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**Sex as an effect modifier in the association between alcohol intake and gastric cancer risk**

Bae JM. Alcohol and gastric cancer risk by sex

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**Author contributions:** Bae JM performed to select related articles, conduct statistical analysis, and write the paper.

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**Abstract**

BACKGROUND

The results of previous meta-analyses evaluating the association between the alcohol intake and gastric cancer risk have reported that a statistical significance only for men.

AIM

To investigate the different association between alcohol intake and gastric cancer risk between men and women.

METHODS

The selection criteria included a prospective cohort study for evaluating alcohol intake and gastric cancer risk, with relative risks adjusted for potential confounders. Adjusted relative risk (RR) for the potential confounders and its 95% confidence interval (CI) in the highest *vs* lowest level were extracted from each study and a random-effects meta-analysis was conducted. Subgroup analyses by region, level of adjustment for smoking status, adjusting for body mass index, and year of publication were conducted.

RESULTS

A meta-analysis of all 27 cohorts showed that alcohol intake increased the risk of gastric cancer (summary RR = 1.13, 95%CI: 1.04-1.23, *I2* = 58.2%). Further, 13 men’s cohorts had higher summary RR while maintaining statistical significance, and only seven women’s cohorts had no statistical significance.

CONCLUSION

The present review suggests that alcohol consumption increases the risk of gastric cancer in men. These findings showed that the sex variable in the association between alcohol intake and gastric cancer risk seemed to be an effect modifier with an interaction term. It is necessary to re-estimate follow-up outcomes after stratifying for sex.

**Key Words:** Alcohol; Stomach neoplasm; Effect modifier; Cohort studies; Meta-analysis; Risk factors

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**Core Tip:** The present review suggests that alcohol consumption increases the risk of gastric cancer, especially in men. These findings showed that the sex variable in the association between alcohol intake and gastric cancer risk seemed to be an effect modifier with an interaction term. It is necessary to re-estimate follow-up outcomes after stratifying for sex.

**INTRODUCTION**

Global cancer statistics 2018 reported that gastric cancer was the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death[1]. As gastric cancer is known to be a multifactorial disease[2], modifiable risk factors such as *Helicobacter pylori* and Epstein–Barr virus infection, diet, smoking status, and alcohol intake have been identified[3-6].

Table 1 summarizes the results of three meta-analyses published in 2017, that evaluated the association between alcohol intake and gastric cancer risk[7-9]. All summary relative risk (sRR) was over 1, but the results of statistical significance conflicted with each other. Interestingly, all meta-analyses reported that the 95% confidence interval (CI) of sRR in men did not involve 1. This indicates a statistically significant association between alcohol intake and gastric cancer risk in men. However, women did not have statistical significance in any of the meta-analyses. In addition, He *et al*[8] reported that light alcohol intake was associated with a reduction in gastric cancer in women (sRR = 0.74, 95%CI: 0.57-0.98).

Based on these findings, the author hypothesized that alcohol intake’s association with gastric cancer risk may differ between men and women. Thus, the aim was to investigate the suggested hypothesis targeting three meta-analyses in Table 1 and Tramacere *et al*[10]’s study by performing a meta-epidemiological review[11].

**MATERIALS AND METHODS**

***Selection strategies***

The selection criterion for this meta-epidemiological study was as follows: A prospective cohort study for evaluating alcohol intake and gastric cancer risk showing RR adjusted for potential confounders.

Of the cohort studies selected for conducting meta-analysis by four existing systematic reviews[7-10], a total of 18 studies met the selection criteria[12-29]. Since the latest year of publication, of the 18 studies, was 2015[29], cohort studies published until July 31, 2020 were needed. The articles that cited the 18 selected studies was listed using the “cited by” option on PubMed[30]. From this, additional cohort studies meeting the selection criteria were secured. After checking for duplication of cohort participants among the selected cohort studies, a study with more gastric cancer patients was selected between duplicate studies.

***Statistical analysis***

Adjusted RR for potential confounders and its 95%CI in the highest *vs* lowest level were extracted by sex from each study. As the reference group of Buckland *et al*[27] was the moderate/high-intake group, the adjusted RR of the study was taken by the reciprocal of the adjusted RR of the no/low-intake group. The level of adjustment for smoking status and the adjustment for body mass index in each cohort study were evaluated. A high level of smoking status was defined as ≥ 3 in the definition suggested by Thomas and Hodges[31]. They defined three levels as adjustments with less than four categories based on smoking status and intensity.

The level of heterogeneity among cohorts was evaluated using the I-squared value, and a random-effects model meta-analysis was performed[32]. In addition, subgroup analyses by region, level of adjustment for smoking status, adjusting for body mass index, and year of publication were conducted to evaluate the effects of potential confounders. The level of statistical significance was set at *P* < 0.05.

**RESULTS**

***Final selection***

The list made using the “cited by” option on PubMed on July 31, 2020 contained a total of 411 articles. Five cohort studies meeting the selection criteria were obtained from the list[33-37]. While checking for duplication of cohort participants, the author found that three studies of the Honolulu Heart Program[12,15], two of the European Prospective Investigation into Cancer and Nutrition cohort[13,27], and two of the NIH-AARP diet and health cohort[14,36] had the same cohort participants, respectively. Thus Nomura *et al*[12], Duell *et al*[13], and Freedman *et al*[14] were excluded based on the number of gastric cancer patients. Finally, 20 cohort studies with a total of 26864280 participants were selected (Figure 1)[15-29,33-37]. There were 10 Asian, 7 European, and 3 American studies in the regional distribution. They consisted of 27 cohorts by sex: 13 men’s, 7 women’s, and 7 adjusted for sex.

***Summary effect size***

A meta-analysis of all 27 cohorts showed that alcohol intake increased the risk of gastric cancer (sRR = 1.13, 95%CI: 1.04-1.23, *I2* = 58.2%) (Figure 2). When subgroup analysis by sex was performed, the 13 men’s cohorts had higher sRR while maintaining statistical significance (sRR = 1.18, 95%CI: 1.06-1.32, *I2* = 55.5%), but the seven women’s cohorts (sRR = 1.07, 95%CI: 0.96-1.19, *I2* = 0.0%) and seven cohorts adjusted for sex (sRR = 1.05, 95%CI: 0.83-1.33, *I2* = 61.6%) had no statistical significance.

The subgroup analysis of the 13 men’s cohorts showed that there was statistical significance in Asians, in the group with a high level of adjustment for smoking status, in the group with the adjustment for body mass index, and in more recently published studies (Table 2). These results were not found in the seven women’s cohorts.

**DISCUSSION**

***Summary of the main finding***

The results show that alcohol intake increased the risk of gastric cancer, especially in men. However, this association was not seen in women.

***Differences between sex groups***

Compared to the sRR of 1.21 in men’s cohorts of Wang *et al*[9] in Table 1, the sRR of 1.13 estimated from 13 cohorts was the almost the same level, but the CI was narrower. The sRR of men’s cohorts published more recently was the highest and was statistically significant. Cumulative meta-analysis showed that the sRR converged as it moved from the past to the present (Figure 3).

However, the results of the women’s cohorts showed that alcohol intake might not increase the risk of gastric cancer. This finding can be supported by the results of He *et al*[8], who reported that light alcohol intake was associated with a reduction in gastric cancer in women (sRR = 0.74, 95%CI: 0.57-0.98). In addition, incidence rates are two-fold higher in men than in women[1]. Thus, the sex variable in the association between alcohol intake and gastric cancer risk seems not to be a simple confounder but be an effect modifier having an interaction term[38]. In other words, seven cohorts adjusted for sex need to re-estimate outcomes stratified by sex.

***Inferences about subgroup analyses***

The subgroup analysis of 13 men’s cohorts indicated that there was statistical significance in Asians, in the group with the high level of adjustment for smoking status, and in the group adjusted for body mass index. Interestingly, the statistical significance was not shown in the group with a low level of adjustment for smoking status, and in the group not adjusted for body mass index. This is because a RR generally shifts to null as the potential confounder is strengthened. These phenomena strongly support the hypothesis that alcohol intake increases the risk of gastric cancer in men.

***Limitations***

The main limitation is that the category of alcohol intake varies in each study, such as times *per* week, amount consumed *per* day, none/moderate/heavy, or never/former/current drinker. Therefore, the author extracted the results of the highest and lowest levels from each study and applied a random effect model. Another limitation is that the author could not perform subgroup analysis for cardia and non-cardia because only three cohorts were selected. Thus, the author could not evaluate the argument by sex that “intestinal non-cardia carcinoma was accompanied by heavy alcohol consumption”[3].

**CONCLUSION**

In conclusion, the present study suggests that alcohol consumption increases the risk of gastric cancer in men. It is necessary to re-estimate the follow-up outcomes by stratification for sex to determine whether there is a sex difference in the association between alcohol intake and gastric cancer risk.

**ARTICLE HIGHLIGHTS**

***Research background***

The previous systematic reviews showed a statistically significant association between alcohol intake and gastric cancer risk in men. However, women did not have statistical significance in any of the meta-analyses.

***Research motivation***

The author hypothesized that alcohol intake’s association with gastric cancer risk may differ between men and women.

***Research objectives***

The aim was to investigate the suggested hypothesis targeting four previous meta-analyses by performing a meta-epidemiological review.

***Research methods***

After securing additional cohort studies meeting the selection criteria, updated meta-analysis and subgroup analysis by sex were conducted.

***Research results***

The subgroup analysis of the 13 men’s cohorts showed that there was statistical significance in Asians, in the group with a high level of adjustment for smoking status, in the group with the adjustment for body mass index, and in more recently published studies. These results were not found in the seven women’s cohorts.

***Research conclusions***

The present study suggests that alcohol consumption increases the risk of gastric cancer in men.

***Research perspectives***

It is necessary to re-estimate the follow-up outcomes by stratification for sex to determine whether there is a sex difference in the association between alcohol intake and gastric cancer risk.

**REFERENCES**

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Yusefi AR**, Bagheri Lankarani K, Bastani P, Radinmanesh M, Kavosi Z. Risk Factors for Gastric Cancer: A Systematic Review *Asian Pac J Cancer Prev* 2018; **19**: 591-603 [PMID: 29579788 DOI: 10.22034/APJCP.2018.19.3.591]

3 **Machlowska J**, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. *Int J Mol Sci* 2020; **21** [PMID: 32512697 DOI: 10.3390/ijms21114012]

4 **Wang C**, Yuan Y, Hunt RH. The association between Helicobacter pylori infection and early gastric cancer: a meta-analysis. *Am J Gastroenterol* 2007; **102**: 1789-1798 [PMID: 17521398 DOI: 10.1111/j.1572-0241.2007.01335.x]

5 **Bae JM**, Kim EH. Epstein-Barr Virus and Gastric Cancer Risk: A Meta-analysis With Meta-regression of Case-control Studies. *J Prev Med Public Health* 2016; **49**: 97-107 [PMID: 27055546 DOI: 10.3961/jpmph.15.068]

6 **Bae JM**, Kim EH. Dietary intakes of citrus fruit and risk of gastric cancer incidence: an adaptive meta-analysis of cohort studies. *Epidemiol Health* 2016; **38**: e2016034 [PMID: 27457064 DOI: 10.4178/epih.e2016034]

7 **Han X**, Xiao L, Yu Y, Chen Y, Shu HH. Alcohol consumption and gastric cancer risk: a meta-analysis of prospective cohort studies. *Oncotarget* 2017; **8**: 83237-83245 [PMID: 29137337 DOI: 10.18632/oncotarget.19177]

8 **He Z**, Zhao TT, Xu HM, Wang ZN, Xu YY, Song YX, Ni ZR, Xu H, Yin SC, Liu XY, Miao ZF. Association between alcohol consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies. *Oncotarget* 2017; **8**: 84459-84472 [PMID: 29137439 DOI: 10.18632/oncotarget.20880]

9 **Wang PL**, Xiao FT, Gong BC, Liu FN. Alcohol drinking and gastric cancer risk: a meta-analysis of observational studies. *Oncotarget* 2017; **8**: 99013-99023 [PMID: 29228746 DOI: 10.18632/oncotarget.20918]

10 **Tramacere I**, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, Islami F, Corrao G, La Vecchia C, Boffetta P. A meta-analysis on alcohol drinking and gastric cancer risk. *Ann Oncol* 2012; **23**: 28-36 [PMID: 21536659 DOI: 10.1093/annonc/mdr135]

11 **Murad MH**, Wang Z. Guidelines for reporting meta-epidemiological methodology research. *Evid Based Med* 2017; **22**: 139-142 [PMID: 28701372 DOI: 10.1136/ebmed-2017-110713]

12 **Nomura A**, Grove JS, Stemmermann GN, Severson RK. A prospective study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption. *Cancer Res* 1990; **50**: 627-631 [PMID: 2297702]

13 **Duell EJ**, Travier N, Lujan-Barroso L, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, Palli D, Krogh V, Panico S, Tumino R, Sacerdote C, Quirós JR, Sánchez-Cantalejo E, Navarro C, Gurrea AB, Dorronsoro M, Khaw KT, Allen NE, Key TJ, Bueno-de-Mesquita HB, Ros MM, Numans ME, Peeters PH, Trichopoulou A, Naska A, Dilis V, Teucher B, Kaaks R, Boeing H, Schütze M, Regner S, Lindkvist B, Johansson I, Hallmans G, Overvad K, Egeberg R, Tjønneland A, Lund E, Weiderpass E, Braaten T, Romieu I, Ferrari P, Jenab M, Stenling R, Aune D, Norat T, Riboli E, González CA. Alcohol consumption and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Am J Clin Nutr* 2011; **94**: 1266-1275 [PMID: 21993435 DOI: 10.3945/ajcn.111.012351]

14 **Freedman ND**, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol* 2007; **165**: 1424-1433 [PMID: 17420181 DOI: 10.1093/aje/kwm051]

15 **Stemmermann GN**, Nomura AM, Chyou PH, Yoshizawa C. Prospective study of alcohol intake and large bowel cancer. *Dig Dis Sci* 1990; **35**: 1414-1420 [PMID: 2226103 DOI: 10.1007/BF01536750]

16 **Galanis DJ**, Kolonel LN, Lee J, Nomura A. Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. *Int J Epidemiol* 1998; **27**: 173-180 [PMID: 9602395 DOI: 10.1093/ije/27.2.173]

17 **Sasazuki S**, Sasaki S, Tsugane S; Japan Public Health Center Study Group. Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. *Int J Cancer* 2002; **101**: 560-566 [PMID: 12237898 DOI: 10.1002/ijc.10649]

18 **Barstad B**, Sørensen TI, Tjønneland A, Johansen D, Becker U, Andersen IB, Grønbaek M. Intake of wine, beer and spirits and risk of gastric cancer. *Eur J Cancer Prev* 2005; **14**: 239-243 [PMID: 15901992 DOI: 10.1097/00008469-200506000-00007]

19 **Nakaya N**, Tsubono Y, Kuriyama S, Hozawa A, Shimazu T, Kurashima K, Fukudo S, Shibuya D, Tsuji I. Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. *Eur J Cancer Prev* 2005; **14**: 169-174 [PMID: 15785321 DOI: 10.1097/00008469-200504000-00013]

20 **Sjödahl K**, Lu Y, Nilsen TI, Ye W, Hveem K, Vatten L, Lagergren J. Smoking and alcohol drinking in relation to risk of gastric cancer: a population-based, prospective cohort study. *Int J Cancer* 2007; **120**: 128-132 [PMID: 17036324 DOI: 10.1002/ijc.22157]

21 **Larsson SC**, Giovannucci E, Wolk A. Alcoholic beverage consumption and gastric cancer risk: a prospective population-based study in women. *Int J Cancer* 2007; **120**: 373-377 [PMID: 17066442 DOI: 10.1002/ijc.22204]

22 **Sung NY**, Choi KS, Park EC, Park K, Lee SY, Lee AK, Choi IJ, Jung KW, Won YJ, Shin HR. Smoking, alcohol and gastric cancer risk in Korean men: the National Health Insurance Corporation Study. *Br J Cancer* 2007; **97**: 700-704 [PMID: 17637680 DOI: 10.1038/sj.bjc.6603893]

23 **Song HJ**, Kim HJ, Choi NK, Hahn S, Cho YJ, Park BJ. Gender differences in gastric cancer incidence in elderly former drinkers. *Alcohol* 2008; **42**: 363-368 [PMID: 18579337 DOI: 10.1016/j.alcohol.2008.04.005]

24 **Steevens J**, Schouten LJ, Goldbohm RA, van den Brandt PA. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. *Gut* 2010; **59**: 39-48 [PMID: 19828467 DOI: 10.1136/gut.2009.191080]

25 **Moy KA**, Fan Y, Wang R, Gao YT, Yu MC, Yuan JM. Alcohol and tobacco use in relation to gastric cancer: a prospective study of men in Shanghai, China. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 2287-2297 [PMID: 20699372 DOI: 10.1158/1055-9965.EPI-10-0362]

26 **Everatt R**, Tamosiunas A, Kuzmickiene I, Virviciute D, Radisauskas R, Reklaitiene R, Milinaviciene E. Alcohol consumption and risk of gastric cancer: a cohort study of men in Kaunas, Lithuania, with up to 30 years follow-up. *BMC Cancer* 2012; **12**: 475 [PMID: 23066954 DOI: 10.1186/1471-2407-12-475]

27 **Buckland G**, Travier N, Huerta JM, Bueno-de-Mesquita HB, Siersema PD, Skeie G, Weiderpass E, Engeset D, Ericson U, Ohlsson B, Agudo A, Romieu I, Ferrari P, Freisling H, Colorado-Yohar S, Li K, Kaaks R, Pala V, Cross AJ, Riboli E, Trichopoulou A, Lagiou P, Bamia C, Boutron-Ruault MC, Fagherazzi G, Dartois L, May AM, Peeters PH, Panico S, Johansson M, Wallner B, Palli D, Key TJ, Khaw KT, Ardanaz E, Overvad K, Tjønneland A, Dorronsoro M, Sánchez MJ, Quirós JR, Naccarati A, Tumino R, Boeing H, Gonzalez CA. Healthy lifestyle index and risk of gastric adenocarcinoma in the EPIC cohort study. *Int J Cancer* 2015; **137**: 598-606 [PMID: 25557932 DOI: 10.1002/ijc.29411]

28 **Jayalekshmi PA**, Hassani S, Nandakumar A, Koriyama C, Sebastian P, Akiba S. Gastric cancer risk in relation to tobacco use and alcohol drinking in Kerala, India--Karunagappally cohort study. *World J Gastroenterol* 2015; **21**: 12676-12685 [PMID: 26640345 DOI: 10.3748/wjg.v21.i44.12676]

29 **Ma SH**, Jung W, Weiderpass E, Jang J, Hwang Y, Ahn C, Ko KP, Chang SH, Shin HR, Yoo KY, Park SK. Impact of alcohol drinking on gastric cancer development according to Helicobacter pylori infection status. *Br J Cancer* 2015; **113**: 1381-1388 [PMID: 26379079 DOI: 10.1038/bjc.2015.333]

30 **Bae JM**, Kim EH. Citation Discovery Tools for Conducting Adaptive Meta-analyses to Update Systematic Reviews. *J Prev Med Public Health* 2016; **49**: 129-133 [PMID: 27055549 DOI: 10.3961/jpmph.15.074]

31 **Thomas DR**, Hodges ID. Dietary Research on Coffee: Improving Adjustment for Confounding. *Curr Dev Nutr* 2020; **4**: nzz142 [PMID: 31938763 DOI: 10.1093/cdn/nzz142]

32 **Harris RJ**, Bradburn MJ, Deeks JJ, Harbord RM, Altman DG, Sterne JAC. metan: Fixed- and random-effects meta-analysis. *Stata J* 2008; **8:** 3-28 [DOI: 10.1007/s00355-007-0273-9]

33 **Allen NE**, Beral V, Casabonne D, Kan SW, Reeves GK, Brown A, Green J; Million Women Study Collaborators. Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst* 2009; **101**: 296-305 [PMID: 19244173 DOI: 10.1093/jnci/djn514]

34 **Choi YJ**, Lee DH, Han KD, Kim HS, Yoon H, Shin CM, Park YS, Kim N. The relationship between drinking alcohol and esophageal, gastric or colorectal cancer: A nationwide population-based cohort study of South Korea. *PLoS One* 2017; **12**: e0185778 [PMID: 28973012 DOI: 10.1371/journal.pone.0185778]

35 **Wang Z**, Koh WP, Jin A, Wang R, Yuan JM. Composite protective lifestyle factors and risk of developing gastric adenocarcinoma: the Singapore Chinese Health Study. *Br J Cancer* 2017; **116**: 679-687 [PMID: 28125822 DOI: 10.1038/bjc.2017.7]

36 **Wang S**, Freedman ND, Loftfield E, Hua X, Abnet CC. Alcohol consumption and risk of gastric cardia adenocarcinoma and gastric noncardia adenocarcinoma: A 16-year prospective analysis from the NIH-AARP diet and health cohort. *Int J Cancer* 2018; **143**: 2749-2757 [PMID: 29992560 DOI: 10.1002/ijc.31740]

37 **Li Y**, Eshak ES, Shirai K, Liu K, Dong JY, Iso H, Tamakoshi A; JACC Study Group. Alcohol Consumption and Risk of Gastric Cancer: The Japan Collaborative Cohort Study. *J Epidemiol* 2021; **31**: 30-36 [PMID: 31902851 DOI: 10.2188/jea.JE20190304]

38 **Deandrea S**, Foschi R, Galeone C, La Vecchia C, Negri E, Hu J. Is temperature an effect modifier of the association between green tea intake and gastric cancer risk? *Eur J Cancer Prev* 2010; **19**: 18-22 [PMID: 19864955 DOI: 10.1097/CEJ.0b013e328330eb1a]

**Footnotes**

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**Figure Legends**



**Figure 1 Flow chart of the final selection of prospective cohort studies.**



**Figure 2 Forest plot of estimating the summary relative risk.** A: All; C: Cardia; N: Non-cardia; H: High level; L: Low level; Y: Yes; N: No; CI: Confidence interval.



**Figure 3 Cumulative meta-analysis for the risk of gastric cancer in men by alcohol intake.** A: All; C: Cardia; N: Non-cardia; CI: Confidence interval.

**Table 1 Summary of previous systematic reviews for evaluating the association between alcohol intake and gastric cancer risk**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Searching** | **Selected studies (Cohort)** | **Group** | **Summary relative risk (95% confidence interval)** | ***I2* (%)** |
| Han *et al*[7], 2017 | December 2016 | (23) | Both, HLL | 1.17 (1.00-1.34) | 79.6 |
|  |  | (7) | Men, HLL | 1.18 (1.06-1.30) | 0.0 |
|  |  | (1) | Women, HLL | 1.13 (0.79-2.25) | 0.0 |
| Wang *et al*[9], 2017 | December 2016 | (17) | Both, HLL | 1.19 (1.06-1.34) | 37.6 |
|  |  | 34 | Men, HLL | 1.21 (1.06-1.37) | 68.2 |
|  |  | 12 | Women, HLL | 1.18 (0.95-1.47) | 26.2 |
| He *et al*[8], 2017 | April 2017 | (22) | Both, HLL | 1.03 (0.99-1.08) | 21.9 |
|  |  |  | Men, heavy  | 1.13 (1.06-1.22) | 28.1 |
|  |  |  | Women, heavy | 1.33 (0.79-2.24) | 2.4 |

HLL: Highest versus lowest level.

**Table 2 Subgroup analysis by potential confounders1**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Men** | **Women** | **Both** |
| All |  | 1.18 (1.06-1.32) [13] | 1.07 (0.95-1.19) [7] | 1.13 (1.04-1.23) [27] |
| Region |
|  | Asia | 1.22 (1.09-1.36) [8] | 1.09 (0.91-1.29) [3] | 1.43 (1.02-1.28) [13] |
|  | Non-Asia | 1.12 (0.83-1.50) [5] | 1.07 (0.83-1.38) [4] | 1.11 (0.99-1.24) [14] |
| Level of adjustment of smoking status |
|  | Low | 1.14 (0.91-1.41) [7] | 1.07 (0.95-1.20) [5] | 1.16 (1.06-1.27) [10] |
|  | High | 1.19 (1.08-1.31) [6] | 1.09 (0.84-1.43) [2] | 1.12 (0.98-1.27) [17] |
| Adjustment of body mass index |
|  | No | 1.05 (0.83-1.34) [5] | 1.48 (0.93-2.36) [2] | 1.12 (0.92-1.36) [8] |
|  | Yes | 1.22 (1.08-1.37) [8] | 1.05 (0.96-1.17) [5] | 1.13 (1.03-1.24) [19] |
| Year of publication |
|  | Approximately 2005 | 1.08 (0.88-1.33) [4] | [0] | 1.08 (0.89-1.33) [5] |
|  | 2006-2010 | 1.07 (0.81-1.41) [3] | 1.48 (0.93-2.36) [2] | 1.14 (0.98-1.32) [8] |
|  | 2011- | 1.26 (1.02-1.56) [6] | 1.05 (0.95-1.17) [5] | 1.14 (1.00-1.29) [14] |
| Site |
|  | Cardia | 1.07 (0.79-1.44) [1] | 1.30 (0.43-3.90) [1] | 1.05 (0.81-1.35) [3] |
|  | Non-cardia | 0.75 (0.53-1.06) [1] | 0.66 (0.24-1.82) [1] | 0.84 (0.65-1.08) [3] |

1Summary relative risk (95% confidence interval) [number of cohorts].