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Long-Term Cardiovascular Mortality in Patients with Gastrectomy: A Meta-Analysis

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1. Abstract

1.1. Aims: A few studies have reported how much gastrectomy quantitatively reduced cardiovascular (CV) risk in patients. This meta-analysis study aimed to assess what percentage the gastrectomy could reduce CV risk in patients with peptic ulcers or gastric neoplasms compared with controls.

1.2. Methods: Through September 2019, studies reporting incidence or mortality ratios of Coronary Heart Disease (CHD) or stroke after gastrectomy were collected from EMBASE and PubMed. The meta-analysis with the random effects model of the estimate of CV mortality risk in patients with gastrectomy was compared with that in controls.

1.3. Results: A total of 130,436 patients who underwent gastrectomy in 14 studies were included in the meta-analysis. The mean follow-up periods ranged from 3.6 to 23.6 years. Compared with controls, gastrectomy was associated with an 11% reduction in the overall risk of CHD [risk ratio (RR) 0.89, 95% confidence interval (CI) 0.79-1.00]. In subgroup analysis, gastrectomy was associated with a 32% reduced risk of CHD incidence (RR 0.68, 95% CI 0.56-0.82), however did not reduce the CHD mortality (RR = 0.94, 95% CI 0.85-1.03). The effect of the overall risk on stroke was not significant (RR 0.97, 0.83-1.13). In subgroup analysis, gastrectomy significantly reduced the incidence of stroke by 24% (RR 0.76, 95% CI 0.67-0.87), while had no significant impact on stroke mortality (RR 1.07, 95% CI 0.87-1.32).

1.4. Conclusions: This meta-analysis showed that gastrectomy reduces the risk of CV incidence in patients and is more effective in reducing the risk of CHD than stroke compared with controls.

2. Introduction

Gastrectomy is currently the main treatment option for patients with gastric neoplasms, and peptic ulcers who failed to response to therapy. Though gastrectomy had been prevalent in patients with ulcers in the past, the incidence of peptic ulcers has decreased considerably over the past decades with the advent of anti-ulcer drugs to eradicate *Helicobacter pylori*, resulting in a decrease in number of gastrectomy in patients with ulcers [1]. Presently, gastrectomy are mostly performed on patients with gastric cancer, nearly half of the global incidence of which occurs in Eastern Asia [2]. The surgical treatment of early gastric cancer results in an excellent survival rate, higher than 90% of the 5-year survival rate [3]. The life expectancy of patients with gastric cancer has now increased.

Bariatric surgery including gastrectomy, improves obesity-related comorbidities by inducing weight loss by restricting the amount of food the stomach can hold. In meta-analyses [4, 5], diabetes was in complete remission in 76.8% of morbidly obese who had undergone bariatric surgery, hyperlipidemia improved in 70% or more of patients and hypertension was resolved in 61.7% of patients. Furthermore, echocardiography demonstrated the improvements in left ventricular mass. These resulted in reduced deaths from cardiovascular

(CV) disease in obese patients. Considering this, the long-term beneficial effects of gastrectomy on CV death in patients who underwent a gastrectomy for other diseases might be expected.

In 1982, Ross et al. reported, in a follow-up study of at least 15 years, that the number of deaths from ischemic heart disease in a cohort of 779 male patients with peptic ulcer surgeries was not significantly different from the predicted value, although rates of all-cause mortality increased. In this study, 80% among patients were heavy smokers and excess mortality was due to smoking-associated disease [6]. Whereas some studies of patients who received surgical treatment for peptic ulcers have shown unchanged and even increased mortality from ischemic heart disease [7, 8]. A few studies have reported stroke mortality after gastrectomy. In a 10-year prospective study of American Japanese men, Stemmermann et al. reported higher stroke mortality among patients who received partial gastrectomies for ulcers than that among the control subjects (mortality rate/1000, 27.9 for patients with a partial gastrectomy *vs.* 8.8 for control subjects) [7]. The positivity of gastrectomy on CV mortality of ulcer patients appeared to be weakened by smoking, however few studies have shown how much gastrectomy affects CV mortality in ulcer patients with smoking.

Meanwhile, a recent study of patients received gastrectomy for early gastric cancer reported a 65% reduction in CV mortality [0.35 Standardized Mortality Ratio (SMR), 95% confidence interval (CI) 0.22-0.53], and that the all-cause mortality was not significantly different from that of the general population [9]. Another recent study of ulcer patients has reported results that the incidence of stroke was lower in patients in the gastrectomy group than that in the control group (adjusted hazard ratio (HR) 0.8, 95% CI, 0.72-0.89) [10]. So far, researches has shown the CV mortality rate of patients with gastrectomy effect varies regardless of disease types.

In this study, we performed a meta-analysis of studies on Coronary Heart Disease (CHD) and stroke mortality in patients with gastrectomies to assess the long-term impact of gastrectomy on CV mortality. Both of diseases, ulcer and gastric cancer were all involved without limitation of time constraints. In addition, we performed subgroup analyses for each of CHD and stoke, disease types (ulcer vs. neoplasm) and smoking status, and discussed for each factor.

3. **Material and Methods**

A systematic review was performed using structured search terms following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]; the PRISMA checklist is presented in Supplemental (Table S1). The research questions regarding the patients, interventions, comparisons, outcomes, and study designs approach are described in Supplemental (Table S2).

Supplemental Table S1: PRISMA check list

Section/topic	#	Checklist item	Report (Y/N)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Y
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Y
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Y
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Y
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Y
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Y
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Y
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Y
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Y
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Y
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Y

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Y
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Y
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Y
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Y
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Y
RESULTS			
Study selection	17	Give the number of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Y
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Y
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Y
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Y
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Y
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	Y
Additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	Y
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Y
Limitations	25	Discuss limitations at the study and outcome levels (e.g., risk of bias), and at the review-level (e.g., incomplete retrieval of identified research, reporting bias).	Y
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Y
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of the funders for the systematic review.	Y

Supplemental Table S2: PICOS table for study question.

	Contents
Patients	Patients with ulcerative disease or gastric tumors
Intervention	Gastrectomy
Comparison	Incidence or mortality ratio of the control group
Outcome	RR
Study	Observational study
RR = risk ratio	

3.1. Search Strategy and Study Selection

In September 2019, two authors (S. J. Lee and T. K. Ha) performed a comprehensive computer literature search of two databases (EMBASE and PubMed) to identify relevant published studies without a time period limitation. An additional manual search using the reference lists of related literature was also performed. The studies identified from the literature search were evaluated for duplicates; then, full-text assessments were independently performed by two authors to determine the eligibility of an article. Studies not relevant to the present research questions were eliminated.

The following search criteria were used: ('gastrectomy' or 'gastric resection') and ('gastric cancer' or 'stomach cancer' or 'gastric tumor' or 'gastric neoplasm' or 'gastric benign disease' or 'gastric ulcer' or 'peptic ulcer' or 'duodenal ulcer') and ('coronary artery disease' or 'coronary heart disease' or 'ischemic heart disease' or 'cardiovascular risk' or 'cardiovascular disease' or 'cardiovascular mortality' or 'stroke' or 'cerebral artery disease'). All searches were limited to human studies written in English. All types of publications, any number of patients, and both prospective and retrospective studies were included. The inclusion criteria for the relevant studies were as follows:

- Patients with gastrectomies
- In patients with gastrectomies, 'Incidence or mortality of CHD or stroke data had been reported' or 'Incidence or mortality of CHD or stroke data should be extractable.'
- In controls, 'Incidence or mortality of CHD or stroke data had been reported' or 'Incidence or mortality of CHD or stroke data should be extractable.'

Studies that had reported SMR, HR, standardized HR (SHR), or observed/expected mortality (O/E) estimates with a corresponding 95% CI were included in this meta-analysis. For studies that provided results and information, based on which risk estimates and 95% CIs could be calculated, the risk estimates and 95% CIs were calculated. For studies that reported only point estimates without corresponding CIs or standard errors, or did not report the distribution of data for the computation of relative risks and CIs, conservative assumptions were made to estimate relative risk and CIs.

Publications such as review articles, conference papers, or letters, which did not contain original data, were excluded. When the data were published in more than one article, the most recent article was included. If incidence and mortality were reported together in one article, only mortality data were included. If two studies from different time periods were reported in one cohort, both studies were enrolled in the meta-analysis, but the number of enrolled patients was counted only once.

3.2. Data Extraction

Two reviewers independently extracted data from each article and recorded the data on a standardized form. The agreement was 78.6%. Any disagreement in data extraction was resolved by consensus. The following data were extracted from each study:

- First author name, article type, year of publication, hospital location, number of patients, age of patients, type of disease of patients, surgery type, follow-up period, CV disease (CHD, and/or stroke) incidence or mortality, and study design
- CV (CHD and/or stroke) incidence or mortality data with 95% CI
- Observed number of CV (CHD and/or stroke) deaths in patients with gastrectomies and expected number of CV (CHD and/or stroke) deaths in controls.
- Raw data as well as the number of CV (CHD and/or stroke) deaths in patients with gastrectomies and controls
- When the data were published separately by gender [male (M), female(F)] and each period, it was analyzed as it is.

3.3. Assessment of Risk of Bias

We generated funnel plots to assess the possibility of publication bias if there were >10 studies available in the meta-analysis. The asymmetricity of plots was tested with trim and fill methods and the pooled risk estimates were recalculated with the addition of those missing studies.

3.4. Quality Assessment

A quality assessment was developed based on the Newcastle-Ottawa scale. The quality assessment was independently performed by the same two reviewers, and the score was determined by consensus. A score of 6 to 8 was considered a high-quality report, while a score of 2 to 5 was considered a low-quality report. After quality assessment, all enrolled studies were assessed as high-quality studies (Supplemental Table S3).

3.5. Statistical Analysis

All analyses and corresponding plots were performed using the statistical software Comprehensive Meta-Analysis, version 2 (Biostat, NJ, USA) and R version 3.6.1 (R Foundation for Statistical Computing) using the "meta" and "metaphor" package. All different effect estimates (e.g. SMR, O/E) represent relative risk ratios (RRs) for the combined risk estimates of all cohorts. Heterogeneity was assessed by the likelihood ratio I^2 index, which was considered high when > 50%. Subgroup analysis was performed to determine whether some individual studies explained heterogeneity and to assess the consistency of the results.

Supplemental Table S3: Newcastle-Ottawa quality assessment scale.

		Selection				Comparability	Outcome			
First author	Year	Representative-ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Quality score
Ross	1982	★	★	★	★	★	★	★	★	8
Fischer	1984	★	★	★	★	★	★	★	★	8
Stemmer-mann	1984	★	★	★	★	★	★	★	★	8

Asano	1987	★	★	★	★	★	★	★	★	8
Tersmette	1991	★	★	★	★	★	★	★	★	8
Macintyre	1994	★	★	★	★	★	★	★	★	8
Lundegardh	1994	★	★	★	★	★	★	★	★	8
Staël von Hostein	1995	★	★	★	★	★	★	★	★	8
Svanes	1999	★	★	★	★	★	★	★	★	8
Lee YH	2013	★	★	★	★	★	★		★	7
Chen	2016	★	★	★	★	★	★		★	7
Chen	2017	★	★	★	★	★	★		★	7
Gendrano	2017	★	★	★	★	★	★	★	★	8
Shin	2018	★	★	★	★	★	★		★	7

4. Results

4.1. Study Selection

A total of 864 publications (184 from EMBASE, 664 from PubMed/MEDLINE, and 16 from manual searches) were identified (Figure 1). After the removal of 59 duplicates, a total of 805 publications remained. Based on the titles and abstracts, 121 publications were judged as potentially relevant and evaluated in more detail. After reviewing the full text, another 103 publications were excluded for not meeting the eligibility criteria. Of the remaining 18 publications, four were excluded from the meta-analysis due to insufficient data. Finally, 14 publications were included in this meta-analysis [6-10, 12-20].

4.2. Characteristics of Included Studies

(Table 1) shows the details of the 18 publications (17 articles and one thesis) related to CV incidence or mortality. Seven articles were from European countries, one article and one thesis were from the USA, specifically Honolulu, and eight articles were from Asian countries. Thirteen studies included patients with ulcers and 5 studies included patients with gastric cancer. Of the 13 studies on ulcer patients, five included a small number of patients with benign tumors and unknown diseases (Stemmermann et al., 12.3% of enrolled patients; Asano et al., 3.8%; Tersmette et al., 5.4%; Stael et al., 3.7%; and Gendrano et al., 2.0%). These patients were counted as ulcer patients in the meta-analysis. More than half of the enrolled patients were men, ranging from 55.3% to 100%. The median/mean age of the patients ranged from 42 to 71.6 years. Billroth I or Billroth II surgery was most common in ulcer patients, and subtotal or total gastrectomy with Billroth anastomosis was performed most frequently in patients with gastric cancer. As shown in (Table 1), the four studies that did not compare mortality in the control group were excluded from the meta-analysis [21-24].

4.3. Meta-Analysis

A total of 130,436 patients with gastrectomies from 14 studies were included in the meta-analysis. There were 29,023 (22.3%) patients with peptic ulcers and 101,413 (77.7%) patients with gastric neoplasms. The mean follow-up periods for the 11 studies reporting mortality RRs ranged from 6.2 to 23.6 years and the 3 studies reporting incidence RRs ranged from 3.6 to 5.4 years. The number of patients included in each study ranged from 347 to 98,936, and the median number of patients per study was 2,359. Seven studies reported both CHD and stoke data, six reported only CHD data, and one reported only stroke data.

(Figure 2) shows an 11% reduction in the overall risk of CHD events among patients with gastrectomies compared with controls who did not have gastrectomies (RR 0.89, 95% CI 0.79-1.00, I^2 88%). In subgroup analysis, gastrectomies were associated with a 32% reduced risk of CHD incidence (RR 0.68, 95% CI 0.56-0.82, I^2 86%), retrospectively, however did not reduce the CHD mortality (RR = 0.94, 95% CI 0.85-1.03, I^2 75%).

As compared with controls, gastrectomy did not reduce the overall risk of stroke events (RR 0.97, 95% CI 0.83-1.13, I^2 88%). In the subgroup analysis, gastrectomy significantly reduced the incidence of a stroke by 24% (RR 0.76, 95% CI 0.67-0.87, I^2 82%), while had no significant impact on stroke mortality (RR 1.07, 95% CI 0.87-1.32, I^2 79%).

Table 1: Details of the studies that mentioned cardiovascular incidence and mortality.

First Author	Year	Country	Enrollment Period (years)*	No. of Gastrectomy (% men)	Age (years)	Disease(n)	Surgical Procedure (n)	Follow-up (years)	Incidence or Mortality (n, rate, O/E, HR, SHR, SMR)
Ross (6)	1982	Scotland, Edinburgh	1947-1965	779 men	Range 30-59	Peptic ulcer	Gastrectomy	Minimum 15	Ischemic heart disease Actual No./ predicted No. of deaths 128/112.5
Koga (22)	1984	Japan, Yonago	1948-1977	1325 -84.50%	Mean 56.0 men, 55.0 women	DU (320), GU(713) Combined ulcer (287), Anastomotic ulcer (5)	BI (747), BII (565) TG (11), Proximal gastrectomy (2)	1-30**	No. of deaths Cerebrovascular 67, Cardiovascular 62

Fischer (12)	1984	Denmark, Copenhagen	1948-1956	1025 (81.0% men among 1000)	Median 44 (range, 18-78)	DU	BII	22-30	Cardiovascular disease mortality O/E, 95% CI 0.99 (0.85-1.13)
Stemmer-mann (7)	1984	USA, Oahu†	1965-1968	407 men, 7599 controls	NA	DU (131), GU(226) Tumor(50)	BI (192), BII (193) NA (22)	10	Mortality rate/1000, SE Stroke 27.9, SE 4.9 Coronary heart disease 18.5, SE 7.2
Asano (13)	1987	Japan, Nagoya	1965-1980	6662 (83.8%)	NA	In 6,169 patients, DU (1868), GU (3066), DU+GU (985), benign tumor (198), other benign disease (52)	In 6,169 patients, BI (5050), BII (215), BII+Braun (871), Total resection (33)	Mean 13.1, Sep. 1984 –May 1986,	Mortality ratio (O/E) Heart M:F 1.15:1.33 Stroke M:F 1.03:0.90
Tersmette (15)	1991	Netherlands, Amsterdam	1931-1960	2633 (84.7%)	Mean 42-45 men, 49-51 women	DU (1683), GU (807), Unknown benign (143)	BI (207), BII (2343) unknown (83)	50 <	Mortality ratio (O/E) Cardiovascular disease M:F 0.9:0.9 Cerebrovascular accidents M:F 0.8:0.9
Macintyre (14)	1994	Scotland, Edinburgh	1947 - 1968	2241 (76.8% men in 1293 deaths)	Median 53 (range 20-83) in 1293 deaths	DU	In 1293 deaths, BI (14), BII (774), gastroenterostomy (101), vagotomy+pyloroplasty (105), vagotomy+gastroenterostomy (272)	20-40	Mortality ratio, O/E (95% CI) Circulatory disease 0.97 (0.87-1.09)
Lundegardh (16)	1994	Sweden + 4 countries within the Uppsala health care region	1950-1958	6459 (83.3%)	NA	DU (3947) GU (7157) Ulcers of unknown location (757)	BI (1738), BII(4693) NA(28)	27-35	Cerebrovascular disease, Heart and vascular system disease, SMR (95% CI) 1951-1968; 0.8 (0.6-0.9), 0.7 (0.6-0.8) 1960-1985; 0.9 (0.8-1.1), 0.9 (0.8-0.9)
Staël von Hostein (17)	1995	Sweden, Lund	1930-1960	1575 (81.7%)	NA	DU (965) GU (551) Others (59)	BI(211), BII(1206), Other resection (3) Gastroentero-anastomosis (155)	29-59	Diseases of the heart and vascular system SMR, (95% CI) 0.91 (0.83-1.00)
Guadagni (21)	1997	Italy	1974-1987	172(55.3%)	< 50 (n=49) 51-57 (58) >58 (65)	Early gastric cancer	TG or SG + D0/D1 (or D2)	Median 7 (2-15)	Cardiovascular disease No. of deaths 2
Svanes (8)	1999	Norway, Bergen	1962-1972	817(NA)	NA	Peptic ulcer perforation (DU, GU)	Operation	Median 18.8	Ischemic heart disease SMR (96% CI) 1.3 (1.03-1.6) Cerebrovascular disease 1.0 (0.6-1.4)
Lee (9)	2013	Korea, Seoul	1995-2004	2,477 (66.8%)	20-88 (46 % between 40 and 59)	Early gastric cancer	ST or TG	Mean ± SD 6.2 ± 2.8	Cardiovascular SMR (95% CI) 0.35 (0.22-0.53)

Matsumoto (23)	2014	Japan, Nara	1997-2011	177 (75.7%)/ 798 (72.1%) controls	Mean 70.5 ± 7.4 severe, 71.6 ±8.3 mild CKD, 63.9 ±11.3 control	Gastric cancer with mild to severe CKD	Distal gastrectomy (120), TG (57)	Median 4.6	No. of deaths from severe CKD (24); mild CKD (32); control (157) Cardiovascular 4:3:6, Cerebrovascular 3:1:1
Matsumoto (24)	2016	Japan, Nara	Jan. 2000-Dec. 2012	1000 (83.9%)	Mean 70.8± 7.7 Group A, 71.5 ±7.7 Group B, 64.1 ±11.1 Group C	Gastric cancer	TG or SG + D1/D+ (or D2)	Median 4.7	Cardiovascular and cerebrovascular disease Deaths, Group A (n=32, ≥3 preoperative risk factor); B (n=142, 2 risk factors); C (n=826, 1 risk factor) Cardiovascular 4:2:6, Cerebrovascular 3:0:1
Chen (10)	2016	Taiwan	1998-2010	6,425 (72.2%)/ 25,602(72.2%)	65.5 ±14.4 for cohort, 65.4±14.4 for control	Peptic ulcer	SG with BII	Mean 3.64±3.73 for cohort, 5.06 ± 3.83 for control	Incidence, Crude HR (95%CI) Stoke 0.82 (0.74-0.90); Ischemic stroke 0.79 (0.70-0.88), Hemorrhagic stroke 1.01 (0.79-1.30)
Chen (18)	2017	Taiwan	1998-2011	5266 (73.4%)/ 20,899 (73.5%) controls	65.1 ±14.6 for cohort, 64.9±14.6 for control	Peptic ulcer	SG with BII	Mean 3.77 for cohort, 5.17 for control	Incidence of CHD, Crude HR (95% CI) 0.75 (0.67, 0.83)
Gendrano (19)	2017	USA, Oahu†	1965-1968	347(100%) 7,659 controls (100%)	NA	DU (113), GU (202), DU+GU (15) Unknown (13)	Gastrectomy with BI (171), BII (169), unknown (7)	Mean 23.6	Mortality of stoke and MI, RR±RD Ischemic stroke (1.91 ± 0.02), Hemorrhagic stroke (1.74 ± 0.01), Late effects of stroke (0.87 ± -0.00), Old MI (1.06 ± 0.00), Acute MI (0.83 ± -0.01)
Shin (20)	2018	Korea	2004-2011	98,936 (66.0%)/ 98,936 (66.0%) controls	57.9±11.7 for cohort, 57.9±11.7 for control	Gastric cancer	SG (79.4%), TG (20.6%)	Mean 5.4 for CHD Mean 5.3 for ischemic stroke	Incidence, SHR (95% CI) CHD; SG 0.62 (0.59-0.65), TG 0.5 (0.45-0.55) Stroke; SG 0.74 (0.71-0.78), TG 0.63 (0.58-0.69)

No. = number; O/E = observed/expected; SMR = Standardized mortality ratio; DU = duodenal ulcer; GU = gastric ulcer; B = Billroth; TG = total gastrectomy; CI = confidence interval; NA = not available; SE = standard error; M = male; F = female; SG = subtotal gastrectomy; HR = hazard ratio; CHD = coronary heart disease; SHR = subdistribution hazard ratio; CKD = chronic kidney disease; MI = myocardial infarction; RR = risk ratio; RD = risk difference

*Operation periods **The death record was confirmed on October 30, 1978. †Japanese ancestry.

Supplemental Table S4: Smoking status of patients from studies in Table 1.

First author	Year	Smoking status
Ross	1982	647 (83%) of 779 men at the time of operation
Koga	1984	NA
Fischer	1984	NA
Stemmermann	1984	Cigarettes/day; mean 14.1 in 407 gastrectomy patients, 10.1 in 7599 controls
Asano	1987	4287 (82.3%) of 5209 men, 254 (26.5%) of 960 women
Tersmette	1991	NA
Macintyre	1994	823 (82.9%) of 993 men, 53% of women*
Lundegardh	1994	NA

Staël von Hostein	1995	NA
Guadagni	1997	NA
Svanes	1999	NA
Lee YH	2013	In subgroup analysis, 16 of 51 gastrectomy patients (31.4%)
Matsumoto	2014	NA
Matsumoto	2016	NA
Chen	2016	NA
Chen	2017	NA
Gendrano	2017	Current smoker: 55% of gastrectomy patients, 36% of controls
Shin	2018	Screening subset population
		9258 (32.3%) of 28,752 gastrectomy patients
		9950 (24.2%) of 41, 187 controls (24.2%)
*Data for women first became available in 1955, NA = not available		

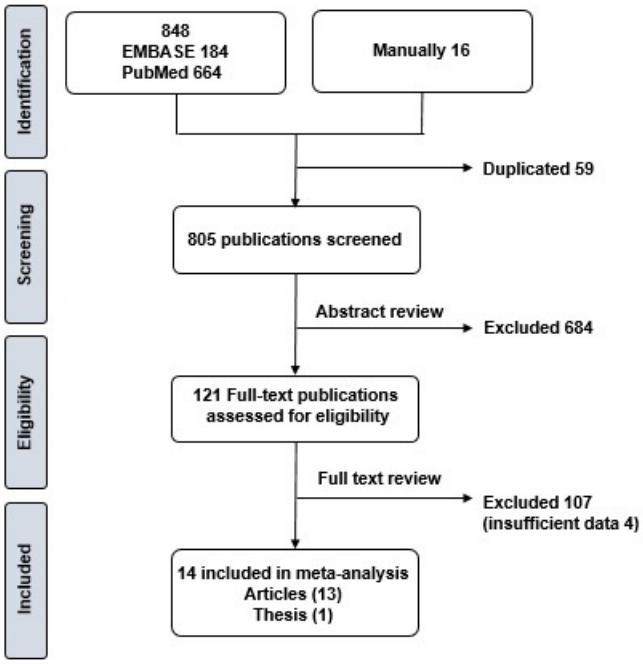


Figure 1: PRISMA study selection flow diagram.

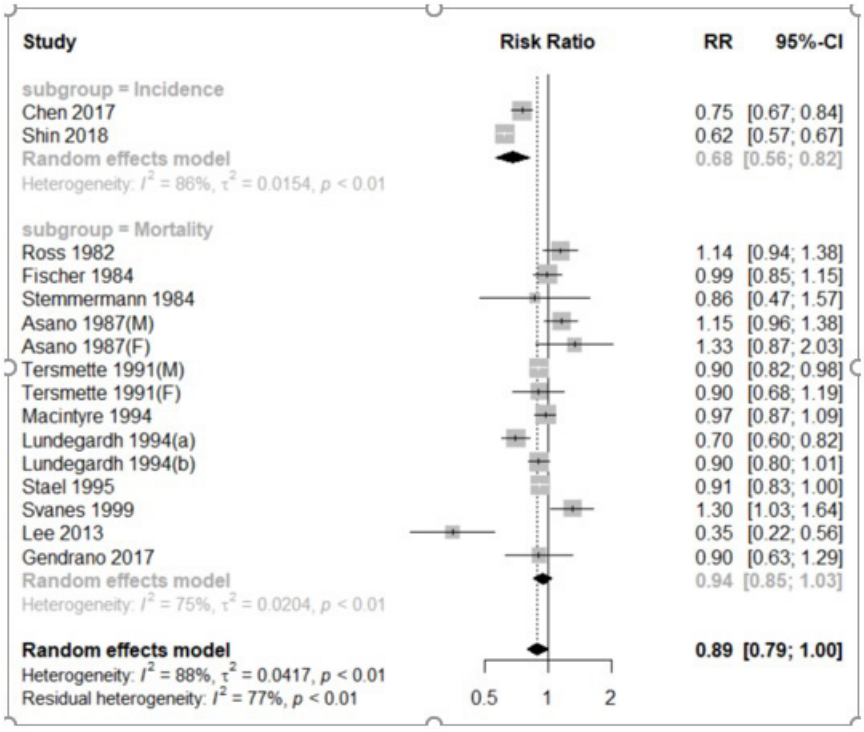


Figure 2: Forrest plots of risk ratios of cardiovascular disease in patients with gastrectomy. (a) Coronary heart disease.

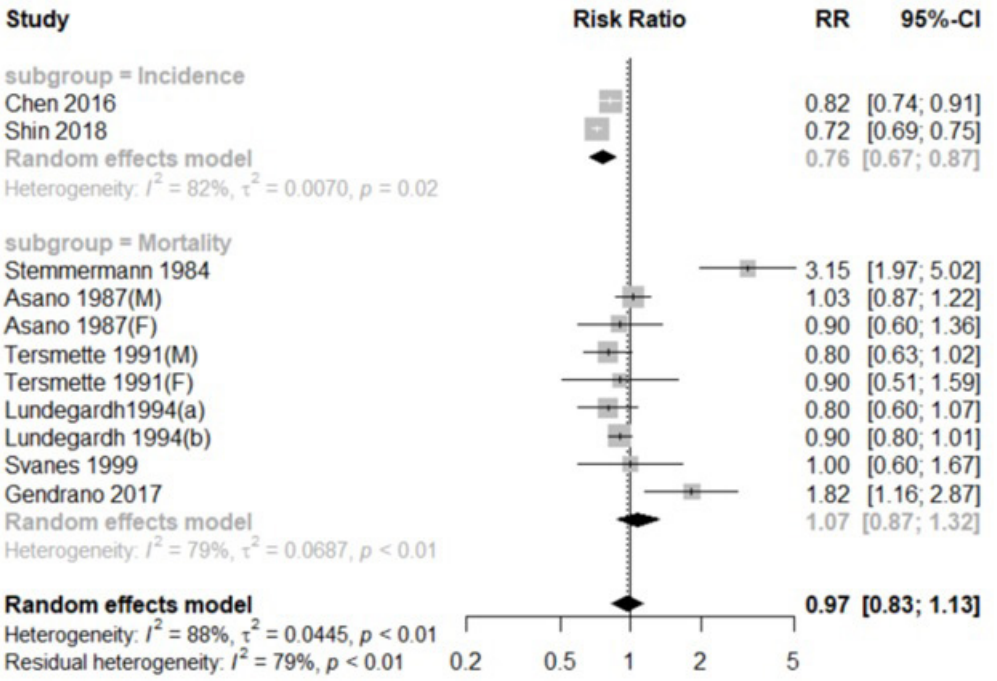


Figure 2(b): Stroke. The analysis is divided according to disease incidence and mortality.

Funnel tests using trim-and-fill methods were conducted for publication bias (Supplemental Figure S1). The figures show the asymmetricity indicating publication bias in both CHD and strokes. After the application of trim and fill, the adjusted pooled analysis for CHD revealed more reduced overall RR (adjusted RR 0.83, 95% CI 0.74-0.93), whereas there was a significant change in overall stroke RR (adjusted RR 0.76, 95% CI 0.65-0.88), indicating positive evidence of publication bias that affects the results.

5. Discussion

In this meta-analysis, gastrectomy significantly reduced the incidence of CHD and stroke by 32% and 24% in patients, respectively. Considering that the risk of myocardial infarction was reduced by approximately 50% in the meta-analysis of bariatric surgery [25], these significant reduction rates in patients are noteworthy. The reduced risk of CV diseases by bariatric surgery has been found to be due to weight reduction and improvement of hypertension, blood sugar levels, and lipid profiles [26, 27]. These are all risk factors associated with CV diseases and echocardiographic parameters that showed improvements in patients with bariatric surgery [5, 25]. Regarding CV mortality, no significant reduction was observed in both CHD and stroke mortality. In seven enrolled studies reporting both CHD and stroke events, gastrectomies were associated with a greater reduction in CHD than in strokes. Chen et al. and Shin et al. reported a 25% and 38% reduction in CHD incidence and 18% and 28% in stroke incidence, based on Taiwan's National Health Insurance program and the Korean National Health Insurance database, respectively [10, 18, 20].

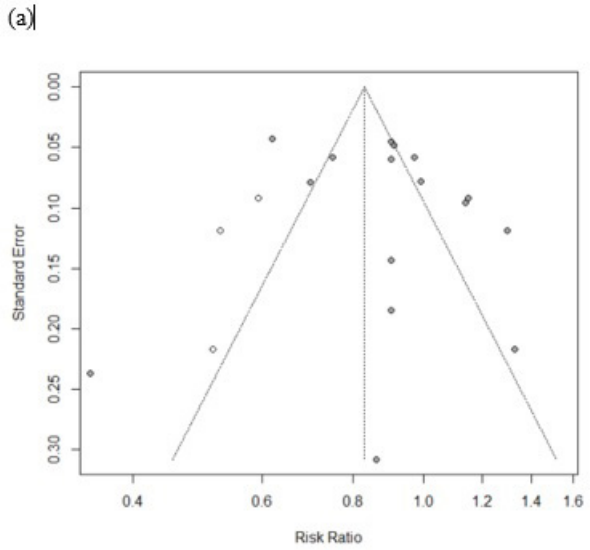
Data of both CHD and stroke were heterogeneous (I^2 88% and I^2 88%). This may be due to smoking status, disease types (ulcers vs. neoplasms) and surgical methods. Subgroup analyses were performed and discussed for each factor.

5.1. Smoking

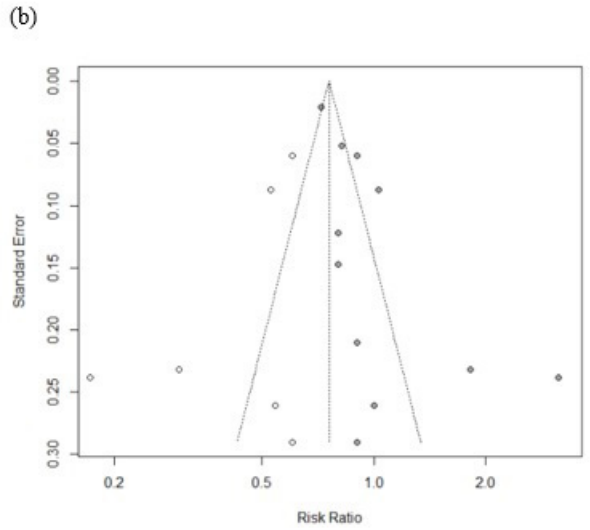
Some enrolled studies reported that gastrectomies were associated with increased mortality. Smoking has been considered one of the main causes for this [6, 13-15]. Smoking is a well-established risk factor for CHD and stroke, and a recent meta-analysis showed that no safe level of smoking exists for CV disease [28]. Six studies mentioned the percentage of patients who smoke (Supplemental Table S4) [6, 9, 13, 14, 19, 20]. To assess the impact of smoking on CV RR, studies were divided into two groups according to smoking status. The study was classified as a heavy smoking study if more than 50% of the enrolled patients were smokers.

In Supplemental (Figure S2a), the heavy smoking studies showed a higher RR for CHD than the light smoking studies (RR 1.06, 95% CI 0.94-1.20, I^2 43% for heavy smoking; RR 0.66, 95% CI 0.38-1.17 for light smoking), however it was not a significant change in RR for CHD. Similar results were found in the stroke analysis (Supplemental Figure S2b). The heavy smoking studies showed higher RR than the light smoking studies (RR 1.32, 95% CI 0.76-2.28, I^2 81% for heavy smoking; RR 0.73, 95% CI 0.66-0.81, for light smoking). We carefully consider that smoking status more affects stoke than CHD.

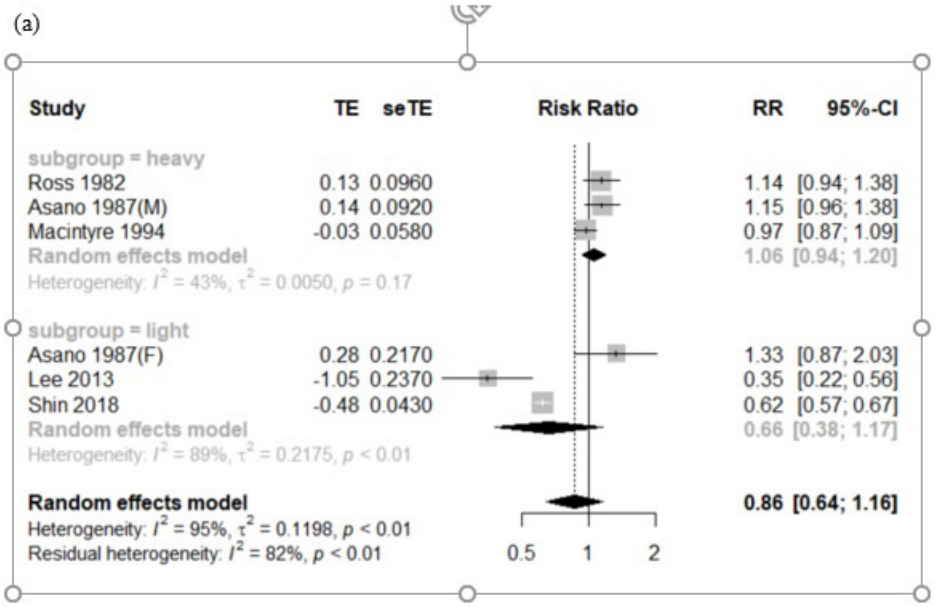
Smoking increased cases of smoking-related diseases, especially lung cancer, in the gastrectomy group [13, 15]. Of the enrolled studies, 9 reported all-cause mortality and 8 lung cancer mortality. The data in Supplemental Figure S3 showed that there were no significant differences in all-cause mortality among the gastrectomy patients (RR 1.06, 95% CI 0.98-1.14, I^2 92%) while lung cancer mortality increased significantly with a doubled risk (RR 1.94 95% CI 1.58-2.38, I^2 71%).



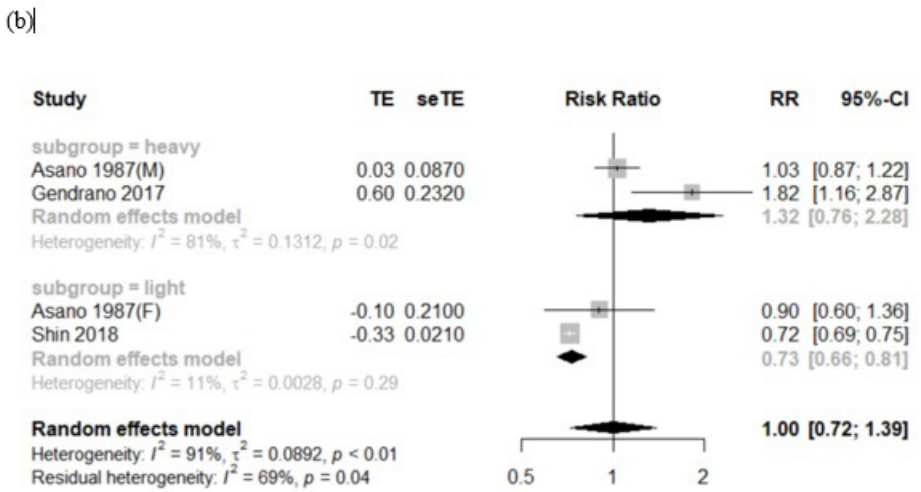
Supplemental Figure S1: Funnel plot with trim and fill. (a) Coronary heart disease



Supplemental Figure S1 (b) stroke: The closed dots indicate observed studies and the open dots indicate the missing studies imputed with the trim and fill method. The dashed lines that create a triangular area indicate the 95% confidence interval and the vertical dashed line represent the overall effect size.



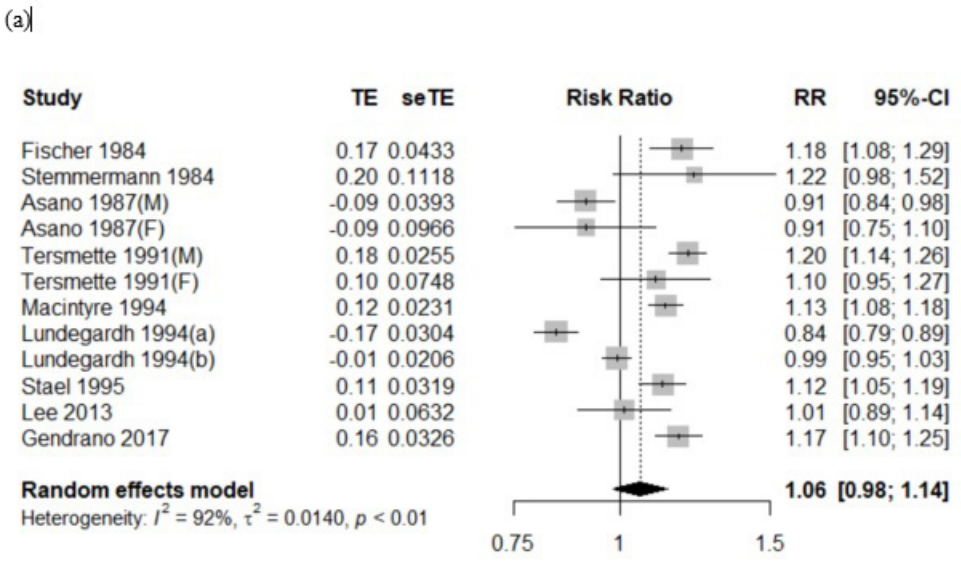
Supplementary Figure S2: Forest plots of risk ratios of cardiovascular disease in patients with gastrectomy according to smoking status. (a) Coronary heart disease



Supplementary Figure S2 (b): Stroke

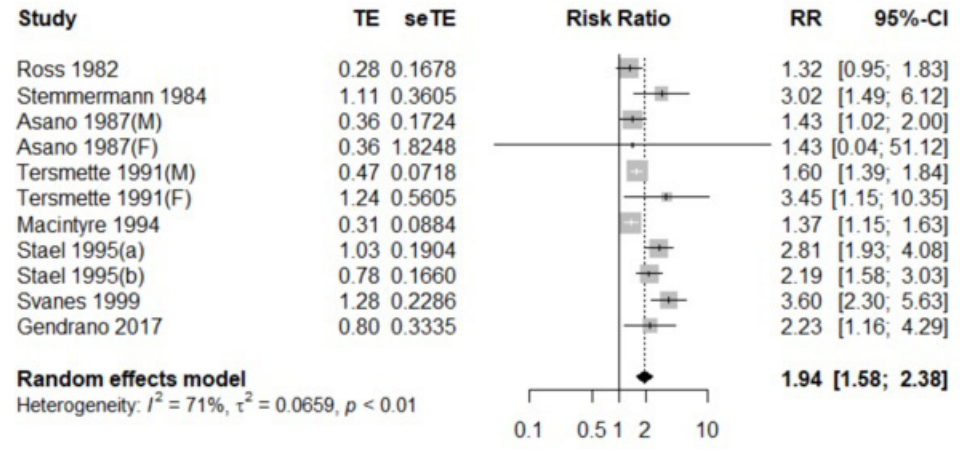
5.2. Diseases Type

The studies were also divided according to disease type (ulcer vs. gastric neoplasm). Supplemental (Figure S4a) shows that gastrectomy decreased the CHD RR by 51% in gastric neoplasm, but not in ulcer patients (RR 0.49, 95% CI 0.28-0.85, I^2 82% for gastric neoplasm; RR 0.94, 95% CI 0.87-1.03, I^2 73% for ulcers). Of the two studies with Korean patients with gastric neoplasm, one evaluated CHD mortality and the other CHD incidence [9, 20]. The RR of gastric neoplasm mortality was reduced by more than half compared with that of incidence [RR 0.35, 95% CI 0.22-0.56 for mortality [9] vs. RR 0.62, 95% CI 0.57-0.67 for incidence [20]]. In Supplemental (Figure S4b), gastrectomy showed a reduced stroke RR in gastric neoplasm patients in one study, and did not improve the stroke RR in ulcer patients (RR 1.02, 95% CI 0.86-1.21, I^2 80%). These differences seem to be due to smoking status, not disease type, as smoking is considered to be one of the major contributors to ulcers [29].



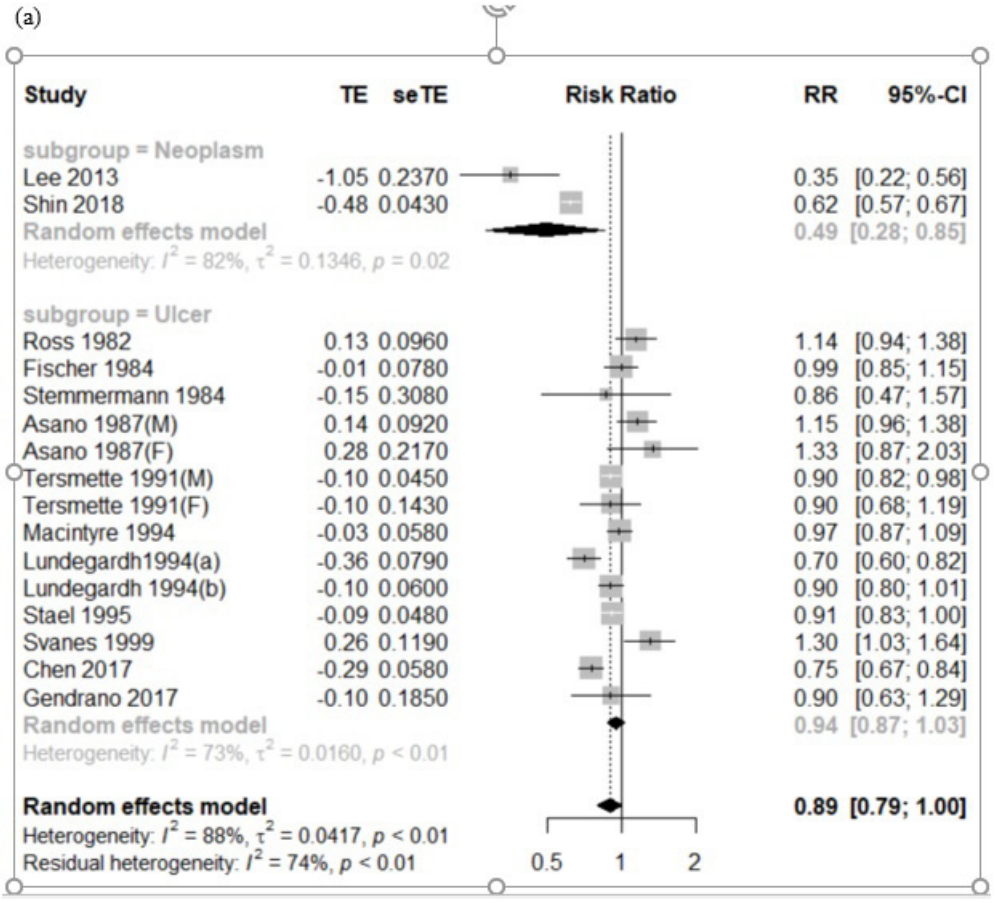
Supplementary Figure S3: Forest plots of mortality of patients with gastrectomy. (a) All-cause mortality.

(b)



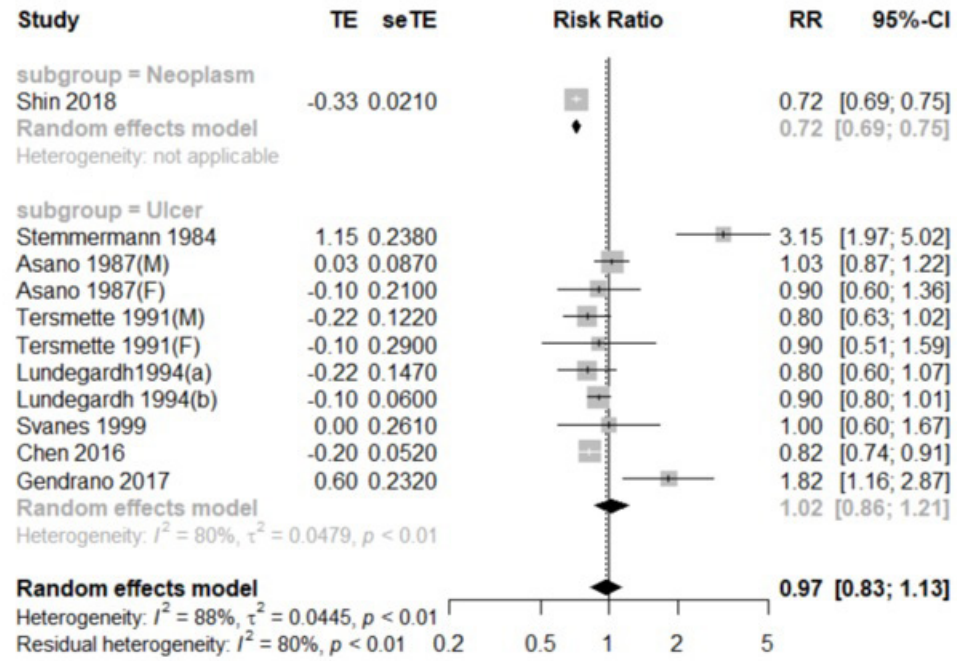
Supplementary Figure S3: (b) Lung cancer.

(a)



Supplementary Figure S4: Forest plots of risk ratios of cardiovascular disease in non-obese patients with gastrectomy according to disease type. (a) Coronary heart disease

(b)



Supplementary Figure S4 (b): Stroke

5.3. Surgical Types

Among enrolled studies in this meta-analysis, only one study assessed the impact of the type of gastrectomy [20]. Shin et al. reported that in patients with gastric cancer, a total gastrectomy reduced the incidence of CHD by 12% (RR 0.62, 95% CI 0.59-0.65 for a subtotal gastrectomy; RR 0.50, 95% CI 0.45-0.55 for a total gastrectomy) and stroke by 11% (RR 0.74, 95% CI 0.71-0.78 for a subtotal gastrectomy; RR 0.63, 95% CI 0.58-0.69 for a total gastrectomy) compared with a subtotal gastrectomy.

5.4. Stroke Types

There are two types of strokes: ischemic and hemorrhagic. Chen et al. only reported that the incidence between these two types was different in gastrectomy patients [10]. In that study, the incidence of ischemic stroke was significantly decreased in the gastrectomy patients, but the incidence of hemorrhagic stroke was not changed (HR 0.79, 95% CI 0.70-0.88 for an ischemic stroke; HR 1.01, 95% CI 0.79-1.30 for a hemorrhagic stroke).

One limitation of this study is heterogeneous data, as there were differences in factors such as smoking status, disease types and surgical methods. However, the quality of the enrolled studies was assessed as high.

6. Conclusion

This study analyzed 130,436 patients with gastrectomies (22.5% ulcers and 77.7% gastric neoplasms) with a follow-up period that ranged from 6.2 to 23.6 years for CV mortality and a follow-up that ranged from 3.6 to 5.4 years for CV incidence. These were sufficient to assess the RR of CV diseases. The degree of reduced incidence of CV disease by gastrectomy was higher in CHD than in stroke (32% and 24% for incidence of CHD and stroke). However, gastrectomy did not reduce the mortality of CHD and stroke, which might be due to smoking status.

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References

1. Hopkins RJ, Girardi LS, Turney EA. Relationship between Helicobacter pylori eradication and reduced duodenal and gastric ulcer recurrence: A review. Gastroenterology. 1996; 110(4): 1244-52.
2. Rahman R, Asombang AW, Ibdah JA. Characteristics of gastric cancer in Asia. World J Gastroenterol. 2014; 20(16): 4483-90.
3. Onodera H, Tokunaga A, Yoshiyuki T, Kiyama T, Kato S, Matsukura N, et al. Surgical outcome of 483 patients with early gastric cancer: prognosis, postoperative morbidity and mortality, and gastric remnant cancer. Hepatogastroenterology. 2004; 51(55): 82-5.
4. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. Jama.

2004; 292(14): 1724-37.
5. Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB. Bariatric surgery and cardiovascular outcomes: a systematic review. Heart. 2012; 98(24): 1763-77.
6. Ross AH, Smith MA, Anderson JR, Small WP. Late mortality after surgery for peptic ulcer. N Engl J Med. 1982; 307(9): 519-22.
7. Stemmermann GN, Heilbrun L, Nomura A, Rhoads GG, Glober GA. Late mortality after partial gastrectomy. Int J Epidemiol. 1984; 13(3): 299-303.
8. Svanes C, Lie SA, Lie RT, Soreide O, Svanes K. Causes of death in patients with peptic ulcer perforation: a long-term follow-up study. Scand J Gastroenterol. 1999; 34(1): 18-24.
9. Lee YH, Han SJ, Kim HC, Hyung WJ, Lim JS, Lee K, et al. Gastrectomy for early gastric cancer is associated with decreased cardiovascular mortality in association with postsurgical metabolic changes. Ann Surg Oncol. 2013; 20(4): 1250-7.
10. Chen CH, Lin CL, Kao CH. Subtotal Gastrectomy With Billroth II Anastomosis Is Associated With a Low Risk of Ischemic Stroke in Peptic Ulcer Disease Patients: A Nationwide Population-Based Study. Medicine (Baltimore). 2016; 95(16): e3481.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339: b2535.
12. Fischer AB. Twenty-five years after Billroth II gastrectomy for duodenal ulcer. World J Surg. 1984;8(3):293-302.
13. Asano A, Mizuno S, Sasaki R, Aoki K, Yokoyama H, Yokoyama Y. The long-term prognosis of patients gastrectomized for benign gastroduodenal diseases. Jpn J Cancer Res. 1987; 78(4): 337-48.
14. Macintyre IM, O'Brien F. Death from malignant disease after surgery for duodenal ulcer. Gut. 1994; 35(4): 451-4.
15. Tersmette AC, Offerhaus GJ, Giardiello FM, Brand R, Tersmette KW, Tytgat GN, et al. Long-term prognosis after partial gastrectomy for benign conditions. Survival and smoking-related death of 2633 Amsterdam postgastrectomy patients followed up since surgery between 1931 and 1960. Gastroenterology. 1991; 101(1): 148-53.
16. Lundegardh G, Helmick C, Zack M, Adami HO. Mortality among patients with partial gastrectomy for benign ulcer disease. Dig Dis Sci. 1994; 39(2): 340-6.
17. Stael von Holstein CC, Anderson H, Eriksson SB, Huldt B. Mortality after remote surgery for benign gastroduodenal disease. Gut. 1995; 37(5): 617-22.
18. Chen CH, Lin CL, Cheng YS, Jeng LB. Association Between Subtotal Gastrectomy with Billroth II Anastomosis and Coronary Heart Disease. Obes Surg. 2017; 27(6): 1604-11.
19. Gendrano. The Impact of gastrectomy on diabetes and related conditions, coronary heart disease, stroke, cancer and survival. 2017.
20. Shin DW, Suh B, Park Y, Lim H, Suh YS, Yun JM, et al. Risk of Coronary Heart Disease and Ischemic Stroke Incidence in Gastric Cancer Survivors: A Nationwide Study in Korea. Ann Surg Oncol. 2018; 25(11): 3248-56.
21. Guadagni S, Catarci M, Kinoshita T, Valenti M, De Bernardinis G, Carboni M. Causes of death and recurrence after surgery for early gastric cancer. World J Surg. 1997; 21(4): 434-9.
22. Koga S, Nishidoi H, Kaibara N, Tamura H, Yurugi E, Kimura O, et al. Follow-up study on the cause of death after surgery for gastric and duodenal ulcers with special reference to the incidence of residual stomach cancer. Zentralbl Chir. 1984; 109(12): 791-6.
23. Matsumoto S, Takayama T, Wakatsuki K, Tanaka T, Migita K, Nakajima Y. Short-term and long-term outcomes after gastrectomy for gastric cancer in patients with chronic kidney disease. World J Surg. 2014; 38(6): 1453-60.
24. Matsumoto S, Takayama T, Wakatsuki K, Tanaka T, Migita K, Ito M, et al. Preoperative Cardiac Risk Assessment and Surgical Outcomes of Patients with Gastric Cancer. Ann Surg Oncol. 2016; 23(2): S222-9.
25. Kwok CS, Pradhan A, Khan MA, Anderson SG, Keavney BD, Myint PK, et al. Bariatric surgery and its impact on cardiovascular disease and mortality: a systematic review and meta-analysis. Int J Cardiol. 2014; 173(1): 20-8.
26. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ : British Medical Journal. 2013; 347: f5934.
27. Ricci C, Gaeta M, Rausa E, Macchitella Y, Bonavina L. Early impact of bariatric surgery on type II diabetes, hypertension, and hyperlipidemia: a systematic review, meta-analysis and meta-regression on 6,587 patients. Obes Surg. 2014; 24(4): 522-8.
28. Hackshaw A, Morris JK, Boniface S, Tang J-L, Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. 2018; 360: j5855.
29. Li LF, Chan RL, Lu L, Shen J, Zhang L, Wu WK, et al. Cigarette smoking and gastrointestinal diseases: the causal relationship and underlying molecular mechanisms (review). Int J Mol Med. 2014; 34(2): 372-80.