (RR = 1.62, 95% CI: 1.50–1.75) and 20% among females (RR = 1.20, 95% CI: 1.01–1.43; Ladeiras-Lopes *et al*, 2008), which

was consistent with our findings (HR = 1.56, 95% CI: 1.27–1.93). Tobacco smoking has been listed as group I carcinogen by IARC (IARC, 2004). Besides more than 70 known carcinogens in cigarette smoke including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons (FDA, 2012), tobacco smoke also contains high level of nicotine, which could promote carcinogenesis. *In vitro* studies showed that nicotine could activate nicotinic acetylcholine receptors and induce cellular proliferation in gastric cancer cell lines by upregulating cyclooxygenase 2 (COX-2; Shin *et al*, 2004). It could also increase phosphorylating extracellular signal-regulated kinase-1/2 (ERK1/2) to further activate the downstream signalling pathways involving COX-2 and ERK (Shin *et al*, 2007).

Heavy alcohol use is associated with elevated gastric cancer risk. In humans, ethanol is metabolised to acetaldehyde, a group I carcinogen classified by IARC (IARC, 2010) and further oxidised into nontoxic acetate (Klyosov, 1996). A review of 15 cohort and 44 case–control studies found that heavy drinkers ($\geqslant 4$ drinks per day) had a 20% higher gastric cancer risk than non-drinkers (RR = 1.20, 95% CI: 1.01–1.44; Tramacere *et al*, 2012). However the association was not found in Asian populations (Tramacere *et al*, 2012). In the present study, we found that even relatively moderate alcohol consumption (approximately one drink per day) was associated with a significant 30% increase in the risk of gastric adenocarcinoma. In the present study, one drink of alcoholic beverage per day already rendered the damage that may only be detectable in a population, of which majority do not drink (81%

Table 3. Composite lifestyle score and gastric cancer risk by gender, the Singapore Chinese Health Study, 1993–2014

Characteristics	N	Cases	Person-years	HR (95% CI)[a]
Male (N = 27 293)				
Composite scores (five factors)				
0/1/2	4866	103	74 708	1.00 (reference)
3	9929	159	158 964	0.72 (0.56–0.92)
4	9543	117	157 918	0.53 (0.40–0.69)
5	2955	33	49 597	0.46 (0.31–0.69)
P_{trend}				<0.001
PAR (95% CI)				0.50 (0.34–0.63)
Composite Z-scores (five factors)				
1st Quartile	6823	127	105 697	1.00 (reference)
2nd Quartile	6824	101	109 148	0.76 (0.58–0.99)
3rd Quartile	6823	97	112 193	0.74 (0.56–0.96)
4th Quartile	6823	87	114 148	0.62 (0.47–0.82)
P_{trend}				0.001
Female (N = 34028)				
Composite scores (five factors)				
0/1/2	1357	19	23 004	1.00 (reference)
3	10 088	88	175 171	0.67 (0.41–1.09)
4	15 256	120	269 223	0.52 (0.32–0.84)
5	7327	52	130 477	0.47 (0.28–0.79)
P_{trend}				0.003
PAR (95% CI)				0.41 (0.18–0.60)
Composite Z-scores (five factors)				
1st Quartile	8507	85	145 331	1.00 (reference)
2nd Quartile	8507	66	149 599	0.76 (0.55–1.05)
3rd Quartile	8507	65	151 211	0.70 (0.50–0.96)
4th Quartile	8507	63	151 733	0.66 (0.48–0.92)
P_{trend}				0.011

Abbreviations: CI = confidence interval; HR = hazard ratio; PAR = population attributable risk.
[a]Model adjusted for age at baseline interview (in years), baseline interview year (1993–1995, 1996–1998), father's dialect (Cantonese, Hokkien), and education (no formal education, primary education, ⩾secondary education).

Table 4. Sensitivity analysis for composite lifestyle score and gastric adenocarcinoma risk by length of follow-up, the Singapore Chinese Health Study, 1993–2014

Follow-up time	Cases	Person-years	HR (95% CI)[a]
Follow-up ⩽5 years			
Composite score (five factors)			
0/1/2	36	30 149	1.00 (reference)
3	68	97 487	0.71 (0.47–1.07)
4	51	121 335	0.44 (0.28–0.68)
5	15	50 499	0.33 (0.18–0.61)
P_{trend}			<0.001
Composite Z-score (five factors)			
1st Quartile	66	74 552	1.00 (reference)
2nd Quartile	40	74 837	0.60 (0.41–0.89)
3rd Quartile	29	75 022	0.43 (0.28–0.66)
4th Quartile	35	75 058	0.50 (0.33–0.76)
P_{trend}			<0.001
Follow-up >5 years			
Composite score (five factors)			
0/1/2	86	67 563	1.00 (reference)
3	178	236 648	0.71 (0.55–0.92)
4	187	305 805	0.57 (0.43–0.74)
5	70	129 575	0.52 (0.38–0.73)
P_{trend}			<0.001
Composite Z-score (five factors)			
1st Quartile	146	176 476	1.00 (reference)
2nd Quartile	127	183 910	0.83 (0.66–1.06)
3rd Quartile	133	188 382	0.84 (0.66–1.07)
4th Quartile	115	190 823	0.70 (0.54–0.89)
P_{trend}			0.007

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a]Model adjusted for age at baseline interview (in years), baseline interview year (1993–1995, 1996–1998), father's dialect (Cantonese, Hokkien), gender, and education (no formal education, primary education, ⩾secondary education).

never drinker). The underlying mechanism is that alcohol can damage gastric mucosa, resulting in enhanced adherence of *H. pylori* bacteria. A previous study reported a high *H. pylori* infection rate in people with high consumption of alcohol in a Chinese population (Zhang *et al*, 2010). Alternatively regular drinkers may choose an unhealthy lifestyle that is associated with risk of gastric adenocarcinoma. For example, daily drinkers were more likely to be current smokers (58% *vs* 18%), consumed higher level of red meat (43.3 *vs* 30.0 g), and consumed low vegetables/fruit and high red meat, all of them are risk factors for gastric cancer. A composite score of these lifestyle factors can summarise their overall effect on gastric cancer risk without worrying about potential confounding effect.

Mounting evidence supports that high intake of red meat or processed meat is associated with increased gastric cancer risk. On the basis of a review of 12 cohort and 30 case–control studies, both red meat and processed meat was associated with a significant 45% increase in risk of gastric cancer (Zhu *et al*, 2013). Haem iron intake from red meat can endogenously be converted to carcinogenic compounds such as *N*-nitroso compounds (NOCs). An experimental study demonstrated a high correlation between haem iron from red meat and endogenous NOCs formation (Jakszyn *et al*, 2006). In the EPIC cohort, highest level of haem iron intake from red meat was found to be associated with a significant 67% increase in gastric adenocarcinoma risk (HR = 1.67, 95% CI: 1.20–2.34) compared with the lowest level (Jakszyn *et al*, 2012).

Antioxidants such as vitamin C in fruit and vegetables can inhibit the endogenous NOC formation (Mirvish, 1996; Iijima *et al*, 2003). A meta-analysis of 24 cohort studies found a significant 10% reduction in risk of gastric cancer associated with highest levels of fruit (RR = 0.90, 95% CI: 0.83–0.98) and fresh vegetables (RR = 0.90, 95% CI: 0.79–1.01; Wang *et al*, 2014). In the present study, the combination of the two dietary patterns, VFS and MDS, was associated with significantly decreased risk of gastric adenocarcinoma.

The association between sodium intake and gastric cancer risk has been extensively studied in different populations. Two *in vivo* studies in rats showed that administration of high concentration of sodium chloride (1.3–4.5 M) caused immediate damage to gastric mucosa, increased cellular proliferation, and altered the viscosity of gastric mucosa (Sorbye *et al*, 1988; Furihata *et al*, 1996). A review of 11 cohort studies found a statistically significant positive association between salt intake and gastric cancer risk, especially in Japan (Wang *et al*, 2009) where both salt intake and gastric cancer incidence rate are highest in the world. Given the ubiquitous presence and lack of information on salt content in some prepared foods, it is very challenging, especially using FFQ or 24-h dietary recalls, for accurately estimating daily salt intake. Urinary excretion of sodium over 24 h is recommended as a better measure for daily salt intake (Wiseman, 2008). A cross-sectional study reported a positive association between urinary sodium excretion and prevalence of gastric cancer in a Korean population ($P = 0.006$), but no association was found when survey-assessed dietary sodium intake was used (Park *et al*, 2014). Studies using urinary biomarkers of sodium with a prospective design are warranted to clarify the role of dietary sodium on gastric adenocarcinoma in humans.

Table 5. Composite lifestyle score and gastric adenocarcinoma risk among subjects with measurement of *Helicobacter pylori* infection (CagA) status, the Singapore Chinese Health Study, 1993–2014

Characteristics	All subjects			*H. pylori*-positive only[a]	
	Ca/Co	OR (95% CI)[b]	OR (95% CI)[c]	Ca/Co	OR (95% CI)[b]
All subjects	133/389			128/329	
Composite score					
0/1/2	26/46	1.00 (reference)	1.00 (reference)	24/39	1.00 (reference)
3	47/112	0.77 (0.43–1.40)	0.78 (0.43–1.42)	46/92	0.78 (0.42–1.46)
4	44/161	0.44 (0.24–0.81)	0.43 (0.23–0.81)	43/139	0.42 (0.21–0.82)
5	16/70	0.37 (0.16–0.82)	0.36 (0.16–0.82)	15/59	0.34 (0.15–0.80)
P_{trend}		0.017	0.017		0.019
PAR (95% CI)		0.62 (0.26, 0.82)	0.62 (0.27, 0.83)		0.64 (0.28, 0.84)
Composite Z-score					
1st Quartile	48/110	1.00 (reference)	1.00 (reference)	46/94	1.00 (reference)
2nd Quartile	28/89	0.71 (0.41–1.22)	0.68 (0.40–1.19)	28/76	0.70 (0.39–1.23)
3rd Quartile	34/90	0.79 (0.46–1.38)	0.80 (0.46–1.41)	32/77	0.75 (0.42–1.35)
4th Quartile	23/100	0.53 (0.28–0.98)	0.56 (0.29–1.06)	22/82	0.54 (0.27–1.05)
P_{trend}		0.068	0.117		0.094
Cardia cases	24/69			21/60	
Composite score					
0/1/2	6/8	1.00 (reference)	1.00 (reference)	5/8	1.00 (reference)
3	7/22	0.46 (0.09–2.42)	0.45 (0.08–2.41)	7/17	0.58 (0.10–3.29)
4	9/27	0.28 (0.06–1.30)	0.28 (0.06–1.33)	8/25	0.33 (0.06–1.68)
5	2/12	0.20 (0.02–1.63)	0.20 (0.02–1.61)	1/10	0.11 (0.01–1.57)
P_{trend}		0.074	0.075		0.065
Composite Z-score					
1st Quartile	11/23	1.00 (reference)	1.00 (reference)	10/20	1.00 (reference)
2nd Quartile	4/15	0.47 (0.12–1.84)	0.47 (0.12–1.87)	4/13	0.53 (0.13–2.17)
3rd Quartile	5/17	0.29 (0.06–1.43)	0.29 (0.06–1.44)	4/14	0.33 (0.07–1.65)
4th Quartile	4/14	0.62 (0.15–2.59)	0.62 (0.15–2.59)	3/13	0.42 (0.08–2.24)
P_{trend}		0.296	0.297		0.195
Non-cardia cases	88/253			87/212	
Composite score					
0/1/2	17/27	1.00 (reference)	1.00 (reference)	16/23	1.00 (reference)
3	34/74	0.69 (0.33–1.44)	0.73 (0.34–1.57)	34/60	0.76 (0.35–1.67)
4	27/106	0.31 (0.14–0.70)	0.34 (0.14–0.79)	27/90	0.35 (0.15–0.83)
5	10/46	0.24 (0.08–0.70)	0.28 (0.10–0.81)	10/39	0.29 (0.10–0.85)
P_{trend}		0.009	0.023		0.026
Composite Z-score					
1st Quartile	31/68	1.00 (reference)	1.00 (reference)	30/59	1.00 (reference)
2nd Quartile	20/58	0.72 (0.37–1.39)	0.72 (0.36–1.43)	20/49	0.72 (0.36–1.44)
3rd Quartile	24/59	0.76 (0.38–1.51)	0.86 (0.42–1.75)	24/50	0.87 (0.42–1.80)
4th Quartile	13/68	0.36 (0.15–0.83)	0.44 (0.19–1.05)	13/54	0.45 (0.19–1.08)
P_{trend}		0.030	0.121		0.139

Abbreviations: Ca = Cases; CI = confidence interval; Co = Controls; OR = odds ratio; PAR = population attributable risk.
[a] *H. pylori* positive defined by positive serum CagA status.
[b] Conditional logistic regression model adjusted for age at baseline interview (in years), baseline interview year (1993–1995, 1996–1998), father's dialect (Cantonese, Hokkien), gender, and education (no formal education, primary education, ⩾secondary education).
[c] Further adjusted for serum *H. pylori* CagA status (positive, negative).

Overweight and obesity (BMI ⩾ 25) are significantly associated with increased risk of gastric cancer in a comprehensive review of 10 cohort studies (Yang *et al*, 2009). The association was weaker in Asian than western populations (Yang *et al*, 2009). Compared with Caucasians, Asians have relatively lower BMI (Deurenberg *et al*, 1998; Pan *et al*, 2004). Using a WHO-recommended cutoff for obesity for Asian populations ($\geqslant 27.5 \, kg \, m^{-2}$; WHO, 2004), we found obesity was associated with borderline significant increase in risk of overall gastric adenocarcinoma and significant increase in risk of adenocarcinoma in the cardia. These results are consistent with previous finding (Yang *et al*, 2009). The biological link between obesity and gastric cancer risk may be through the pro-inflammatory cytokines produced from excess body fat that can lead to chronic inflammation (Roberts *et al*, 2010). Overexpression of interlukin-1β resulted in inflammation in gastric cells and eventual formation of carcinoma in experimental studies (Tu *et al*, 2008). Excess body fat may also upregulate insulin-like growth factor-1 that stimulates cellular proliferation and inhibits apoptosis (Bianchini *et al*, 2002).

Z-score-based lifestyle composite score is significantly associated with risk of gastric adenocarcinoma in a dose-response manner although its association was slightly weaker than the categorical-based composite score. As a complementary approach to the categorical-based composite score, Z-score method corroborates the inverse association between adaption of healthy lifestyle factors and reduced risk of gastric adenocarcinoma. Z-score-based composite score was based on the standardised values for each factor with equal weight, which addressed the issue of data overfitting. However, this complete data-driven approach may not optimise the stratification of study subjects at risk, thus could lead to a weaker association between the summed Z-score and gastric cancer risk.

The strengths of our study include the prospective study design, unique study population (Southeast Asians), a relatively large sample size (63 000 participants), long-term follow-up (17 years), and serological status of *H. pylori* infection. A summary lifestyle factor score can classify individuals into more homogenous groups by their risk profile that minimises potential misclassification and residual confounding effect. The main limitation is that all the information on lifestyle factors was self-reported at baseline with

inherent non-differential misclassification that could bias the risk estimates towards null. Therefore, the observed risk estimates may be lower than the true effect of these lifestyle factors on the risk of gastric adenocarcinoma. It should also be noted that our estimate of daily sodium intake may have missed some dietary sources, which may cause some biased results. Given a prospective study design, both cancer cases and non-cancer individuals answered to the same dietary questionnaire. Thus, if there is any misclassification, it would be non-differential and lead to an underestimated risk association. Future studies using urinary excretion of sodium over 24 h are warranted to confirm our findings.

In conclusion, we observed a strong, statistically significant association between high composite score of protective lifestyle factors and reduced risk of gastric adenocarcinoma. Altogether these factors can account for up to almost half of disease burden in this Asian population with a very high prevalence of *H. pylori*. These findings are very encouraging for a comprehensive strategy for promoting healthy living that could be effective for primary prevention of gastric cancer even in populations with a relatively high background risk of gastric cancer and high prevalence of *H. pylori*.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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