# The Impact of Gastrectomy on Diabetes and Related Conditions, Coronary Heart Disease, Stroke, Cancer, and Survival: Follow-Up From the Honolulu Heart Program

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ABSTRACT OF THE DISSERTATION

The Impact of Gastrectomy on Diabetes and Related Conditions,

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**Rationale for the study**

Gastric surgery is coming into widespread use to treat obesity, but the effects of these operations for health in old age are not known. Here we examine the long term effects of partial gastrectomy which was used in the 20th century to treat peptic ulcers and shares features with some of today's bariatric (weight loss) operations. We compare long-term outcomes in 347 men with a partial gastrectomy who were subjects in a prospective study of 8006 American Japanese men in Honolulu with their non-operated peers.

**Methods**

Subjects were age 45-68 at the baseline examination in 1965-68 and survivors were assessed for diabetes and insulin resistance 25 years later. Incidence of heart attacks and strokes was ascertained from hospital records and incidence of cancer was obtained from the Hawaii Tumor Registry. Mortality data were collected by the state health department.

**Results**

Mean weight for the men with a prior gastrectomy was 11 pounds less than for their peers, a difference that persisted throughout. A substantially larger proportion of the gastrectomy group smoked cigarettes. At enrollment, the gastrectomy men had lower serum cholesterol, triglycerides, glucose and blood pressure than the other men. These differences also persisted except for blood pressure which increased more over time in the gastrectomy men than in the others. At the 25 year exam, systolic blood pressure was significantly higher in the gastrectomy men.

The gastrectomy men had a 50% lower incidence of diabetes and significantly less insulin resistance than their peers. There was no difference in the occurrence of coronary disease, but stroke incidence and mortality were both higher in the gastrectomy group. Mortality from smoking related causes (lung cancer and emphysema) were also increased. Stomach cancer was decreased by more than half after controlling for confounders.

**Conclusion**

The protection against diabetes is consistent with other reports and appears long-lasting and robust. “Remnant” stomach cancers that have been reported after gastrectomy were not found. The increase in blood pressure and stroke is worrisome and suggests the need for evaluation of this potential problem following the several bariatric surgical procedures now in widespread use.

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## INTRODUCTION

The famous 19th century American Transcendentalist poet, philosopher, and essayist Ralph Waldo Emerson was quoted as saying, “All diseases run into one, old age”. This quote speaks to the nature of chronic illness and how aging is inextricably connected to chronic illness. Aging as explained by Harris et al.[1] is a complex process involving a decline in physiological processes that are essential for life. As people age, there is a heightened susceptibility to life-threatening acute and chronic diseases. Further refining that definition, Harris goes on to say more broadly that, aging can be viewed as the general deterioration in human health over the life span generally associated with development of debilitating and life-threatening disease processes. Taking a different perspective, Medawar et al.[2] goes on to say that aging has been defined as the spectrum of changes that render human beings progressively more likely to die.

Globally, chronic non-communicable diseases such as heart disease, stroke, cancer, COPD; non-infectious diseases such as liver cirrhosis, diabetes, neurological disorders such as Alzheimer’s disease, and chronic renal failure accounted for about 60% of all deaths amounting to about 36 million people in 2009.[3] As these chronic diseases develop over time, for some, lifestyle changes or more formal health interventions may impact disease progression. For example, smoking cessation reduces the risk of heart attack and stroke by 50% within the first year after quitting[1] and sustained smoking cessation produces a gradual decrease in the risk of developing lung cancer as well as other tobacco-related cancers.[4]

As another example, with the continuing obesity epidemic, bariatric surgery, or surgery for purposes of weight loss, beyond being one of the most effective methods of weight loss has become one of the most commonly performed gastrointestinal operations

worldwide.[5] Aside from the weight loss, bariatric surgery has shown improvements in a variety of obesity-related comorbidities after a short-term follow-up.[6] Of all of the bariatric surgeries available, the sleeve gastrectomy has become the most utilized of them all.[7]

In a meta-analysis performed by Vest et al.[8] follow-up in studies examining sleeve gastrectomy ranged in length from 3 months to 14.5 years (mean, 4.8 years). Among those studies, the rates of partial or complete remission due to sleeve gastrectomy were 73% for diabetes, 63% for hypertension, and 73% for hyperlipidemia. In a systematic review by Gill et al.[9] the effect of sleeve gastrectomy on diabetes mellitus showed complete and partial remission rates at 13 months of follow-up of 66% and 27%, respectively. Sarkhosh et al.[10] reviewed the effect of sleeve gastrecomy on hypertension and found that 58% of patients showed remission at a mean of 17 months. The key and common point here is that the follow-up post procedure was relatively short. So, understanding long term-follow up of obesity related co-morbidities following sleeve gastrectomy is warranted.

A gastrectomy is a significant medical procedure where part or all of the stomach is surgically removed.[11] Initially, gastrecotmies were performed to treat stomach ulcers and remove cancers. The first successful partial gastrectomy was performed by Professor Theodor Billroth at his clinic in Vienna on January 29$^{th}$ 1881 to treat a patient who had developed pyloric cancer.[12] Over the years, the gastrectomy procedure evolved and improved helping many patients suffering from ulcers or cancer. With the advances in pharmaceutical agents to treat ulcers which later were found to be driven primarily by *Heliobacter Pylori* bacterial infection, gastrectomy to treat stomach or peptic ulcers has decreased shifting the majority of more current partial or total gastrectomies to treat malignant as well as benign cancers. During this evolution of the gastrectomy and its procedures, great success has been observed when gastrectomy has been utilized to

treat life-theatening obesity. In fact, the original partial gastrectomy Professor Billroth performed in 1881 is viewed as the predecessor and foundation for modern bariatric surgeries combating obesity.

Despite the long history and variations on gastrectomy, there have been few, if any studies that have examined the long-term effects of partial or complete gastrectomy. In a systematic review of bariatric surgeries by Puzziferri, et al.[13] 7,371 clinical studies were reviewed and 29 of them encompassing 7,971 met study criteria for inclusion. Studies were included if they described outcomes for gastric bypass, gastric band, or sleeve gastrectomy (common and current bariatric surgeries) procedures performed on patients who had a body mass index (BMI) of 35 or greater, had at least 2 years of outcome information, and had follow-up measures for at least 80% of the initial cohort. The results showed significant weight loss, type 2 diabetes remission, hypertension remission, and hyperlipidemia remission. What the study authors also concluded was that there were few bariatric surgeries that reported long-term results with sufficient patient follow up.[13]

There have been a few cohort-type epidemiological studies undertaken to explore the progression of disease over a long time horizon. One of the more famous studies was the Framingham Heart Study with the objective to identify the common factors or characteristics that contribute to cardiovascular disease over a long period of time in a large group of participants who had not yet developed overt symptoms of cardiovascular disease or suffered a heart attack or stroke.[14] It appears though that only one study in the elite class of ultra-long-term follow up studies collected data on study participants who had undergone gastrectomy prior to entering the study. The Honolulu Heart Program (HHP), an ultra-long-term cohort study, was designed to investigate the incidence of coronary heart disease and mortality in folks living in Hawaii who were of Japanese ancestry. A total of 8,006 men of Japanese ancestry were enrolled into the

trial and approximately 25 years of follow-up data was collected over 4 study visits (examinations). Additional surveillance and registry data beyond 25 years were collected to follow mortality as well as cancer development beyond the initial bounds of the study. Glober, et al. in 1974[15] were the first to publish on the gastrectomy component of the HHP via a cross-sectional study showing the men with a history of gastrectomy weighed less and had lower values for serum cholesterol, triglyceride, and blood pressure compared to the balance of the study population, the control group, who did not undergo a gastrectomy prior to entering the HHP.

Ten years later, Stemmerman, et al.[16] published a paper following up on the gastrectomy patients in the HHP in a paper titled “Late Mortality after Partial Gastrectomy”. The 10-year prospective study showed that “the age adjusted mortality rates in men with partial gastrectomy were slightly higher than in those with an intact stomach, but the difference failed to achieve statistical significance.” The excess of mortality was believed, in part, to be due to excess smoking by men who had ulcers of the stomach. “Death from coronary heart disease, an illness with a substantial association with smoking in men with an intact stomach was less frequent in men with gastrectomy, but the difference was not statistically significant”. The author surmised that men with partial gastrectomy had other characteristics that weakened the impact of smoking upon coronary disease risk: low blood pressure, low serum cholesterol, low body weight and increased alcohol consumption.[16]

The present thesis aims to follow-up and expand on the group of patients initially enrolled in the Honolulu Heart Program (HHP) over the 25+ years of follow-up who were identified as having partial gastrectomies and had been previously examined by Glober and Stemmerman,[15,16] In the first chapter, diabetes and related conditions of metabolic syndrome and insulin resistance will be examined in HHP patients who had undergone a

partial gastrectomy prior to entering the study. In the second chapter, overall mortality, survival, coronary heart disease (CHD), and cerebrovascular accidents (CVA)/stroke, will be examined in those same gastrectomy patients. And finally, in the third chapter, cancer, including lung cancer, prostate cancer, colorectal cancer, and stomach cancer will be examined to explore if gastrectomy patients fared differently than their non-gastrectomy counterparts. To our knowledge, this will be the first thesis to examine the putative effect of gastrectomy on health in old age.

## CHAPTER 1: THE IMPACT OF GASTRECTOMY ON DIABETES, METABOLIC SYNDROME, AND INSULIN RESISTANCE


### Abstract

#### Background/Purpose

Gastrectomy is a major surgical procedure involving the partial or complete removal of the stomach. Partial gastrectomy was widely used for treatment of peptic ulcer disease in the middle years of the 20$^{th}$ Century, and continues to be used for treatment of gastric cancer. The use of gastric surgery for the treatment of obesity has been growing rapidly in recent decades. A number of studies have documented favorable effects of gastrectomy on excess body weight and glucose metabolism, but few have followed subjects into old age. This study followed 45-68 year old men with a prior partial gastrectomy for 25 years and assessed the incidence of diabetes over this period as well as the prevalence of Metabolic Syndrome (MetS), and Insulin Resistance (IR) at the end of follow-up.

#### Methods

Three-hundred forty-seven men of Japanese ancestry participating in the Honolulu Heart Program (HHP) who had a partial gastrectomy prior to entering the study were compared to the remaining 7,659 HHP participants and their outcomes regarding incidence of T2DM, MetS, and IR were examined.

#### Results/Findings

The prevalence rates of T2DM at HHP study entry, were 7.20% (25/347) and 9.55% (730/7640) for the gastrectomy (GS) group and non-gastrectomy (NGS) group, respectively. The difference was not significant ($X^2$=2.1423, p=0.1433). Among the 3,323 participants participating in the first and the fourth exam (25 years of follow-up), the incidence rates of T2DM were 13.3% (18/135) and 26.51% (845/3188) for the GS and

NGS groups, respectively, a nearly two-fold significant reduction ($X^2$=11.6885, p=0.0006).

At the fourth exam, over 25 years after the study began, after controlling for age, smoking and alcohol use, the relative risk of developing T2DM in the GS group was 0.419 (95%CI: 0.253, 0.694, p=0.0007) compared to the NGS group suggesting a 58% reduction in risk among those who had a partial gastrectomy.

At the beginning of the HHP, among those patients surviving to Exam 4, 11.18% (17 of 152) of the GS group and 20.66% of the NGS group (763 of 3693) met the definition of MetS, ($X^2$=8.1076, p=0.0044). At the end of the HHP study, 11.36% of GS participants and 17.42% of NGS participants developed MetS ($X^2$=3.2536, p=0.0713). Mean waist circumference was significantly smaller for GS versus NGS patients (81.03 cm vs. 85.86 cm, t(1,2926) = 6.18, p< 0.0001) and presence of elevated glucose/diabetic factors were significantly different between the GS and NGS groups (14.06% of GS patients vs. 26.83% of NGS patients, $X^2$=10.29, p=0.0013). After controlling for age, smoking, and alcohol use, the relative risk of developing MetS in the GS group was 0.536 (95%CI: 0.298, 0.962, p=0.0366) compared to the NGS group suggesting a 46% reduction in risk after having a partial gastrectomy.

At study end, mean HOMA-IR values were significantly lower for GS compared to NGS participants ((3.40 (95%CI: 2.80, 4.00) versus 4.65 (95%CI: 4.42, 4.89), p=0.0002). After controlling for age, smoking and alcohol use, the relative risk of developing IR having had a GS was 0.502 (95%CI: 0.352, 0.716, p=0.0001), suggesting a 50% reduction in risk compared to those who did not have a partial gastrectomy.

Over the 26 years between the first and last exam, mean body mass index (BMI) remained significantly lower for GS patients (p<0.0001), but the between group

difference was relatively constant. while percentages of BMI categories between GS and NGS groups showed a shift in BMI category. At study entry (Exam 1), the percentages for patients who were non-diabetic and survived through Exam 4 in the categories underweight, normal weight, overweight, and obese were: 9.93%, 69.50%, 20.57%, and 0.00%, respectively, for the GS group and 2.22%, 62.24%, 33.53%, and 1.96%, respectively, for the NGS group. By the last exam (Exam 4), with the non-diabetic patients who survived through Exam 4, these percentages had shifted showing 18.44%, 69.50%, 11.35%, and 0.71%, respectively, for the GS group and 11.04%, 60.21%, 26.73%, and 2.02%, respectively, for the NGS group. There were more underweight patients and less overweight patients in both the GS and NGS groups. Weight, which remained significantly different between GS and NGS patients ($F,(3202)=34.16$, $p<0.0001$) across all examinations decreased between exam 3 and exam 4 after remaining relatively unchanged from Exam 1 through 3.

**Conclusions/Implications**

Study participants who had a gastrectomy prior to entering the HHP exhibited significant protection from T2DM incidence over 25 years of follow-up and had significantly less MetS than study participants who did not have a gastrectomy, although the difference became non-significant at study end. Men with partial gastrectomy were also less likely to develop IR than their NGS counterparts. A relatively constant mean BMI in addition to a category shift in WHO BMI definition away from overweight in favor of normal and underweight categories between the GS and NGS groups across all exams coupled with decreases in weight over the last 20 years of the study suggest gastrectomy provided no such similar protection from loss of lean muscle mass and/or decreased bone density, both hallmarks of the aging process.

## Introduction/Background

### Gastrectomy

In 1974, Glober et al.[15] reported on a group of 347 ambulant Japanese-American men with a prior partial gastrectomy for peptic ulcer disease who were among the 8006 participants in the Honolulu Heart Program, a prospective study of cardiovascular disease in the Hawaii Japanese. These individuals weighed less and had lower values for serum cholesterol and triglycerides, and blood pressure than did the other participating 7,598 men. A follow-up paper published ten years later showed that mortality rates in the men with partial gastrectomy were slightly, but not statistically significantly higher than in those with an intact stomach. The higher mortality was attributed by the authors to excess smoking by the operated men who had been selected for surgery because of their prior ulcer disease (an illness known to be associated with smoking). Despite the excess smoking, coronary heart disease deaths were slightly less frequent in the gastrectomy group, which was attributed to differences in other risk factors: lower blood pressure, serum cholesterol, and body weight and increased alcohol consumption.[16]

The present study extends the follow-up of these men to 25 years and focuses on Type 2 diabetes (T2DM) and related metabolic conditions, insulin resistance (IR) and metabolic syndrome (MetS). This is believed to be one of the longest detailed follow-ups of the effects of gastric resection and is unusual, too, in the advanced age (70-92) at which assessment of these outcomes was made.

### Type II Diabetes Mellitus

T2DM is a complex chronic metabolic disease characterized by high fasting blood glucose.[1] In classic T2DM, which develops primarily in adults and accounts for 90-95% of all diabetics, insulin is still produced and secreted by the pancreas. But, because of

insulin resistance of target cells coupled with relative insulin insufficiency, there is compromised glucose uptake and elevated blood glucose (hyperglycemia). Thus, T2DM is characterized by a mismatch between the amount of insulin that is produced and secreted by the Beta (β) cells of the pancreas and the amount needed to maintain normal blood glucose levels.[17]

Currently, T2DM is the most frequently diagnosed of the major, non-communicable diseases and the fastest growing chronic disease in the world.[18,19] Based on a survey of its 216 member nations and territories, the International Diabetes Federation (IDF) estimated that over 285 million people had diabetes in 2010. This was a 67% increase from the estimated 171 million people with diabetes in 2000.[20] The worldwide prevalence of T2DM more than doubled from 2000 to 2010, increasing from 2.8% to 6.4%.[20] The prevalence of T2DM increases exponentially with age reaching a maximum of approximately 14% in adults 80 years of age and older in European populations.[21] The greatest increase in prevalence has occurred among the elderly rising from less than 5% in 1970 to nearly 15% in 2010 for adults 65 years or older.[1] Deaths worldwide attributable to T2DM were estimated to be about 3.96 million, or 6.8% of deaths.[22]

**Metabolic Syndrome (MetS)**

Metabolic Syndrome (Syndrome X) is a constellation of clinical characteristics that pre-dispose patients to more serious, health conditions like T2DM.[1] Identifying MetS or components of MetS early enough in the disease process, may allow time to delay or even prevent subsequent, more serious disease by addressing the individual conditions comprising Mets.

Data from the National Health and Nutrition Examination Survey (NHANES) for the time period of 2003-2006, showed that about 34% of US adults met the criteria for MetS.

Prevalence estimates increased with age reaching levels higher than 50% for men and women 60 years and older. Currently, it is estimated that almost one-third of United States (US) adults or 66 million people are afflicted by MetS.[23]

A number of studies have shown that MetS, as well as its individual components, are predictive of the development of T2DM.[24,25,26,27] Estimates from the US, Western Europe, Japan, Australia, and elsewhere suggest that 75% of patients with pre-diabetes and 86% of patients diagnosed with T2DM also have MetS.[28] In fact, some investigators suggest that without treatment, virtually all patients with MetS will progress to T2DM. Other studies have also shown that the presence of MetS doubled the risk of myocardial infraction and stroke[29], while a meta-analysis of 21 prospective studies revealed that patients with MetS compared to those without, had a 35% increase in all-cause mortality, a 74% increased risk of cardiovascular disease, and a 76% increased risk of stroke.[30]

Several definitions of MetS have been proposed. The National Cholesterol Education Program's Adult Treatment Panel III (NCE ATP III) Report released by the National Institutes of Health-National Heart, Lung, and Blood Institute (NIH-NHLBI) and American Heart Association (AHA), lists a constellation of symptoms defining MetS as consisting of any three of the following conditions: (1) abdominal obesity (increased waist circumference); (2) atherogenic dyslipidemia (increased triglycerides and decreased HDL-cholesterol); (3) hypertension (high blood pressure); (4) insulin resistance (impaired glucose uptake in the presence of normal or elevated insulin levels); (5) a pro-inflammatory state (elevated C-reactive protein), and (6) a prothrombotic state (increased plasminogen activator inhibitor)[31]. There are other recognized definitions of MetS from the World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), and International Diabetes Foundation (IDF). The different

definitions have a number of commonalities, but there are nuances reflecting each group's priorities.[32]

While the underlying physiology and even the defining clinical components of MetS remain subjects of hot debate, it is undeniable that the complicated relationship of obesity, insulin resistance, hypertension, hyperlipidemia, and MetS markedly heightens the risk of T2DM as well other serious diseases.[1]

**Insulin Resistance (IR)**

Insulin resistance (IR) is a condition in which the body produces insulin but does not use it effectively. When people have IR, glucose builds up in the blood instead of being absorbed by the cells, leading to T2DM[33] as well as increased rates of hypertension.[34] In IR, muscle fat, and liver cells do not respond properly to insulin and cannot easily absorb glucose from the bloodstream. As a result, the body needs higher levels of insulin to help glucose cells. The β-cells in the pancreas try to keep up with this increased demand for insulin by producing more. As long as the β-cells are able to produce enough insulin to overcome the insulin resistance, blood glucose levels stay in the normal range. Over time though, IR can lead to pre-diabetes and even T2DM because the β-cells fail to keep up with the body's increased need for insulin. Without enough insulin, excess glucose builds up in the bloodstream, leading to diabetes, pre-diabetes, and other serious health disorders.[33] Longitudinal studies in adults have shown that IR is strongly predictive of the development of T2DM.[35] Although IR can be caused by a number of factors[36], the most common cause of insulin resistance is relative weight gain or obesity.

**Obesity**

The global epidemic of obesity is one of the most significant public health threats of the 21st century. Fueled primarily by excess calories and physical inactivity, the dramatic

increase in overweight and obesity over the past several decades is considered the major cause for the parallel rise in incident and prevalent diabetes.[37,38,39,40] The WHO defines obesity as excessive body fat that has accumulated to the point where health is negatively affected.[37,41]

The most recent global data reflect persisting upward trends in the number of overweight and obese adults and clearly indicate that the worldwide obesity pandemic is continuing unabated in the 21st century. In 2000, there were approximately 750 million overweight and 300 million obese adults, ages 15 years or older[41,42]; whereas 5 years later in 2005, 1 billion adults were overweight and more than 400 million were obese.[43] Thus, obesity is increasing at an annual rate of about 6.6%, which is at least five times greater than the current annual world population growth rate of 1.3%. The WHO had projected that by 2015, 1.6 billion adults would be overweight, with more than 700 million classified as obese, more than doubling the worldwide burden of these conditions within the first 15 years of the 21st century.[44] If global secular trends continue, by the year 2030, approximately 2.2 billion people will be overweight and 1.1 billion people will be obese.[45]

Obesity is the strongest modifiable predictor of T2DM. Maintaining a healthy weight or losing a moderate amount of excess weight have both been shown to improve metabolic health.[46,47,48,49,50,51] Weight gain is monotonically related to the risk of diabetes, meaning for every kilogram gained, there is a corresponding increase in diabetes risk. In fact, Koh et al.[52] demonstrated that compared to individuals of stable weight, those who gained weight more than doubled, tripled, or even increased by 9-fold their risk of diabetes, depending on how much weight they gained. Reciprocally, those who decreased their weight reduced their risk of diabetes. The levels of decreased risk were dependent on the amount of weight they lost[52] Not surprisingly, compared with a BMI of 21 $kg/m^2$ (roughly the mid-point of the WHO BMI normal category), the relative risk of developing

T2DM appears to rise exponentially with increasing BMI; relative risk rising to more than 40 for morbidly obese (greater than 40 kg/m$^2$) men and to more than 90 for morbidly obese women. Multifold-risk elevations are notable even for modest increases in BMI.[51] It is important to note that Asians (e.g. Japanese, Chinese, Korean, etc.) have a higher risk for T2DM than Caucasians, and that it occurs at a lower BMI and fat mass compared to other ethno-racial groups.[53,54] Although Asians have a low prevalence of obesity, they are still at higher risk of developing T2DM compared to Caucasian Americans, African Americans, and Hispanic Americans.[53]

Previous studies have examined obesity and weight in the HHP population. One study demonstrated significant differences in mean weight (61.1 kg versus 62.8 kg) and mean waist circumference (85.8 cm versus 87.4 cm) between non-diabetic and diabetic men, respectively, in the fourth and final examination of the HHP.[55] Another study investigating adiposity and coronary heart disease, reported a mean BMI of patients participating in examination 4 of 23.43 kg/m$^2$ (SD=3.1) and a waist circumference of 86.09 cm (SD=8.7).[56] And a third study, showed BMIs of 25.5 kg/m$^2$ (SEM=0.1) and 22.9 kg/m$^2$ (SEM=0.1) between patients in the HHP who were hyperinsulemic or not, respectively.[57] Taken together, these results show a consistent pattern among obesity indicators that describe HHP patients as normal in weight or barely overweight, but certainly well below what would be considered obese.

In summary, the present study aims to follow-up and expand on a group of patients initially enrolled in the Honolulu Heart Program (HHP) who were identified as having partial gastrectomies before study entry.[15] This is the first paper, to our knowledge to examine the putative effect of gastrectomy on T2DM, MetS, and IR in old age.

## Methods

### Study Design

### Data Source-Honolulu Heart Program

In the 1950's, Gordon and others observed that while overall mortality rates for men in the US and Japan were similar, the mortality from stroke was substantially higher and for coronary heart disease (CHD) was much lower in Japan.[58] To explore this phenomenon. the Honolulu Heart Program (HHP) was initiated in Hawaii, and plans were made to compare its findings to cohorts of Japanese men in Japan and in California. The purpose of this effort was to assess formally the magnitude of the difference in CHD and mortality between Japanese living in Japan and those living in Hawaii.

The target participants for the Hawaii study were "non-institutionalized men of Japanese ancestry, born 1900-1919, …{and} resident on the island of Oahu."[59] To identify these individuals, 165,000 selective service registry cards from World War II were reviewed, looking for birthdates between 1900 and 1919 and Japanese last names or a notation of Japanese national origin.[59] Of the 22,892 names that met these criteria, 12,417 and had an apparent mailing address on Oahu. A letter introducing these individuals to the study was sent with a preliminary questionnaire in 1965. After appropriate follow-up 1,269 questionnaires were returned unopened by the post office, and 1,270 were simply not returned. Of the remaining 9,878 potential participants, 1,692 refused examination and 180 died before the study could begin. From October 1965 to 1968 the 9878 questionnaire respondents were sequentially invited to participate in a baseline interview and health examination. Of these, 8,006 men ultimately participated and became the HHP study population.[59]

The interview at the first examination included informed consent procedures and captured family and personal history of illness, sociological history, smoking status,

dietary habits, and physical activity level. As part of a medical examination, measurements of blood pressure, weight, height, skinfold thickness, and other anthropometric measures were made and an electrocardiogram (ECG), spirometry, and urinalysis were done. The men were not fasting, but blood was collected 1 hour after a 50g glucose load and analyzed for serum cholesterol, triglycerides, glucose, uric acid, and hematocrit.[60] Surveillance for all relevant hospitalizations of these men was initiated in 1965 in cooperation with all civilian acute care Oahu hospitals, and diagnoses “of any type of heart disease, CVA, or pulmonary embolus" triggered medical record abstraction by trained research personnel.[60] These abstracts were adjudicated by a panel of physician investigators to confirm that there was evidence to support the coded diagnosis. Participants were also periodically mailed questionnaires on illnesses "suggestive of cerebrovascular disease or CHD."[60] Mortality was measured by daily reviews of death certificates filed at the Hawaii State Health Department and the obituary section of local newspapers.[59] Cancer surveillance was accomplished by matching the names and birth dates of the participants to the state cancer registry.

HHP participants returned to complete follow-up examinations collecting information similar to that from the initial exam (Exam1) at Exam 2 (1967-1970), Exam 3 (1971-1974), and Exam 4 (1991-1993). Additionally, a subset of HHP participants came back for additional follow-up visits as part of a sub-study on lipids at Lipoprotein Exam 1 (1970-1972), Lipoprotein Exam 2 (1975-1978), and Lipoprotein Exam 3 (1980-1982).

**Study Participants**

**Gastrectomy Group (GS) and Non-Gastrectomy Group (NGS)**

At the first examination the subjects were asked about previous surgeries and the relevant medical records of all those reporting stomach surgery were independently reviewed (Glober et al, 1974).[15] This led to the identification of 347 men with a

documented previous partial gastrectomy, nearly all for peptic ulcer disease, termed here “the gastrectomy (GS) group”. The remainder of the men in the cohort are termed the non-gastrectomy group (NGS). Of GS men, 171 (49.3%) had gastroduodenal anastomoses (Billroth I), 169 (48.7%) had gastrojejunal anastomoses (Billroth II), and 7 (2%) had a reconstruction that could not be determined from medical records (Table 1). Within this same set of patients, 113 (33.7%) were diagnosed with a duodenal ulcer, 202 (58.2%) were diagnosed with a gastric ulcer, 15 (4.3%) were diagnosed with both a duodenal ulcer and a gastric ulcer, and 13 (3.7%) had a diagnosis of either ‘other’ or ‘unknown’ (Table 2). Regarding vagotomy, 267 (77.0%) patients did not have a vagotomy, 65 (18.7%) patients did have a vagotomy, and in 15 (4.3%) patients this could not be determined (Table 3). The extent of gastric resection was recorded for two-thirds of the group. Nearly all the men had a resection in the range of 26%-90% of their gastric tissue with the median falling between 50% and 67% (Table 4).

Table 1: Summary of Gastrectomy Reconstructions in GS Group

| Operation | Frequency | Percent of Total |
|---|---|---|
| Billroth I | 171 | 49.28% |
| Billroth II | 169 | 48.70% |
| Pyloroplasty | 0 | 0.00% |
| Unknown | 7 | 2.02% |
| Total | 347 | 100.00% |

Table 2: Summary of Diagnoses Leading to Gastrectomy in GS Group

| Diagnosis | Frequency | Percent of Total |
|---|---|---|
| Duodenal Ulcer | 117 | 33.72% |
| Gastric Ulcer | 202 | 58.21% |
| Both Duodenal and Gastric Ulcers | 15 | 4.32% |
| Other | 11 | 3.17% |
| Unknown | 2 | 0.58% |
| Total | 347 | 100.00% |

Table 3: Summary of Vagotomy Status in GS Group

| Vagotomy Status | Frequency | Percent of Total |
|---|---|---|
| No | 267 | 76.95% |
| Yes | 65 | 18.73% |
| Unknown | 15 | 4.32% |
| Total | 347 | 100.00% |

Table 4: Percent of Stomach Removed Among GS Group

| % Stomach Removed | Frequency | Percent of Total |
|---|---|---|
| None | 0 | 0% |
| 1 -25% | 1 | 0.29% |
| 26-40% | 9 | 2.59% |
| 41-50% | 42 | 12.10% |
| 51-66% | 89 | 25.65% |
| 67-75% | 78 | 22.48% |
| 76-90% | 12 | 3.46% |
| 91-99% | 3 | 0.86% |
| Unknown | 113 | 32.56% |
| Total | 347 | 100.00% |

**Study Endpoints/Definitions**

**Prevalence of Diabetes**

Prevalence of diabetes was evaluated at Exam 1. Between 1965 and 1968, patients who answered “yes” to the question “Have you ever had diabetes?" or who said they were taking medications for diabetes were considered to be prevalent cases at study entry.

**Incidence of Diabetes**

Incidence of new cases of T2DM was evaluated at Exam 4 among those without diabetes at Exam 1. A composite variable was created where T2DM was considered to be present if one or more of the following three conditions were met: 1) fasting glucose greater than or equal to 126 mg/dL, 2) 2-hour post-prandial glucose greater than 200 mg/dL after an oral glucose load, or 3) reporting current use of medications to treat T2DM. All incident cases of diabetes were considered to be Type 2.

### Metabolic Syndrome (MetS)

Incident cases of MetS were evaluated via analyses of Exam 4 data. Following the International Diabetes Foundation (IDF)-Joint consensus definition, MetS was defined by: a) a waistline circumference > 90cm; b) a systolic blood pressure greater than 130 mmHg or a diastolic blood pressure greater than 85 mmHg; and c) meeting at least one of three criteria for T2DM: fasting blood glucose greater than 125 mg/dL or a 2-hour post-load blood glucose > 200 mg/dL, or taking diabetes medication at Exam 4.[32]

### Insulin Resistance (IR)

Insulin resistance was calculated by entering fasting insulin and fasting glucose values collected from available patients providing data at Exam 4 into the equations of homeostatic model assessment for insulin resistance (HOMA-IR). The homeostatic model assessment for insulin resistance (HOMA-IR) is a widely used surrogate measure for insulin resistance that has been validated against the gold standard of the glucose clamp procedure.[61]

### Physical Activity Index (PAI)

A physical activity index (PAI) was collected at Exam 1 and Exam 4. It was estimated for each study participant by recording the number of hours usually spent in a 24 hour period that fell into one of five different activity level categories. Those categories were basal (e.g. sleeping or reclining), slight (causal walking), moderate (carpentry or gardening), and heavy (lifting or digging). The estimate of physical activity was calculated by multiplying the number of hours spent in each activity by a weighting factor that was based on the estimated amount of oxygen consumed (in liters per minute) that was needed to perform the activities at each of the five levels. To arrive at the overall score, the weighted estimates across the five activity levels were summed.[62]

### Body Mass Index (BMI)/Percent Body Fat

Body mass index (BMI) was collected at Exams 1, 2, 3, and 4 as the ratio of weight in kilograms to the square of the height in meters. It is a global metric used to measure and classify levels of general adiposity and associated obesity-related chronic disease risk among adults.[1] For classification purposes, the 'International Classification of adult underweight, overweight and obesity according to BMI' table created by the WHO was utilized.[63] See Table 5

Table 5: The International Classification of adult underweight, overweight and obesity according to BMI

| **Classification** | **BMI [kg/m$^2$]** | |
|---|---|---|
| | **Principal cut-off points** | **Additional Cut-off points** |
| **Underweight** | < 18.50 | <18.50 |
| Severe thinness | <16.00 | <16.00 |
| Moderate Thinness | 16.00 – 16.99 | 16.00 - 16.99 |
| Mild thinness | 17.00 – 18.49 | 17.00 – 18.49 |
| **Normal range** | 18.50 - 24.99 | 18.50 – 22.99 |
| | | 23.00 - 24.99 |
| **Overweight** | ≥ 25.00 | ≥ 25.00 |
| Pre-obese | 25.00 – 29.99 | 25.00 – 27.49 |
| | | 27.50 – 29.99 |
| **Obese** | ≥ 30.00 | ≥ 30.00 |
| Obese Class I | 30.00 – 34.99 | 30.00 – 32.49 |
| | | 32.50 – 34.99 |
| Obese Class II | 35.00 – 39.99 | 35.00 – 37.49 |
| | | 37.50 – 39.99 |
| Obese Class III | ≥ 40.00 | ≥ 40.00 |

Even though BMI is a highly reproducible and widely accepted obesity metric, providing a good indication of adiposity for the majority of people, it is not a perfect measure as it is influenced by the extent of musculature and weight of bone. Skinfold measurements, which are a more direct measure of adiposity (but are less reproducible), were also collected as described below.[64]

### Blood Pressure

At the first exam, sitting blood pressure was collected twice by a nurse and once by a physician. The mean systolic and diastolic measurements were used. Although for the purposes of determining MetS blood pressure cutoffs are 130 mmHg systolic and 85 mmHg diastolic, interpretation of blood pressure follows the American Heart Association healthy and unhealthy blood pressure ranges[65] as shown in Table 6 below:

Table 6: Table of Blood Pressure Categories

| Blood Pressure Category | Systolic (mmHg) | | Diastolic (mmHg) |
|---|---|---|---|
| Normal | < 120 | And | < 80 |
| Prehypertension | 120-139 | Or | 80-89 |
| High Blood Pressure (Hypertension) Stage 1 | 140-159 | Or | 90-99 |
| High Blood Pressure (Hypertension) Stage 2 | ≥ 160 | Or | ≥ 100 |
| Hypertensive Crisis (Emergency care needed) | > 180 | Or | > 110 |

### Study Oversight

This analysis of HHP data was approved by the Kuakini Medical Center as well as the Rutgers University institutional review boards.

### Statistical Analyses

#### Summary Statistics

For all continuous variables, means and 95% confidence intervals were reported by Exam and gastrectomy status as either a gastrectomy patient (GS) or a non-gastrectomy patient (NGS). For all categorical variables, frequencies and percentages were reported by Exam and gastrectomy status as either a gastrectomy patient (GS) or a non-gastrectomy patient (NGS).

To examine changes in individual variables from Exam 1 through Exam 4 between the GS and NGS groups, chi-square tables, independent samples t-tests and repeated

measures ANOVA models were constructed. Variables were examined at all visits from Exams 1 through 4 that have data at those visits. Analyses focused on study participants who survived through and were able to provide data at Exam 4, but baseline data for the other men participating in Exam 1 are also analyzed. Overall between-group and within-group differences between the GS and NGS groups were analyzed using the ANOVA models. Individual comparisons of variables at each visit by GS versus NGS group were analyzed using independent samples t-tests. Differences in frequencies were analyzed using chi-square analysis on 2 x k tables.

Correlational matrices were constructed to examine the correlations among variables.

**Type 2 Diabetes Mellitus (T2DM)**

For calculating prevalence of T2DM, frequency counts by gastrectomy status and prevalence of diabetes at Exam 1 contingency tables and chi-square analysis were used. For calculating incidence, a similar analysis was done except that T2DM frequency counts were run at Exam 4 (end of study) and prevalent cases of diabetes at Exam 1 were excluded. Univariate logistic regression was performed on all variables of interest to examine their individual relationships to the outcome of T2DM development at Exam 4.

**Metabolic Syndrome**

After determining MetS status at Exam 4, a chi-square analysis was used to determine if the proportion of those patients meeting the MetS definition in the GS was significantly different form the proportion of patients meeting the MetS definition in the NGS group. Individual MetS components were also examined at Exam 4 by gastrectomy group (GS vs. NGS). This was also examined using the entire study population, as well as the study population excluding T2DM at Exam 1 to see if there was an appreciable difference.

Chi-square analyses again was used to determine significant differences. Univariate and multivariate analyses were employed with variables at each of the 4 exams, as appropriate, to assess prediction of MetS at Exam 4. Independent variables related to MetS development from the univariate analyses, were entered in a forced fashion to model the binary outcome of MetS at Exam 4

**Insulin Resistance**

Variables from the homeostasis model including Insulin resistance (IR), insulin sensitivity, % β cell function, and disposition index were calculated. Mean values were calculated for GS vs. NGS groups with 95% CIs. Independent sample t-tests were used to compare the mean values. IR was further categorized into IR vs no-IR and chi-square analyses were undertaken to examine the proportions of those patients in the GS group having IR compared to those patients in the NGS group. Sensitivity was further examined by implementing 2 different cut-off thresholds (2.5 and 1.7) representing the broad definition of IR and the optimized and more conservative definition of IR. Correlation matrices were constructed to examine the association of each of the HOMA variables with each of the others. Univariate and multivariate regression models were constructed predicting development of IR at Exam 4.

**For Obesity Variables**

BMI was calculated for each patient at each Exam following the standard definition and group means by gastrectomy status with 95% CIs were constructed. In addition, individual BMI was characterized following the WHO classification table (See Table 5). Skinfold measurements, particularly triceps and subscapular, were calculated. At each Exam and for gastrectomy and non-gastrectomy groups, means and 95% CIs were constructed. Repeated measure ANOVAs were applied to examine the between and within-subject effects overall and by individual Exams.

## Results

### Gastrectomy

Among the patients who had a gastrectomy, those who had a duodenal ulcer usually had a Billroth II reconstruction, while those who had only a gastric ulcer usually had a Billroth I reconstruction. See Table 7. There was no clear difference in how much stomach was removed by ulcer location or by type of reconstruction. However, this information was often missing from the operative note, especially with Billroth II reconstructions. (Table 7 and Table 8)

Table 7: Percentage (%) of Reconstruction by Ulcer Type

| Ulcer Type | N | Billroth - I | Billroth - II | Unknown |
|---|---|---|---|---|
| **DU** | 117 | 29.91 | 66.67 | 3.42 |
| **GU** | 202 | 61.39 | 37.62 | 0.5 |
| **Both** | 15 | 33.33 | 66.67 | 0.00 |
| **Other** | 11 | 54.55 | 36.36 | 9.09 |
| **Unknown** | 2 | 50.00 | 50.00 | 0.00 |

DU=duodenal ulcer; GU=gastric ulcer

Table 8: Percentage of Stomach Removed by Ulcer Type and Reconstruction

| Ulcer type | n | 1-25 | 26-40 | 41-50 | 51-60 | 67-75 | 76-90 | 91-99 | Unknown |
|---|---|---|---|---|---|---|---|---|---|
| **DU** | 117 | 0 | 5.13 | 11.97 | 20.51 | 27.35 | 1.71 | 0 | 33.33 |
| **GU** | 202 | 0 | 1.49 | 12.87 | 28.71 | 19.31 | 4.95 | 1.49 | 31.19 |
| **Both** | 15 | 6.67 | 0 | 6.67 | 33.33 | 33.33 | 0 | 0 | 20.00 |
| **Reconstruction** | | | | | | | | | |
| **B-I** | 171 | 0 | 4.09 | 15.20 | 29.24 | 19.88 | 4.68 | 1.75 | 25.15 |
| **B-II** | 169 | 0.59 | 1.18 | 9.47 | 23.08 | 26.04 | 2.37 | 0.00 | 37.28 |

DU=duodenal ulcer; GU=gastric ulcer; B-I=Billroth I; B-II=Billroth II

**Baseline & Follow-Up Characteristics**

Table 9a shows means with 95% confidence intervals and t-tests examining the differences between GS and NGS participants at each study visit (examination) excluding those participants who had T2DM at Exam 1 Table 10 shows the same data, but is limited to those participating in Exam 4.

Table 9: Baseline and Follow-Up Visit Characteristics Excluding T2DM at Baseline (Exam 1)

| | EXAM 1 | | EXAM 2 | | EXAM 3 | | EXAM 4 | |
|---|---|---|---|---|---|---|---|---|
| | Non-GS | GS | Non-GS | GS | Non-GS | GS | Non-GS | GS |
| | n = 6910 | n = 322 | n = 6468 | n = 303 | n = 5957 | n = 267 | n = 3430 | n =141 |
| | Mean<br>95% CI | Mean<br>95% CI | Mean<br>95%CI | Mean<br>95%CI | Mean<br>95%CI | Mean<br>95%CI | Mean<br>95%CI | Mean<br>95%CI |
| Age (yrs) | 54.72<br>54.58, 54.85 | 55.61<br>55.01,56.22 | 56.65<br>56.62,56.79 | 57.65<br>57.02,58.27 | 60.53<br>60.39,60.67 | 61.27<br>60.61,61.93 | 78.30<br>78.15,78.46 | 78.87<br>78.09,79.65 |
| Pr > \|t\| | **p = 0.0045** | | **p = 0.0021** | | **p = 0.0329** | | p = 0.1590 | |
| Weight (lbs) | 139.30<br>139.30,140.29 | 128.70<br>126.43,130.97 | 139.62<br>139.11,140.12 | 129.18<br>126.85,131.51 | 139.08<br>138.55.139.61 | 128.56<br>126.08,131.04 | 135.65<br>134.92,136.38 | 124.76<br>121.17,128.33 |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | **p < 0.0001** | | p < 0.0001 | |
| Height (in) | 64.09<br>64.03, 64.14 | 64.38<br>64.12, 64.64 | 64.26<br>64.21, 64.32 | 64.58<br>64.31, 64.84 | 64.15<br>64.09, 64.21 | 64.43<br>64.16, 64.71 | 63.65<br>63.57, 63.73 | 63.46<br>63.06, 63.86 |
| Pr > \|t\| | **p = 0.0241** | | **p = 0.0196** | | **p = 0.0490** | | p = 0.3433 | |
| BMI | 23.89<br>23.82,23.96 | 21.79<br>21.46,22.12 | 23.78<br>23.70,23.85 | 21.79<br>21.45,22.14 | 23.72<br>23.64,23.80 | 21.74<br>21.37,22.11 | 23.54<br>23.43,23.65 | 21.87<br>21.34, 22.41 |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | **p < 0.0001** | | **p < 0.0001** | |
| Education (yrs) | 10.34<br>10.27,10.41 | 10.23<br>9.93,10.53 | --- | --- | --- | --- | 10.49<br>10.38,10.60 | 10.27<br>9.78,10.76 |
| Pr > \|t\| | p = 0.5063 | | --- | | --- | | p = 0.4253 | |
| Cigarettes per day | 10.25<br>9.92,10.58 | 14.51<br>13.01,16.01 | 9.24<br>8.91,9.57 | 13.58<br>12.02,15.14 | 25.03<br>24.60, 25.46 | 25.30<br>23.52, 27.09 | 14.04<br>12.66,15.42 | 17.60<br>9.90,25.30 |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | p = 0.7696 | | p = 0.3537 | |
| Cigarettes per day (Excl.never smoked) | 14.80<br>14.39, 15.22 | 16.33<br>14.77, 17.90 | 13.36<br>12.93, 13.78 | 15.30<br>13.65, 16.95 | 25.03<br>24.60, 25.46 | 25.30<br>23.52, 27.09 | 14.04<br>12.66, 15.42 | 17.60<br>9.90, 25.30 |
| Pr > \|t\| | p = 0.0844 | | **p = 0.0313** | | p = 0.7696 | | p = 0.3537 | |
| Cigarettes per day (current smokers only) | 23.61<br>23.20, 24.03 | 23.36<br>22.00, 24.71 | 23.10<br>22.65, 23.54 | 22.78<br>21.24, 24.31 | 22.72<br>22.24, 23.20 | 22.62<br>20.83, 24.40 | 14.04<br>12.66, 15.42 | 17.60<br>9.90, 25.30 |
| Pr > \|t\| | p = 0.7195 | | p = 0.7189 | | p = 0.9137 | | p = 0.3537 | |
| Never Smoked (%) | 30.64% | 11.18% | 30.82% | 11.26% | 32.79% | 12.88% | 37.93% | 17.69% |
| Former Smoker (%) | 25.78% | 26.71% | 29.15% | 29.14% | 33.13% | 32.95% | 54.80% | 66.92% |
| Current Smoker (%) | 43.58% | 62.11% | 40.02% | 59.60% | 34.08% | 54.17% | 7.27% | 15.38% |
| Pack-years | 23.53<br>22.95,24.12 | 34.21<br>31.77,36.64 | --- | --- | --- | --- | 25.96<br>24.74,27.17 | 42.54<br>35.26,49.82 |
| Pr > \|t\| | **p < 0.0001** | | --- | | --- | | **p < 0.0001** | |
| Pack-years (Excl. never smoked) | 34.19<br>33.55, 34.84 | 38.54<br>36.25, 40.84 | | | | | 42.47<br>40.89, 44.06 | 51.95<br>44.14, 59.75 |
| Pr > \|t\| | **p = 0.0004** | | --- | | --- | | **p = 0.0201** | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Alcohol (oz/mo) | 13.82<br>13.24,14.39 | 16.72<br>14.01,19.43 | --- | --- | --- | --- | 18.44<br>17.07,19.81 | 32.40<br>23.41,41.40 |
| Pr > \|t\| | **p = 0.0377** | | --- | | --- | | **p = 0.0029** | |
| Systolic blood pressure (mmHg) | 134.07<br>133.58,134.56 | 128.93<br>126.67,131.20 | 133.89<br>133.39,134.39 | 130.72<br>128.27,133.18 | 136.91<br>136.38,137.44 | 133.15<br>130.52,135.77 | 149.11<br>148.31,149.91 | 153.22<br>(149.00,157.45) |
| Pr > \|t\| | **p < 0.0001** | | **p = 0.0091** | | **p = 0.0039** | | **p = 0.0443** | |
| Diastolic blood pressure (mmHg) | 82.53<br>82.25,82.80 | 77.34<br>76.00,78.67 | 84.30<br>83.93,84.48 | 81.64<br>80.25,83.03 | 84.56<br>84.28,84.85 | 82.33<br>80.96,83.69 | 80.02<br>79.63,80.41 | 80.78<br>78.90. 82.67 |
| Pr > \|t\| | **p < 0.0001** | | **p = 0.0004** | | **p = 0.0013** | | P = 0.4402 | |
| Blood Glucose (non-fasting) (mg/dL) | 155.92<br>154.76,157.08 | 141.85<br>135.55,148.14 | 116.36<br>114.38,118.35 | 128.03<br>105.66,149.41 | --- | --- | --- | --- |
| Pr > \|t\| | **p < 0.0001** | | p = 0.2753 | | --- | | --- | |
| Blood Glucose (fasting) (mg/dL) | --- | --- | --- | --- | --- | --- | 111.40<br>110.40, 112.30 | 107.7<br>104.20, 111.10 |
| Pr > \|t\| | --- | | --- | | --- | | **p = 0.0446** | |
| Insulin (fasting) (mg/dL) | --- | --- | --- | --- | --- | --- | 15.94<br>15.25, 16.63 | 12.10<br>10.44, 13.76 |
| Pr > \|t\| | --- | | --- | | --- | | **p < 0.0001** | |
| Serum cholesterol (mg/dL) | 218.55<br>217.66,219.45 | 203.88<br>199.93,207.83 | 210.53<br>208.96,212.21 | 192.56<br>184.00,201.13 | --- | --- | --- | --- |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | --- | | --- | |
| Random Triglyceride (mg/dL) | 236.81<br>231.99,241.63 | 188.03<br>172.06,204.01 | 235.50<br>226.18,244.81 | 187.79<br>138.38,237.21 | --- | --- | --- | --- |
| Pr > \|t\| | **p < 0.0001** | | **p = 0.0377** | | --- | | --- | |
| Uric acid (mg/dL) | 60.39<br>60.04,60.75 | 59.49<br>57.74,61.25 | --- | --- | --- | --- | --- | --- |
| Pr > \|t\| | p = 0.2986 | | --- | | --- | | --- | |
| Physical Activity Index | 32.90<br>32.79,33.00 | 32.47<br>32.00,32.95 | --- | --- | --- | --- | 30.82<br>30.66,30.98 | 31.09<br>30.11,32.07 |
| Pr > \|t\| | p = 0.1044 | | --- | | --- | | p = 0.5927 | |
| Waist Circumference (cm) | --- | --- | --- | --- | --- | --- | 86.32<br>86.02,86.62 | 81.89<br>80.37,83.40 |
| Pr > \|t\| | --- | | --- | | --- | | **p < 0.0001** | |
| Hip Circumference (cm) | --- | --- | --- | --- | --- | --- | 91.25<br>91.03,91.48 | 88.31<br>87.25,89.37 |
| Pr > \|t\| | --- | | --- | | --- | | **p < 0.0001** | |
| Biacromial Diameter (cm) | 38.01<br>37.97,38.06 | 37.82<br>37.258,38.05 | 38.66<br>38.61,38.71 | 38.33<br>38.10,38.56 | --- | --- | --- | --- |
| Pr > \|t\| | p = 0.1064 | | **p = 0.0057** | | --- | | --- | |
| Bi-iliac diameter (cm) | 28.87<br>28.83,28.92 | 28.73<br>28.49,28.96 | 27.89<br>27.85,27.93 | 27.62<br>27.42,27.82 | --- | --- | --- | --- |
| Pr > \|t\| | p = 0.1929 | | **p = 0.0060** | | --- | | --- | |
| Skinfold-left triceps (mm) | 8.01<br>7.93,8.09 | 6.56<br>6.21,6.91 | 8.54<br>8.45,8.63 | 7.13<br>6.69,7.57 | --- | --- | 10.13<br>9.99,10.26 | 9.17<br>8.46,9.87 |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | --- | | **p = 0.0050** | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Skinfold left-subscapular (mm) | 16.50<br>16.34,16.66 | 12.91<br>12.20,13.62 | 14.71<br>14.57,14.86 | 11.96<br>11.32,12.60 | --- | --- | 16.22<br>16.01,16.43 | 13.79<br>12.69, 14.89 |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | --- | | **p < 0.0001** | |
| Girth-Left upper arm (cm) | 279.53<br>278.88,280.19 | 264.63<br>261.42,267.83 | 287.56<br>286.89,288.23 | 270.86<br>267.54,274.19 | --- | --- | --- | --- |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | --- | | --- | |
| Chest Depth (cm) | 19.30<br>19.25, 19.34 | 18.60<br>18.40, 18.80 | 19.38<br>19.33, 19.43 | 18.51<br>18.27, 18.75 | --- | --- | --- | --- |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | --- | | --- | |
| Hematocrit (%) | 44.72<br>(44.65,44.79) | 43.95<br>43.60,44.30 | 44.38<br>44.23,44.54 | 42.66<br>41.83,43.49 | 44.15<br>44.07,44.24 | 43.02<br>42.64,43.40 | --- | --- |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | **p < 0.0001** | | --- | |
| Rate General Health | --- | --- | --- | --- | --- | --- | 2.24<br>2.21, 2.26 | 2.31<br>2.18, 2.43 |
| Pr > \|t\| | --- | | --- | | --- | | p = 0.2572 | |
| Satisfied with Quality of Life | --- | --- | --- | --- | --- | --- | 1.83<br>1.80, 1.85 | 1.86<br>1.74, 1.98 |
| Pr > \|t\| | --- | | --- | | --- | | p = 0.5831 | |
| Note: Skinfolds triceps and subscapular measures were not evaluated at Exam 3 due to a large amount of missing data.<br>Note: Significant values are bolded | | | | | | | | |

| Table 10: Baseline and Follow-Up Visit Characteristics of Men Surviving to Exam 4 Excluding T2DM at Baseline (Exam 1) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | EXAM 1 | | EXAM 2 | | EXAM 3 | | EXAM 4 | |
| | Non-GS | GS | Non-GS | GS | Non-GS | GS | Non-GS | GS |
| | n = 3430 | n = 141 | n = 3359 | n = 138 | n = 3293 | n = 134 | n = 3430 | n = 141 |
| | Mean<br>95% CI | Mean<br>95% CI | Mean<br>95%CI | Mean<br>95%CI | Mean<br>95%CI | Mean<br>95%CI | Mean<br>95%CI | Mean<br>95%CI |
| Age (yrs) | 53.11<br>52.96, 53.27 | 53.73<br>52.92, 54.54 | 55.15<br>54.99, 55.31 | 55.85<br>55.02, 56.67 | 59.18<br>59.02, 59.34 | 59.64<br>58.83, 60.45 | 78.30<br>78.15, 78.46 | 78.87<br>78.09, 79.65 |
| Pr > \|t\| | p = 0.1301 | | p = 0.0869 | | p = 0.2693 | | p = 0.1590 | |
| Weight (lbs) | 141.00<br>140.40, 141.70 | 130.40<br>127.20, 133.60 | 140.90<br>140.30, 141.60 | 131.10<br>127.80, 134.30 | 140.40<br>139.80, 141.10 | 131.70<br>128.4, 135.00 | 135.70<br>134.90, 136.40 | 124.80<br>121.20, 128.40 |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | **p < 0.0001** | | **p < 0.0001** | |
| Height (in) | 64.27<br>64.19, 64.35 | 64.26<br>63.88, 64.64 | 64.41<br>64.33, 64.49 | 64.48<br>64.10, 64.85 | 64.29<br>64.21, 64.37 | 64.36<br>63.97, 64.75 | 63.65<br>63.57, 63.73 | 63.46<br>63.06, 63.86 |
| Pr > \|t\| | p = 0.9684 | | p = 0.7246 | | p = 0.7259 | | p = 0.3433 | |
| BMI | 23.97<br>23.88, 24.07 | 22.18<br>21.71, 22.65 | 23.90<br>23.81, 24.00 | 22.20<br>21.70, 22.69 | 23.86<br>23.76, 23.95 | 22.33<br>21.83, 22.82 | 23.54<br>23.43, 23.65 | 21.87<br>21.34, 22.41 |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | **p < 0.0001** | | **p < 0.0001** | |
| Education (yrs) | 10.71<br>10.61, 10.80 | 10.69<br>10.24, 11.15 | --- | --- | --- | --- | 10.49<br>10.38, 10.60 | 10.27<br>9.78, 10.76 |
| Pr > \|t\| | p = 0.9593 | | --- | | --- | | p = 0.4253 | |
| Cigarettes per day | 8.19<br>7.76, 8.62 | 12.63<br>10.37, 14.89 | 7.53<br>7.11,7.95 | 11.68<br>9.30, 14.13 | 24.56<br>23.97, 25.14 | 26.63<br>23.84, 29.41 | 25.24<br>24.50, 25.97 | 27.44<br>24.24, 30.64 |
| Pr > \|t\| | **p < 0.0001** | | **p = 0.0009** | | p = 0.1176 | | p = 0.1994 | |
| Cigarettes per day (Excl. never smoked) | 12.76<br>12.17, 13.34 | 14.72<br>12.28, 17.16 | 11.70<br>11.11, 12.29 | 13.55<br>10.94, 16.16 | 24.88<br>24.29, 25.47 | 26.82<br>24.03, 29.61 | 25.68<br>24.94, 26.43 | 27.44<br>24.24, 30.64 |
| Pr > \|t\| | p = 0.1327 | | p = 0.1588 | | p = 0.1428 | | p = 0.3030 | |
| Cigarettes per day (current smokers only) | 22.69<br>22.07, 23.31 | 23.13<br>20.94, 25.32 | 22.53<br>21.87, 23.19 | 23.36<br>20.67,26.06 | 21.86<br>21.19,22.52 | 23.61<br>20.37, 26.84 | 14.04<br>12.66, 15.42 | 17.60<br>9.90, 25.30 |
| Pr > \|t\| | p = 0.7323 | | p = 0.5524 | | p = 0.2929 | | p = 0.3537 | |
| Never Smoked (%) | 35.72 % | 14.18 % | 35.70 % | 13.77 % | 36.77 % | 15.79 % | 37.93% | 17.69% |
| Former Smoker (%) | 28.05 % | 31.21 % | 30.87 % | 36.23 % | 34.70 % | 38.35 % | 54.80% | 66.92% |
| Current Smoker (%) | 36.22 % | 54.61 % | 33.43 % | 50.00 % | 28.53 % | 45.86 % | 7.27% | 15.38% |
| Pack-years | 19.07<br>18.34, 19.80 | 28.57<br>25.07, 32.08 | --- | --- | --- | --- | 25.96<br>24.74, 27.17 | 42.54<br>35.26, 49.82 |
| Pr > \|t\| | **p < 0.0001** | | --- | | --- | | **p < 0.0001** | |
| Pack-years (Excl. never smoked) | 29.88<br>29.03, 30.73 | 33.37<br>29.98, 36.77 | --- | --- | --- | --- | 42.47<br>40.89, 44.06 | 51.95<br>44.14, 59.75 |
| Pr > \|t\| | p = 0.0651 | | --- | | --- | | **p = 0.0201** | |
| Alcohol (oz/mo) | 12.12 | 16.51 | --- | --- | --- | --- | 18.44 | 32.40 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 11.40, 12.83 | 12.62, 20.40 | | | | | 17.07, 19.81 | 23.41, 41.40 |
| Pr > \|t\| | **p = 0.0173** | | --- | | --- | | **p = 0.0029** | |
| Systolic blood pressure (mmHg) | 130.30<br>129.70, 131.00 | 126.50<br>123.60, 129.30 | 130.40<br>129.80, 131.00 | 127.50<br>124.60, 130.40 | 133.70<br>133.10, 134.40 | 133.50<br>130.10, 136.80 | 149.10<br>148.30, 149.90 | 153.20<br>149.00, 157.40 |
| Pr > \|t\| | **p = 0.0161** | | p = 0.0681 | | p = 0.8761 | | **p = 0.0443** | |
| Diastolic blood pressure (mmHg) | 81.65<br>81.28, 82.02 | 76.98<br>75.12, 78.85 | 83.47<br>83.11, 83.83 | 81.31<br>79.51, 83.12 | 84.02<br>83.66, 84.39 | 83.29<br>81.54, 84.04 | 80.02<br>79.63, 80.41 | 80.78<br>78.90, 82.67 |
| Pr > \|t\| | **p < 0.0001** | | **p = 0.0200** | | p = 0.4333 | | p = 0.4402 | |
| Blood Glucose (non-fasting) (mg/dL) | 149.10<br>147.70, 150.50 | 140.00<br>129.80, 150.20 | 113.80<br>111.20, 116.30 | 114.70<br>90.39, 138.90 | --- | --- | --- | --- |
| Pr > \|t\| | P = 0.0826 | | P = 0.8859 | | --- | | --- | |
| Blood Glucose (fasting) (mg/dL) | --- | --- | --- | --- | --- | --- | 111.40<br>110.40, 112.30 | 107.70<br>104.20, 111.10 |
| Pr > \|t\| | --- | | --- | | --- | | **p = 0.0446** | |
| Insulin (fasting) (mg/dL) | --- | --- | --- | --- | --- | --- | 15.94<br>15.25, 16.63 | 12.10<br>10.44, 13.76 |
| Pr > \|t\| | --- | | --- | | --- | | **p < 0.0001** | |
| Serum cholesterol (mg/dL) | 218.50<br>217.30, 219.70 | 207.80<br>201.80, 213.80 | 210.20<br>208.00, 212.40 | 199.70<br>186.40, 213.00 | --- | --- | --- | --- |
| Pr > \|t\| | **p = 0.0005** | | p = 0.0677 | | --- | | --- | |
| Random Triglyceride (mg/dL) | 233.50<br>227.30, 239.70 | 196.20<br>168.70, 223.70 | 231.60<br>219.30, 244.00 | 168.50<br>132.40, 204.70 | --- | --- | --- | --- |
| Pr > \|t\| | **p= 0.0098** | | **p = 0.0017** | | --- | | --- | |
| Uric acid (mg/dL) | 59.84<br>59.37, 60.33 | 58.03<br>55.43, 60.63 | --- | --- | --- | --- | --- | --- |
| Pr > \|t\| | p = 0.1481 | | --- | | --- | | --- | |
| Physical Activity Index | 32.88<br>32.73, 33.04 | 32.90<br>32.13, 33.67 | --- | --- | --- | --- | 30.82<br>30.66, 30.98 | 31.09<br>30.11, 32.07 |
| Pr > \|t\| | p = 0.9653 | | --- | | --- | | p = 0.5927 | |
| Waist Circumference (cm) | --- | --- | --- | --- | --- | | 86.32<br>86.02, 86.62 | 81.89<br>80.37, 83.40 |
| Pr > \|t\| | --- | | --- | | --- | | -**p < 0.0001** | |
| Hip Circumference (cm) | --- | --- | --- | --- | --- | --- | 91.25<br>91.03, 91.47 | 88.31<br>87.25, 89.37 |
| Pr > \|t\| | --- | | --- | | --- | | **p < 0.0001** | |
| Biacromial Diameter (cm) | 38.14<br>38.08, 38.21 | 37.52<br>37.18, 37.87 | 38.82<br>38.76, 38.89 | 38.35<br>38.04, 38.66 | --- | --- | --- | --- |
| Pr > \|t\| | **p = 0.0002** | | **p = 0.0054** | | --- | | --- | |
| Bi-iliac diameter (cm) | 28.88<br>28.82, 28.95 | 28.50<br>28.13, 28.86 | 27.87<br>27.81, 27.93 | 27.50<br>27.22, 27.78 | --- | --- | --- | --- |
| Pr > \|t\| | **p = 0.0423** | | **p = 0.0106** | | --- | | --- | |
| Skinfold-left triceps (mm) | 7.96<br>7.85, 8.06 | 6.74<br>6.23, 7.24 | 8.58<br>8.46, 8.70 | 7.38<br>6.78, 7.97 | --- | --- | 10.13<br>9.99, 10.26 | 9.17<br>8.46, 9.87 |
| Pr > \|t\| | **p < 0.0001** | | **p = 0.0001** | | --- | | **p = 0.0050** | |
| Skinfold left-subscapular | 16.69 | 13.64 | 14.83 | 12.62 | --- | --- | 16.22 | 13.79 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (mm) | 16.47, 16.90 | 12.53, 14.74 | 14.64, 15.03 | 11.38, 13.57 | | | 16.01, 16.43 | 12.69, 14.89 |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | --- | | **p < 0.0001** | |
| Girth-Left upper arm (cm) | 281.80<br>280.90, 282.70 | 267.90<br>263.10, 272.80 | 290.40<br>289.50, 291.30 | 276.40<br>271.80, 281.10 | --- | --- | --- | --- |
| Pr > \|t\| | **p < 0.0001** | | **p < 0.0001** | | --- | | --- | |
| Chest Depth (cm) | --- | --- | 19.32<br>19.25, 19.39 | 18.68<br>18.34, 19.03 | --- | --- | --- | --- |
| Pr > \|t\| | | | **p = 0.0003** | | --- | | --- | |
| Hematocrit (%) | 44.71<br>44.61, 44.80 | 44.06<br>43.58, 44.55 | --- | --- | 44.11<br>44.01, 44.22 | 42.93<br>42.44, 43.41 | --- | --- |
| Pr > \|t\| | **p = 0.0083** | | --- | | **p < 0.0001** | | --- | |
| Rate General Health | --- | --- | --- | --- | --- | --- | 2.24<br>2.22, 2.26 | 2.31<br>2.18, 2.43 |
| Pr > \|t\| | --- | | --- | | --- | | p = 0.2572 | |
| Satisfied with Quality of Life | --- | --- | --- | --- | --- | --- | 1.83<br>1.80, 1.84 | 1.86<br>1.74, 1.98 |
| Pr > \|t\| | --- | | --- | | --- | | p = 0.5831 | |
| Note: Skinfolds triceps and subscapular measures were not evaluated at Exam 3 due to a large amount of missing data.<br>Note: Significant values are bolded | | | | | | | | |

## Age

Study participants in the HHP entered the study at a mean age of 53 years (range 45-68 years). Those attending Exam 4, averaged about 78 years of age. From Exam 1 through Exam 4, the mean ages of the GS group and NGS group were less than one year apart, with the GS group being slightly older at each visit. See Table 10 The age difference narrowed slightly over time as the older gastrectomy subjects had somewhat higher mortality. Comparing the two tables, it can be seen that the average age of those surviving and attending Exam 4 was about 1.6 years younger for the NGS group and about 1.9 years younger for the GS group. Except as otherwise noted, the following discussion will focus on the second of the two tables so that longitudinal changes in variables can be tracked in the same participants.

## Education

Both the GS group and the NGS group had a mean of about 10.5 years of education. This was seen at Exam 1 (10.69 vs. 10.71; (t=0.05, p=0.9593)) as well as Exam 4 (t=0.80, p=0.4253). Overall between-groups comparison was not significant (F(1,3567)=0.21, p=0.6433). The slightly lower educational level reported at Exam 4 is surprising and likely resulted from some small difference in the way the question was asked.

## Smoking

### Current Smokers

We discuss the smoking findings based mainly on Table 10 which is restricted to men who participated in Exam 4 since this allows comparisons to be made across time in the same individuals. There was a very substantial difference in the proportion of men who smoked cigarettes between the GS and NGS groups. At baseline 36% of the NGS

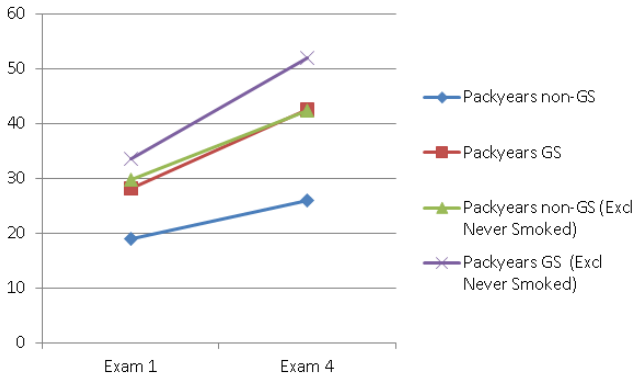
group smoked while 55% of the GS men were smokers. In contrast, more than a third of the NGS group had never smoked vs only a seventh of the GS group. These differences persisted through the first six years of follow-up (Exams 2 and 3) though smoking rates dropped slightly in both groups over this period. At 25 years, current smoking had dropped substantially to 15% and 7%. Current smokers in both groups smoked 22-24 cigarettes per day through the first six years. By the 25 year follow–up current smokers in both groups were smoking 14 to 18 cigarettes per day.

### Pack-Years

At Exam 1, the GS group had a mean value of 28.57 pack-years while the NGS group had a mean value of 19.07 pack-years ($p<0.0001$; see Table 10 Excluding those patients at Exam 1 who indicated they had never smoked, the mean value for the GS group was 33.37 pack-years while the NGS group had a mean of 29.88 pack-years, showing a smaller difference of borderline significance. This difference grew through Exam 4 when the GS mean value of 42.54 was substantially higher than the NGS mean value of 25.96 pack-years reflecting the more persistent smoking among the gastrectomy men. After excluding patients who had never smoked and survived through to Exam 4, the mean number of pack-years was 51.95 for the GS group and 42.47 for the NGS group. This difference was less, but also still significant, ($t(1,112) =-2.36$, $p=0.0201$). Comparing overall between and within subjects effects there were significant differences between groups ($F(1,3170)=30.18$, $p<0.0001$) and within groups ($F(1,3170)=95.75$, $p< 0.0001$), there was a significant interaction between pack-years and GS group versus NGS group ($F(1,3170)=9.38$, $p=0.0022$) meaning that the number of pack-years for the GS group increased more sharply over time than in the NGS group. Running the same analysis but excluding those patients surviving to Exam 4 and having never smoked, the between-group ($F(1,1959)=7.03$, $p=0.0081$)) and within-group

(F(1,1959)=109.59, p<.0001) effects remained significantly different. However, the interaction with gastrectomy weakened and became non-significant (F(1,1959)=3.13, p=0.0771). The GS group smoked more to begin with and increased their smoking just marginally more so than the NGS group. See Figure 1.

Figure 1: Pack-years by Exam by Gastrectomy Status All Participants and Excluding Non-Smokers




### Smoking Status

Notably, when analyzing never, former and current smokers across Exams 1 through 4 among patients who survived and were able to provide data at exam 4, the percentages of never smokers remained constant across exams, roughly 14% for GS patients and 36% for NGS patients. The roughly 20% consistent difference suggests there were few, new smokers. The results also show a steady increase of former smokers and consequently a steady decrease in current smokers, with the percentage of GS patients smoking staying higher at each exam compared to NGS patients, see Table 10. Within the GS group, between Exam 1 and Exam 4, the number of current smokers dropped 39.23% from 54.61% to 15.38%. In the NGS group, the number of current smokers dropped 28.95% from 36.22% to 7.27%. Consequently, the number of former smokers

increased, see Table 10. So, as shown in Figures 2 and 3, there was a significant reduction in smoking over the 25 years since entry in both the GS and NGS group.

Figure 2: Percentages of Smoking Status by Exam (GS)

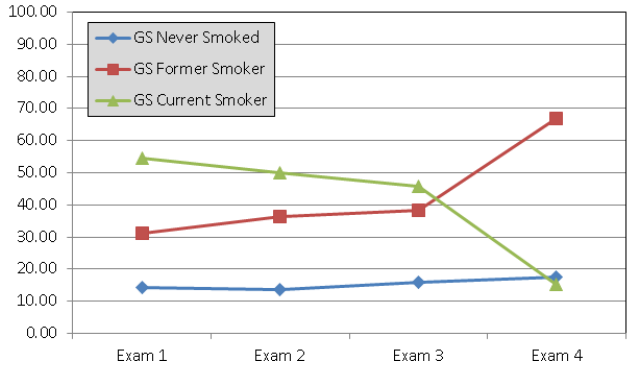
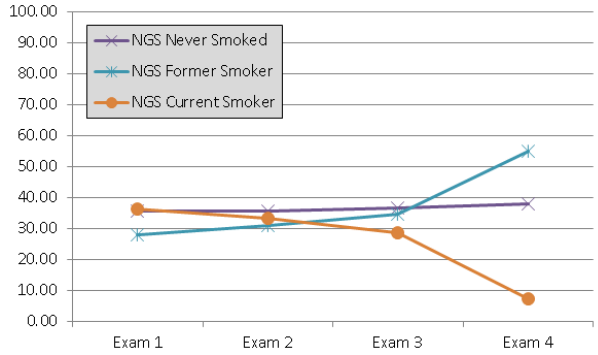



Figure 3: Percentages of Smoking Status by Exam (NGS)

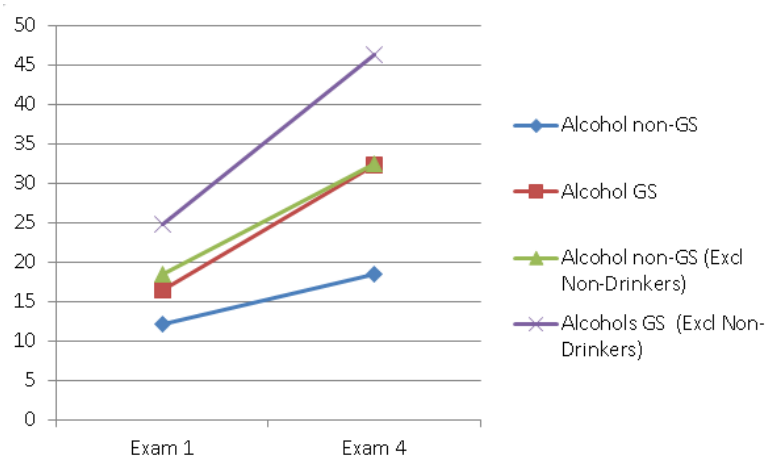



**Alcohol**

Alcohol consumption was measured as the number of ounces of alcoholic beverages consumed per month. Wine, beer, and liquor were weighted by 0.1, 0.037, and 0.38 units per ounce of beverage, respectively, to reflect their approximate alcohol content. A composite measure of alcohol consumption was generated during the HHP study only at Exam 1 and Exam 4. That composite measure was utilized in the present study to be consistent with other publications that used alcohol consumption in their analyses.

At Exam 1, the mean alcohol consumption for the GS group was 16.51 oz/month while the mean value for the NGS group was 12.12 oz/month (p=0.0173). See Table 10. Beer was the predominant source of alcohol in this population and at 5% estimated alcohol content this would reflect a difference of 6-7, 12 oz cans per month. Excluding those patients who did not drink (teetotalers), the GS group had a mean of 24.81 ounces per month while the NGS group had 18.42 ounces. This difference was still significantly different ($t(1,2479)=-2.55$, $p=0.0107$). At Exam 4, the mean alcohol consumption for the GS group increased to 32.4 oz/month almost doubling from what it was at Exam 1. The mean alcohol consumption for the NGS group also increased - to 18.44 oz/month, although the increase was not as dramatic. The difference between the 2 groups also remained significantly different ($t(1,3231)=-3.95$, $p=<0.0001$). Again, excluding the teetotalers at Exam 4, the mean alcohol consumption in the GS group was 46.29 ounces per month while the NGS group exhibited 32.42 ounces. See Figure 4 The difference remained significantly different even after excluding teetotalers ($t(1,1854)=-2.72$, $p=0.0066$). The difference within each of the two groups was significant ($F(1,3228)=49.17$, $p=<0.0001$), and the interaction term of alcohol and gastrectomy status was also significant ($F(1,3228)=9.97$, $p=0.0016$). The overall between subjects effect was also significant ($F(1,3228)=15.18$, $p<0.0001$) Even after excluding teetotalers, the within subjects difference was significant ($t(1,1853)=55.13$, $p<0.0001$) as was the interaction term ($t(1,1853)=5.22$, $p=0.0224$). The between subjects effect also remained significant ($t(1,1853)=6.66$, $p=0.0099$). It is not clear if this increase could reflect differences in the manner in which the alcohol information was obtained between the two examinations although this would not easily account for difference in the changes between the groups.

Figure 4: Alcohol Consumed (oz/month) by Exam and Gastrectomy Status (GS) All Participants and Excluding Teetotalers

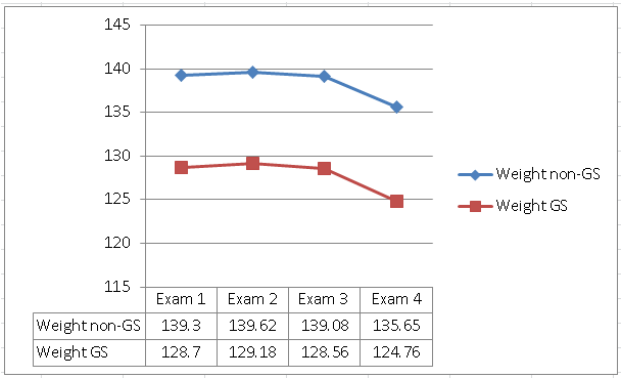



**Weight, Height, and BMI**

**Weight**

Among patients surviving to Exam 4, beginning at Exam 1, the mean weight in pounds (lbs) of the GS group was 130.40 lbs, while the mean weight for the NGS group was 141.00 lbs, showing a significant difference ($t=6.35$, $p<0.0001$). This roughly 11 lbs difference between the 2 groups carried through Exam 2 (131.10 lbs vs. 140.90lbs;$t=5.80$, $p<0.0001$), Exam 3 (131.70 lbs vs. 140.40 lbs; $t = 5.04$, $p< 0.0001$), and Exam 4 (124.80lbs vs. 135.70lbs; $t=5.92$, $p<0.0001$) and was statistically significant at each Exam. In addition, of note, there was a parallel decrease in weight of 4 lbs between Exam 3 and Exam 4. There was a significant difference in weight overall between ($F(1,3088)=18.43$) and within $F(1,9264)=34.09$, $p<0.0001$ the GS and NGS group See Table 10 and Figure 5.

Figure 5: Weight by Gastrectomy Status and Exam

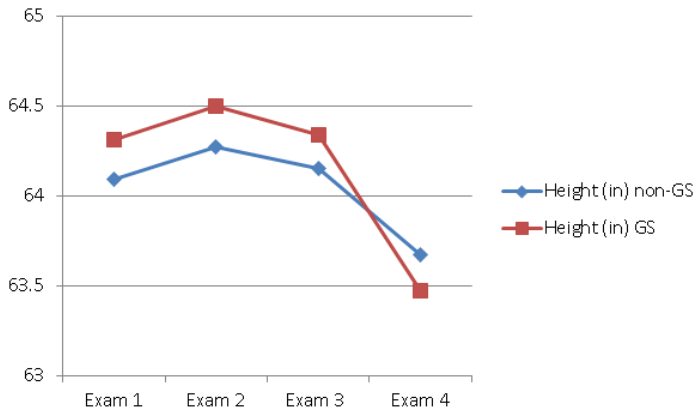



| | Exam 1 | Exam 2 | Exam 3 | Exam 4 |
|---|---|---|---|---|
| Weight non-GS | 139.3 | 139.62 | 139.08 | 135.65 |
| Weight GS | 128.7 | 129.18 | 128.56 | 124.76 |

## Height

There was no between-subjects effect meaning there was no difference in height between the GS and NGS groups. However, the within-subjects effect was significant ($F(3,9576)=294.03$, $p<0.0001$) indicating there was a decrease in height overall across exams. Converting from inches to centimeters, this translates into a 2 cm decrease in height for the GS group and a 1 cm decrease in height for the NGS group, comparing Exam 1 to Exam 4. The greater height loss in old age in the gastrectomy group suggests the possibility of an excess of osteoporosis in the gastrectomy group. (See Table 10 and Figure 6).

Figure 6: Height by GS and Exam



**Body Mass Index (BMI**

At Exam 1, the mean BMI for the GS group was 22.18 kg/$m^2$ while the mean BMI for the NGS group was 23.97 kg/$m^2$, a roughly 2 unit significant difference (t=7.93, p<0.0001). This difference was maintained through Exam 2 (22.20 vs. 23.90;t = 6.94, p< 0.0001), Exam 3 (22.33 vs. 23.86;t = 6.02, p< 0.0001), and Exam 4 (21.87 vs. 23.54;t = 6.00, p< 0.0001). This means both the GS group and NGS on the whole maintained a normal weight throughout the course of the study. With the mean BMI remaining more or less the same across all 4 examination periods and mean weight remaining the same for Exams 1, 2, 3 with about a 4 lbs mean decrease in weight by Exam 4 in both the GS and NGS group. See Table 10.

Mean BMI in Table 9b appeared to stay steady. Further analyses of each BMI category yielded additional detail. Using the WHO cutoff points for BMI (categorizing BMI into underweight, normal weight, overweight, and obese) and examining patients who survived to Exam 4, between Exam 1 and Exam 4 there was an absolute 8-9% increase in the proportion of both groups that were underweight. See Table 11. There were less overweight patients between Exam 1 and Exam 4, about a 7% decrease (33.53% to 26.73%) in NGS and an almost 2-fold decrease (20.57% to 11.35%) in the GS group. With obesity, the NGS group remained about the same between Exam 1 and Exam 4 (1.96% to 2.02%) NGS, while the GS group dropped almost 3-fold from 1.98% to 0.71%. The percentages for normal BMI between Exam 1 and Exam 4 remained relatively the same in the NGS group (62.24% to 60.21%) and GS group (69.50% staying at 69.50%) Those results reflected an overall trend in decreased weight over time in both groups, with a greater decreasing effect in the GS group. A repeated measures ANOVA confirmed these results showing a highly significant overall between subjects effect

(F(1,3164)=42.98, p<0.0001) as well as a highly significant within subjects effect (F(3,9492)=8.34, p<0.0001).

Table 11: Percentages of BMI by WHO Category for GS vs. NGS Patients, Exam 1 through 4 (Restricted only to patients surviving to Exam 4)

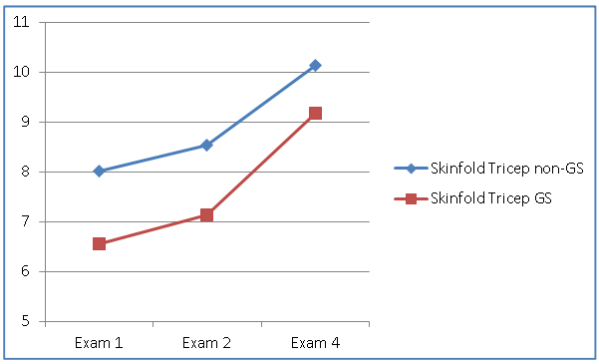
| | Exam 1 | | Exam 2 | | Exam 3 | | Exam 4 | |
|---|---|---|---|---|---|---|---|---|
| | n=3568 | | n=3571 | | n=3566 | | n=3564 | |
| **BMI Category** | **NGS** | **GS** | **NGS** | **GS** | **NGS** | **GS** | **NGS** | **GS** |
| Underweight | 2.22 | 9.93 | 2.19 | 8.51 | 6.72 | 14.18 | 11.04 | 18.44 |
| Normal Weight | 62.24 | 69.50 | 62.10 | 71.63 | 61.46 | 67.38 | 60.21 | 69.50 |
| Overweight | 33.53 | 20.57 | 31.31 | 17.02 | 29.96 | 18.44 | 26.73 | 11.35 |
| Obese | 1.96 | 0.00 | 1.98 | 0.71 | 1.87 | 0.00 | 2.02 | 0.71 |
| Missing | 0.06 | 0.00 | 2.42 | 2.13 | 0.00 | 0.00 | 0.00 | 0.00 |

**Skinfolds (Tricep, Subscapular), Waist circumference, Hip circumference**

**Left Triceps Skinfold**

Starting at Exam 1, the mean triceps skinfold value of 6.74 mm for the GS group was significantly different from the mean triceps skinfold value of 7.96 mm in the NGS group (t=4.50, p<0.0001). At Exam 2, the value increased slightly in both groups bringing the values to 7.38 mm for the GS group and 8.58 mm for the NGS, and still remaining significantly different (t=3.83, p<0.0001). Skinfolds results at Exam 3 were not included as greater than 92% of the data were missing from the dataset calling into question the reliability of the estimates observed from the data that were present. Lastly, at Exam 4 the mean values changed to 9.17 mm in the GS group and 10.13 in the NGS group with the number of evaluable observations increasing and the difference between the two groups being non-significant (F(1,156)=0.18, p=0.6736) and the difference within the groups being significant (F(1,468)=4.22, p=0.0050). See Table 10 and Figure 7.

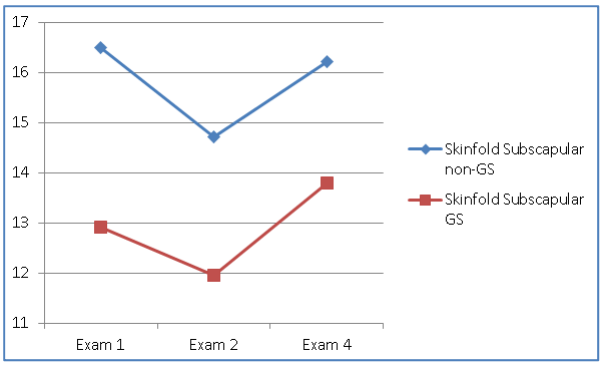
Figure 7: Skinfold Triceps by GS and Exam




### Left sub-scapular skinfold

From Exam 1, the mean subscapular skinfold value of 13.64 mm in the GS group approached significance from the mean subscapular skinfold value of 16.69 mm in the NGS group ($t=5.46$, $p<0.0001$). At Exam 2, the values decreased in both groups bring the values to 12.62 mm in the GS group and 14.83 mm in the NGS group, continuing a significant difference ($t=4.46$, $p<0.0001$ By Exam 4, both the GS and NGS group had diverged with their mean subscapular values changing to 13.79 mm and 16.22 mg, respectively. This difference was significant ($t=4.52$, $p <0.0001$). There were no significant between subjects effects ($F(1,153)=0.12$, $p=0.7349$) or within-subjects effects ($F(1,469)=0.23$, $p=0.8784$; see Table 10 and Figure 8.

Figure 8: Skinfold Subscapular by GS and Exam



### Waist Circumference and Hip Circumference

Waist circumference and hip circumference were not added until Exam 4, roughly 25 years after the beginning of the trial. Aligned with weight and BMI, waist circumference was smaller (81.89 cm vs. 86.32 cm; t=5.87, p<0.0001) as was hip circumference (88.31cm vs. 91.25cm; t=5.27, p<0.0001) for the group who had gastrectomies prior to entering Exam 1. At Exam 4, the GS group had significantly smaller waists and smaller hip circumferences as compared to the NGS group. See Table 10.

### Blood Pressure

Referencing the WHO criteria for hypertension, at each exam, participants within the GS and NGS groups were characterized as having one of the blood pressure categories (Normal, Pre-hypertension, Stage 1 hypertension, Stage 2 hypertension, or Hypertensive crisis) and the percentages of their frequencies reported in Table 12 below.

Table 12: Percentages of Hypertension Status by AHA Category for GS vs. NGS Patients, Exam 1 through 4 (Restricted to only patients surviving to Exam 4)

| Blood Pressure | | | | Exam 1 | | Exam 2 | | Exam 3 | | Exam 4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n = 3571 | | n = 3571 | | n = 3571 | | n = 3571 | |
| **BP Category** | **S** | **AND/ OR** | **D** | **NGS** | **GS** | **NGS** | **GS** | **NGS** | **GS** | **NGS** | **GS** |
| Normal | <120 | AND | <80 | 26.21 | 34.04 | 24.31 | 31.21 | 17.87 | 17.02 | 7.78 | 6.38 |
| Pre-HTN | 120-139 | OR | 80-89 | 41.84 | 41.13 | 39.45 | 37.59 | 38.63 | 40.43 | 26.59 | 21.28 |
| HBP (HTN Stage 1) | 140-159 | OR | 90-99 | 21.78 | 20.57 | 23.24 | 20.57 | 27.58 | 23.40 | 31.78 | 37.59 |
| HBP (HTN Stage 2) | ≥160 | OR | ≥100 | 7.67 | 2.84 | 8.60 | 7.80 | 8.92 | 10.64 | 20.73 | 17.02 |
| HC (Emergency Care Needed) | >180 | OR | >110 | 2.51 | 1.42 | 2.33 | 0.71 | 3.00 | 3.55 | 10.26 | 16.31 |
| Missing | | | | 0.00 | 0.00 | 2.07 | 2.13 | 3.99 | 4.96 | 2.86 | 1.42 |

HBP=High Blood Pressure; HTN=Hypertension; HC-Hypertensive Crisis; S=Systolic; D = Diastolic

There were greater percentages of GS categorized as normal at the beginning of the study, but towards study end that difference disappeared. Pre-hypertension was roughly the same for the first 3 exams and was slightly lower for GS participants at Exam 4. The percentages of Stage 1 hypertension were roughly the same with GS participants

showing slightly less. But, that relationship flipped at Exam 4 when GS participants were 37.59% Stage 1 hypertensive and NGS were 31.78% Stage 1 hypertensive. With Stage 2 hypertension, GS participants again had lower percentages at Exams 1 and 2, but then the relationship flipped at Exam 3 (10.64% for GS and 8.92% for NGS) and then reverted at Exam 4 (17.02% for GS and 20.73% for NGS). Overall, between the 2 groups, normal blood pressure and pre-hypertensive blood pressure decreased over the course of the study while Stage 1 and Stage 2 hypertension, as well as hypertension requiring emergency care increased, particularly in the intervening years between Exam 3 and Exam 4.

### Systolic Blood Pressure (SBP)

Beginning at Exam 1, the mean SBP of the GS group was 126.50 mmHg while the mean SBP for the NGS group was 130.30 mmHg, showing a significant difference ($t(1,3569)=2.41$, $p=0.0161$). See Table 10 At Exam 2, the gap closed where the SBP for the GS group increased slightly while the SBP for the NGS group remained the same (127.50 mmHg vs. 130.40 mmHg; $t(1,3459) = 1.82$, $p = 0.0681$) showing a marginal statistically significant difference. By Exam 3, though the statistically significant difference between groups had disappeared with mean SBP for the GS group at 133.50 while the NGS group had a mean SBP of 133.70 ($t(1,3425)=0.16$, $p=0.8761$). Finally at Exam 4, the SBP increased substantially from Exam 3 in both the GS and NGS groups (153.20mm Hg vs. 149.10 mmHg), widening the gap again with the SBP from the GS group being significantly different from the NGS group ($t(1,3569)=2.41$, $p=0.0443$), An interesting find here was that mean SBP in the GS group had been less, even significantly less at Exam 1 compared to the NGS group. At Exam 4 mean SBP crossed over and was significantly higher than the NGS group. So, something inherent within the GS group, like heavier, more cumulative smoking or maybe increased alcohol

consumption drove this increase in crossover and increase in mean SBP. Also notable was that based on blood pressure categories for SBP from the American Heart Association[65] (see Table 13) percentages of high blood pressure/ hypertension stage 1 and hypertensive crisis increased and were higher for GS participants compared to NGS participants at Exam 4. High blood pressure stage 2 was slightly higher for NGS participants at Exam 4. Percentages of participants showing normal and prehypertension SBP drastically decreased between Exam 1 and Exam 4, while Hypertension Stage 1, Hypertension stage 2, and hypertensive crisis all increased dramatically from Exam 1; see Table 13 and Figure 9.

Table 13: Percentages of SBP by AHA Category for GS versus NGS Patients, Exam 1 through 4 (Restricted to only patients surviving to Exam 4)

| Blood Pressure | | | | Exam 1 | | Exam 2 | | Exam 3 | | Exam 4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | n = 3571 | | n = 3571 | | n = 3571 | | n = 3571 | |
| **BP Category** | **S** | **AND/ OR** | **D** | **NGS** | **GS** | **NGS** | **GS** | **NGS** | **GS** | **NGS** | **GS** |
| Normal | <120 | AND | <80 | 30.03 | 36.88 | 30.09 | 35.46 | 22.57 | 22.70 | 8.43 | 7.80 |
| Prehypertension | 120-139 | OR | 80-89 | 42.77 | 40.43 | 41.66 | 36.88 | 40.76 | 42.55 | 26.97 | 20.57 |
| HBP (HTN Stage 1) | 140-159 | OR | 90-99 | 19.80 | 20.57 | 18.63 | 20.57 | 23.50 | 17.73 | 31.37 | 36.88 |
| HBP (HTN Stage 2) | ≥160 | OR | ≥100 | 6.03 | 1.42 | 6.24 | 4.96 | 7.08 | 8.51 | 20.47 | 17.73 |
| HC (Emergency Care Needed) | >180 | OR | >110 | 1.37 | 0.71 | 1.31 | 0.00 | 2.10 | 3.55 | 9.94 | 15.60 |
| Missing | | | | 0.00 | 0.00 | 2.07 | 2.13 | 3.99 | 4.96 | 2.86 | 1.42 |

HBP=High Blood Pressure; HTN=Hypertension; HC-Hypertensive Crisis; S=Systolic; D = Diastolic

### Diastolic Blood Pressure (DBP)

At Exam 1, the mean DBP of the GS group was 76.98 mmHg while the mean DBP for the NGS group was 81.65 mmHg, showing a significant difference ($t(1,3569)=4.93$, $p<0.0001$). At Exam 2, the gap closed where the DBP for the GS group increased about 4 mmHg versus 2 mmHg for the NGS group landing at values of 81.31 mmHg for the GS group and 83.47 for the non-GS group which remained significantly different ($t(1,3495)=2.33$, $p=0.0200$). At Exam 3, the gap between the two groups had diminished

and stopped being significantly different with the GS group having a mean DBP of 83.29 mmHg, while the NGS group had a mean DBP of 84.02 mmHg ($t(1,3425)=0.78$, $p=0.4333$). By Exam 4, the gap between groups closed with the mean DBP of 80.78 in the GS group and the mean DBP of 80.02 in the NGS group ($t(1,3569)=0.70$, $p=0.4402$).

Based on blood pressure categories for DBP from the American Heart Association[65] (see Table 14) it appears at Exam 1 there were more normal blood pressure patients in the GS group versus the NGS group (61.70% vs. 45.22%)) while there were more elevated DBPs in the NGS group in the prehypertension all through the remaining BP categories through hypertensive crisis. What is most interesting here is that by Exam 4, the differences in BP category between GS and NGS had closed and the percentages were relatively the same. DBP appeared to be better for GS patients at Exam 1 but 25 years later, that difference was negligible. See Figure 10.

Table 14: Percentages of DBP by AHA Category for GS vs. NGS Patients, Exam 1 through 4 (Restricted to only patients surviving to Exam 4)

| | **Exam 1** | | **Exam 2** | | **Exam 3** | | **Exam 4** | |
|---|---|---|---|---|---|---|---|---|
| | **n = 3571** | | **n = 3571** | | **n = 3571** | | **n = 3571** | |
| **BP Category** | **NGS** | **GS** | **NGS** | **GS** | **NGS** | **GS** | **NGS** | **GS** |
| Normal | 45.22 | 61.70 | 37.23 | 48.94 | 32.54 | 33.33 | 46.30 | 45.39 |
| Prehypertension | 33.06 | 26.24 | 34.49 | 31.21 | 35.60 | 35.46 | 32.24 | 31.91 |
| High Blood Pressure Hypertension Stage 1 | 15.48 | 9.93 | 19.04 | 11.35 | 20.96 | 21.99 | 14.23 | 16.31 |
| High Blood Pressure Hypertension Stage 2 | 4.75 | 1.42 | 5.77 | 5.67 | 5.19 | 3.55 | 3.50 | 4.26 |
| Hypertensive Crisis (Emergency Care Needed) | 1.49 | 0.71 | 1.40 | 0.71 | 1.72 | 0.71 | 0.87 | 0.71 |
| Missing | 0.00 | 0.00 | 2.07 | 2.13 | 3.99 | 4.96 | 2.86 | 1.42 |

Figure 9: Mean SBP by GS Status and Exam

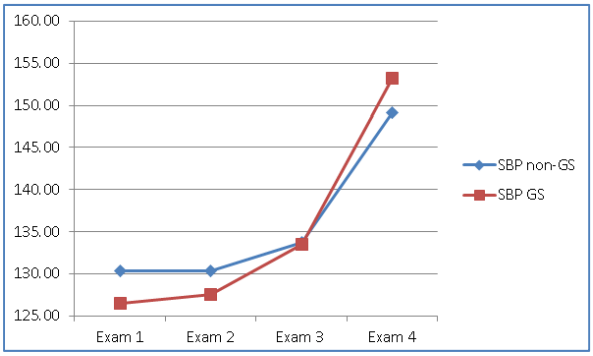
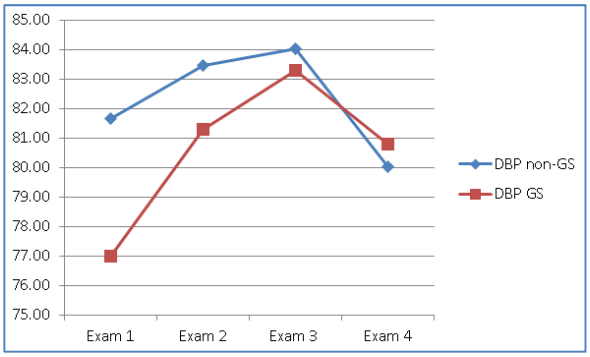



Figure 10: Mean DBP by GS Status and Exam




## Blood Glucose

### Non-Fasting Glucose

At Exam 1, excluding diabetics from the participants providing data at Exam 4, the mean blood glucose for the GS group was 140.00 mg/dL while the mean value for the NGS group was 149.10 mg/dL. Even though there was a roughly 9 unit difference between the two groups showing lower blood glucose for the GS group at entry into study, this difference was not statistically significant (t(1,143.19)=1.75, p=0.0826). Two years later, the mean blood glucose for the GS group dropped about 25 units to 114.70 mg/dL, but the mean value for the NGS group dropped almost 36 units to 113.80 mg/dL. The difference remained non-significant (t(1,14.378)=-0.08, p=0.8859). Overall, the between

groups (GS vs NGS) effect was not significant (F(1,299)=2.26, p=0.1339), but the exam effect within subjects effect was significant (F(1,299)=12.16, p=0.0006). It is possible that laboratory shift may have contributed to some of the differences across exams. The interaction between blood glucose and gastrectomy group (F(1,299)=3.53, p=0.0612) was approaching significance; see Table 10.

### Fasting Glucose and Fasting Insulin

Fasting glucose and fasting insulin were only collected at Exam 4. Mean fasting glucose was significantly lower for GS participants than for NGS participants (107.70 mg/dL vs. 111.40 mg/dL, p=0.0446; see Table 10). Categorizing glucose into normal, pre-diabetes, and diabetes following the American Diabetes Association guidelines.[66] GS participants tended to have more normal glucose while NGS participants tended to be more pre-diabetic and diabetic. The differences though were not significant ($X^2$=4.7939, p=0.0910); see Table 15). Mean fasting insulin was also significantly lower for GS participants compared to NGS participants (12.10 µU/mL vs. 15.95 µU/mL, p<0.0001). When comparing categories of normal versus greater than normal insulin between the GS and NGS participants[67], GS participants tended to have more normal insulin, while NGS participants tended to have more elevated insulin. This difference was significant ($X^2$=5.0873, p=0.0241); see Table 16.

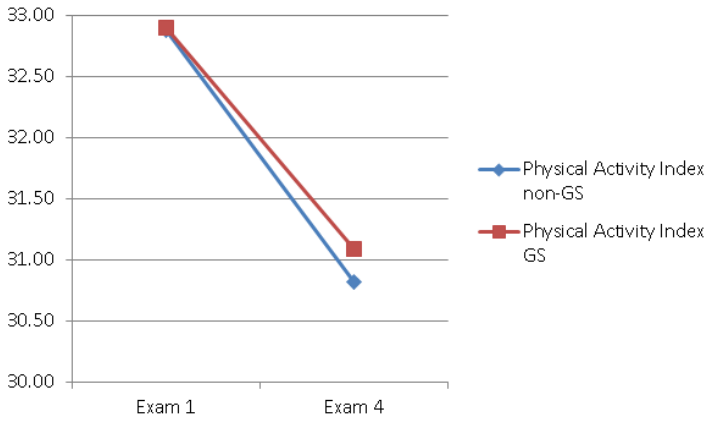
| Table 15: Exam 4 Subjects Categorized by Fasting Glucose Levels | | |
|---|---|---|
| n = 3571 | NGS | GS |
| Normal Glucose (<100 mg/dL) | 30.96% | 39.58% |
| Pre-Diabetes (100-125 mg/dL) | 53.55% | 47.22% |
| Diabetes (>126 mg/dL)) | 15.49% | 13.19% |
| $X^2$=4.7939, p=0.0910 | | |

| Table 16: Percentages of Categorized Fasting Insulin Values at Exam 4 by GS Status | | |
|---|---|---|
| n = 3571 | NGS | GS |
| Normal Insulin (<25mIU/L) | 87.45% | 93.75% |
| Elevated Insulin (≥25mIU/L) | 12.55% | 6.25% |
| $X^2$=5.0873, **p=0.0241** | | |

**Physical Activity Index (PAI)**

At Exam 1, the mean PAI for the GS group was 32.90 while the mean value for the NGS group was 32.88. There was no difference at study entry between the 2 groups (t(1,3552=-0.04, p=0.9653). At Exam 4, the mean PAI for the GS group decreased slightly to 31.09 and the mean PAI for the non-GS group followed suit and decreased slightly to 30.82 The difference between the 2 groups here was also not significant (t(1,3282)=-0.64, p=0.5242). The overall between-subjects effect was not significantly different (F(1,3267)=0.04, p=0.8509 while the overall within subjects difference was significant (F(1,3267)=40.17, p<0.0001) indicating both groups decreased physical activity in parallel. The interaction term of PAI and gastrectomy status was not significant (F(1,3267)=0.74, p=0.3894), indicating no difference by gastrectomy group; see Figure 11 Table 10).

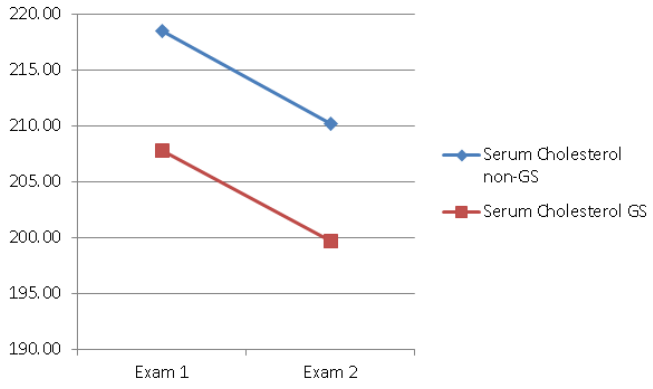
Figure 11: Physical Activity Index by GS Status and Exam



**Serum Cholesterol**

At Exam 1, the mean serum cholesterol for the GS group was 207.80 mg/dL while the mean value for the NGS group was 218.50 mg/dL. This roughly 11 point difference showed that cholesterol was statistically significant (t(1,3548=3.49, p=0.0005). At Exam 2, the mean serum cholesterol for the GS group decreased to 199.70 mg/dL while the mean serum cholesterol for the NGS group decreased to 210.20 mg/dL. This difference, based on smaller numbers, was marginally non-significant (t(1,890)=1.83, p=0.0677). The shift between exams within subjects was highly significant (F(1,885)=7.40, p=0.0006), but they were essentially parallel in their decrease as the interaction term of serum cholesterol and gastrectomy status was not significant (F(1,885)=0.99, p=0.3197; see Table 10 and Figure 12). Based on desirable, borderline high, and high cholesterol categories outlined by the National Institutes of Health,[68] at Exam 1, the GS group had significantly greater percentage of participants with desirable cholesterol levels compared to the NGS group, 43.26% vs. 30.44% (p=0.0054). See Table 17. At Exam 2, the GS group continued to have a greater percentage of desirable cholesterol. But, the gap narrowed making the difference between the GS and GS group no longer significant (p=0.5634).

Figure 12: Serum Cholesterol by GS and Exam

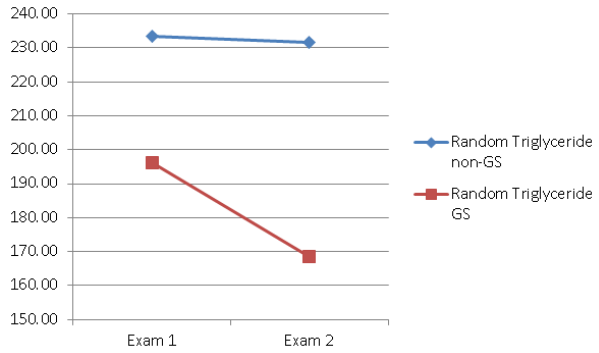


| Table 17: Percentages of Total Cholesterol for GS vs NGS Patients, Exam 1 and 2 (Restricted to only patients surviving to Exam 4) | | | | |
|---|---|---|---|---|
| | **Exam 1** | | **Exam 2** | |
| | **n = 3751** | | **n = 3571** | |
| **Total Cholesterol Category** | **NGS** | **GS** | **NGS** | **GS** |
| Desirable (<200mg/dL) | 30.44 | 43.26 | 84.64 | 87.94 |
| Borderline High (200-239 mg/dL)) | 43.99 | 36.17 | 10.85 | 8.51 |
| High (240 mg/dL and above) | 25.57 | 20.57 | 4.52 | 3.55 |
| | **p = 0.0054** | | p = 0.5634 | |

**Random Triglyceride Concentration**

At Exam 1, the mean random triglyceride for the GS group was 196.20 mg/dL while the mean value for the NGS group was 233.50 mg/dL. (t(1,141.53=2.62, p=0.0098). At Exam 2, the mean random triglycerides for the GS group decreased to 168.50 mg/dL while the mean random triglycerides for the NGS group remained relatively the same at 231.60 mg/dL. The difference between the 2 groups remained significant (t(1,42.979)=3.35, p=0.0017).The within-group differences were not significant (F(1,847)=0.16, p=0.6885), and the interaction term of random triglycerides and gastrectomy status was not significant either (F(1,847)=0.55, p=0.4590). The between group differences were significant (F(1,847)=4.27, p=0.0392; see Table 10 and Figure 13). So, again the GS exhibited lower non-fasting triglycerides over the first few years of the study. Based on desirable, borderline high, and high triglyceride categories outlined by the National Institutes of Health,[68] at Exam 1, the GS group had significantly greater percentage of participants with desirable triglycerides compared to the NGS group, 51.06% vs. 37.73% (p=0.0008; see Table 18). At Exam 2, the GS group continued to have a greater percentage of desirable cholesterol. But, the gap narrowed making the difference between the GS and GS group no longer significant. (p=0.2956)

Figure 13: Random Triglyceride by GS and Exam




| Table 18: Percentages of Random Triglycerides for GS vs. NGS Patients, Exam 1 and 2 (Restricted to only patients surviving to Exam 4) | | | | |
|---|---|---|---|---|
| | **Exam 1** | | **Exam 2** | |
| | **n = 3751** | | **n = 3571** | |
| **Total Cholesterol Category** | **NGS** | **GS** | **NGS** | **GS** |
| Desirable (<200mg/dL) | 37.73 | 51.06 | 83.88 | 87.23 |
| Borderline High (200-239 mg/dL)) | 18.40 | 20.57 | 4.90 | 5.67 |
| High (240 mg/dL and above) | 43.88 | 28.37 | 11.22 | 7.09 |
| | **p = 0.0008** | | p = 0.2956 | |

**Type 2 Diabetes Mellitus**

**Evaluable Study Participants**

Of the original 8,006 study participants in the Honolulu Heart Program (HHP), there were 7,232 study participants in the current analysis after excluding those study participants who had Diabetes Mellitus at Exam 1. Of those 7,232 study participants, 322 out of the original 347 study participants from Glober's 1974 analysis[15] who had a gastrectomy prior to completing Exam 1 remained, while 6910 of the original 7659 study participants who did not have a gastrectomy prior to Exam 1 were retained. Over the course of the HHP spanning Exams 2, 3, and 4 and 25 years of follow up, the number of study participants decreased from 303 GS and 6468 NGS at Exam 2 and 267 GS and 5957 non-GS at Exam 3, to 141 GS and 3430 NGS at Exam 4. See Table 19.

| Table 19: Count and Change from Exam 1 of HHP Study Participants at Exams 1, 2, 3, and 4 by Gastrectomy Group | | | | | | |
|---|---|---|---|---|---|---|
| | Total | % change from Exam 1 (All) | NGS | % change from Exam 1 (Non-GS) | GS | % change from Exam 1 (GS) |
| Exam 1 | 7232 | --- | 6910 | --- | 322 | --- |
| Exam 2 | 6771 | -6.33 | 6468 | -6.40 | 303 | -5.90 |
| Exam 3 | 6224 | -13.94 | 5957 | -13.79 | 267 | -17.08 |
| Exam 4 | 3571 | -50.62 | 3430 | -50.36 | 141 | -56.21 |
| $X^2$ = 4.21, df=1, **p = 0.0400** | | | | | | |

Comparing study participants who had a GS to those who did not have a GS (see Table 19), it is apparent that the dropout rate is a bit higher in the gastrectomy group. The difference in the proportion participating in Exam 4 is statistically significant ($X^2$=4.21, df=1, p=0.0400).

**Incidence of Diabetes**

Of the 3,571 patients participating in Exam 4, about 3,323 contributed complete information on incident diabetes. Of those 3,323 patients, 3,188 were part of the NGS group while 135 were part of the GS. Among these participants, the percentage who developed new cases of T2DM differed between the GS and NGS group: (26.51%) of NGS study participants developed T2DM while only 18 (13.33%) of GS study participants developed T2DM, a nearly two-fold difference ($X^2$=11.6885, p=0.0006).

Of the 135 GS patients surviving through Exam 4 and contributing data, there was no difference ($X^2$=1.2936, p = 0.8453) between patients whose diagnosis leading to gastrectomy was either duodenal ulcer (DU) or gastric ulcer (GU). Six of forty-nine (12.24%) patients who had a DU and 10 of 74 (13.51%) patients who had a GU developed diabetes between study entry at Exam 1 through Exam 4. There was also no difference ($X^2$=2.5888, p=0.4595) between patients who had either a Billroth I or Billroth II reconstruction. Eight of 67 Billroth I patients (11.94%) and 9 of 65 Billroth II patients

(13.85%) developed diabetes between study entry at Exam 1 and Exam 4. The percentage of stomach removed was known for 85 GS patients. Examining those 85 patients, 2 of 23 (8.70%) patients with 0% to 50% of their stomach removed and 7 of 62 (11.29%) with 51% to 100% of their stomach removed developed diabetes. This difference was not significant ($X^2$=0.1179, p=0.7313). Considering the lack of difference between gastrectomy sub-groups, but more importantly the relatively small cell sizes when attempting to run those sub-group analyses with the gastrectomy patients, subsequent analyses were conducted focusing on gastrectomy patients as a single group.

**Univariate Baseline (Exam 1) and Cross sectional (Exam 4) Predictors of Diabetes**

As noted previously, 26.51% NGS patients developed diabetes while only 13.33% of GS patients developed diabetes in the years after study entry and prior to study end, suggesting a nearly two-fold difference. Logistic regression predicting T2DM at Exam 4 with gastrectomy status as the single predictor (see Table 20), revealed an odds ratio (OR) of 0.427 (95%CI: 0.258, 0.705). So, from this starting point there was a 57.3% reduction in development of diabetes in the GS group compared to the NGS group not taking into account any other variables.

Table 20: Univariate Logistic Regression Models for T2DM Regressing Exam 1 and Exam 4 Variables

| | Exam 1 | | | Exam 4 | | |
|---|---|---|---|---|---|---|
| Variable | Odds ratio | (95% CI) | p | Odds ratio | (95% CI) | p |
| Gastrectomy | 0.427 | 0.258, 0.705 | **0.0009** | --- | --- | --- |
| Age (yrs) | 0.994 | 0.978, 1.011 | 0.4958 | 0.994 | 0.978, 1.011 | 0.4958 |
| Education (yrs) | 0.984 | 0.958, 1.011 | 0.2390 | 0.992 | 0.968, 1.017 | 0.5252 |
| Cigarettes Per Day | 1.005 | 1.000, 1.011 | 0.0710 | 1.007 | 1.000, 1.013 | **0.0585** |
| Cigarettes Per Day (Smokers only) | 1.008 | 1.001, 1.015 | **0.0214** | 1.007 | 1.000, 1.013 | **0.0585** |
| Smoking Status | 1.015 | 0.926, 1.112 | 0.7491 | 0.934 | 0.817, 1.067 | 0.3131 |
| Pack-years | 1.002 | 0.999, 1.006 | 0.2315 | 1.002 | 0.999, 1.004 | 0.1902 |
| Alcohol | 1.000 | 0.996, 1.004 | 0.9716 | 1.002 | 1.000 1.004 | 0.0688 |
| Hypertension Meds | 1.759 | 1.332, 2.325 | **<0.0001** | 1.649 | 1.407, 1.932 | **<0.0001** |
| Cholesterol meds | 1.118 | 0.862, 1.451 | 0.4008 | 1.291 | 1.013, 1.644 | **0.0386** |
| Hypertension-Stage 1 | 1.821 | 1.520, 2.180 | **<0.0001** | 1.518 | 1.259, 1.830 | **<.0001** |
| Hypertension-Stage 2 | 1.966 | 1.568, 2.465 | **<0.0001** | 1.667 | 1.421, 1.954 | **<0.0001** |
| Weight (lb) | 1.018 | 1.014, 1.022 | **< 0.0001** | 1.013 | 1.009, 1.017 | **<0.0001** |
| Height (in) | 1.007 | 0.973, 1.043 | 0.6761 | 1.026 | 0.991, 1.061 | 0.1429 |
| Body Mass Index (BMI) | 1.146 | 1.114, 1.178 | **< 0.0001** | 1.092 | 1.064, 1.120 | **<0.0001** |
| Skinfold-Triceps (mm) | 1.056 | 1.031, 1.082 | **< 0.0001** | 1.058 | 1.038, 1.078 | **<0.0001** |
| Skinfold-Subscapular (mm) | 1.055 | 1.043, 1.068 | **< 0.0001** | 1.054 | 1.041, 1.068 | **<0.0001** |
| Systolic Blood Pressure (mmHg) | 1.019 | 1.015, 1.026 | **< 0.0001** | 1.005 | 1.002, 1.009 | **0.0016** |
| Diastolic Blood Pressure (mmHg) | 1.028 | 1.021, 1.035 | **< 0.0001** | 0.994 | 0.988, 1.001 | 0.0997 |
| Physical Activity Index | 1.005 | 0.988, 1.022 | 0.5501 | 0.995 | 0.978, 1.012 | 0.5465 |
| CHD Prevalence | 1.907 | 1.166, 3.119 | **0.0101** | --- | --- | --- |
| Cancer Prevalence | 0.777 | 0.216, 2.791 | 0.6985 | --- | --- | --- |
| Chest Depth (cm) | 1.192 | 1.142, 1.244 | **< 0.0001** | --- | --- | --- |
| Biacromial Diameter (cm) | 1.054 | 1.012, 1.098 | **0.0106** | --- | --- | --- |
| Bi-iliac diameter (cm) | 1.068 | 1.027, 1.111 | **0.0011** | --- | --- | --- |
| Girth-Arm (cm) | 1.009 | 1.006, 1.012 | **< 0.0001** | --- | --- | --- |
| Hematocrit (%) | 1.069 | 1.040, 1.099 | **< 0.0001** | --- | --- | --- |
| Uric Acid (mg/dL) | 1.015 | 1.010, 1.021 | **< 0.0001** | --- | --- | --- |
| Random Triglyceridemg/dL | 1.002 | 1.001, 1.002 | **< 0.0001** | --- | --- | --- |
| Non-fasting glucose (mg/dL) | 1.016 | 1.014, 1.018 | **< 0.0001** | --- | --- | --- |
| Serum cholesterol (mg/dL) | 1.004 | 1.002, 1.006 | **0.0003** | --- | --- | --- |

| | | | | | | |
|---|---|---|---|---|---|---|
| Waist Circumference (cm) | --- | --- | --- | 1.037 | 1.028, 1.047 | **<0.0001** |
| Hip Circumference (cm) | --- | --- | --- | 1.039 | 1.026, 1.052 | **<0.0001** |
| Fasting insulin (mg/dL) | --- | --- | --- | 1.057 | 1.048, 1.065 | **<0.0001** |
| Fasting Glucose (mg/dL) | --- | --- | --- | 1.123 | 1.112, 1.133 | **<0.0001** |
| Rate General Health | --- | --- | --- | 1.275 | 1.130, 1.438 | **<0.0001** |
| Quality of Life | --- | --- | --- | 1.069 | 0.939, 1.216 | 0.3128 |
| Insulin Resistance | --- | --- | -- | 1.338 | 1.297, 1.381 | **<0.0001** |
| Insulin Sensitivity | --- | --- | --- | 0.950 | 0.945, 0.956 | **<0.0001** |
| Disposition Index | --- | --- | --- | <0.001 | <0.001, 0.002 | **<0.0001** |
| Note: Where cells indicate "---", data were not collected or results ascertained<br>Note: Significant values are bolded | | | | | | |

### Univariate Baseline (Exam 1) Predictors of Diabetes

At Exam 1, a number of significant predictors of diabetes were evident. Table 20 details all of the available variables predicting diabetes as well as their 95% confidence intervals and p-values.

Having had a gastectomy prior to entering the HHP at Exam 1 was associated with a 57% protection from developing diabetes over the next 25 years (to Exam 4). Other predictors included measures of obesity and body size, blood pressure and hypertension, and blood lipids. Taking medications to treat hypertension increased the risk of developing diabetes at Exam 4 by 76%, but if you added blood pressure signaling Stage 1 hypertension (greater than or equal to 140 systolic over 90 diastolic) or Stage 2 hypertension (greater than or equal to 160 systolic over 95 diastolic) the risk increased to 81.1% and 96.6%, respectively. Lastly, having coronary heart disease (CHD) at study entry was associated with a 90.7% increased risk of developing diabetes.

### Univariate Cross sectional (Exam 4) Predictors of Diabetes

Utilizing a cross-sectional analysis of Exam 4 variables predicting diabetes at Exam 4 also yielded many significant predictors (Table 20). Most of these were in the same

categories as the first exam predictors. For instance, taking hypertension medications showed a 65% increased risk of diabetes. This aligns with the increased risk of diabetes at Exam 4 for those HHP study participants exhibiting Stage 1 hypertension (52%) or Stage 2 hypertension (67%). Taking cholesterol medications at Exam 4, not significant at baseline, showed a 29% increased risk of developing diabetes. At Exam 4, fasting glucose and insulin resistance showed a 12% and 34% increased risk of having diabetes at Exam 4. Self-rating of general health at Exam 4 was associated with a 28% increased risk of diabetes meaning those characterizing their health as worse were more likely to develop diabetes. Lastly, waist circumference and hip circumference showed minimal increased risk, about 4%,

**Adjusting the Gastrectomy Effect for Confounders**

We used a multiple logistic model to test whether the apparent protective effect of partial gastrectomy on subsequent development of diabetes was independent of confounding by other diabetes risk factors. After controlling for age as well as, smoking, and alcohol consumption at Exam 1, the OR for the GS group was essentially unchanged at 0.42. See Model 4 in Table 21. To test whether the reduced adiposity induced by gastrectomy might explain its favorable effect, we introduced BMI into the model (Model 5) and found that the odds ratio for gastrectomy moved to 0.51 indicating that the BMI difference between the GS and NGS groups explained only a modest proportion of the protective effect of gastrectomy, while BMI showed a 14.5% increased risk. In Model 6, we added skinfolds and found the OR for gastrectomy the same (0.51), the OR for BMI decreasing to 1.10 but still significant, and subscapular skinfold with an OR of 1.03 and signifcant.

Coronary heart disease (CHD) at Exam 1 was a significant univariate predictor of diabetes. Including CHD prevalence into the model, CHD conferred an 80.2% increased

risk of diabetes per unit of CHD, while increased risk of BMI dropped to 10.3%%, and the gastrectomy protection slid to 51.0%.

Recognizing hypertension is another major risk factor for developing diabetes stage 1 and stage 2 hypertension were also predictive in the model. See models 8 and 9, respectively. When Stage 1 hypertension was added to the model, it showed a 50.3% increased risk of diabetes, while Stage 2 hypertension showed a 67.0% increased risk. In each of those 2 models, the risk CHD prevalence played decreased 75.6% and 73.0%, respectively while the odds ratio for gastrectomy conferred about a 49% decreased risk or protection.

So, having a gastrectomy consistently showed significant protection while obesity, coronary heart disease, and hypertension conferred consistent increased risk while controlling for age, smoking, and alcohol in the model.

Table 21: Multivariate Logistic Regression Models Showing Odds Ratios of Diabetes Incidence at Exam 4

| M | Gast | Age | cigs/ day | Alcohol | BMI | SF-Tri | SF-Sub | CHD Prev | HTN-1 | HTN-2 | AIC | GOF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.427¥ | --- | --- | --- | --- | --- | --- | --- | --- | --- | 3797.133 | --- |
| 2 | 0.428¥ | 0.995NS | --- | --- | --- | --- | --- | --- | --- | --- | 3798.782 | 0.8014 |
| 3 | 0.415¥ | 0.997NS | 1.006† | --- | --- | --- | --- | --- | --- | --- | 3788.472 | 0.8448 |
| 4 | 0.419¥ | 0.997NS | 1.006† | 0.999NS | --- | --- | --- | --- | --- | --- | 3788.904 | 0.7131 |
| 5 | 0.510† | 1.006NS | 1.009£ | 0.999NS | 1.145‡ | --- | --- | --- | --- | --- | 3698.508 | 0.7459 |
| 6 | 0.506† | 1.008NS | 1.009£ | 1.000NS | 1.102‡ | 0.977NS | 1.033¥ | --- | --- | --- | 3685.334 | 0.8396 |
| 7 | 0.510£ | 1.007NS | 1.009£ | 1.000NS | 1.103‡ | 0.977NS | 1.033¥ | 1.802† | --- | --- | 3682.300 | 0.7272 |
| 8 | 0.512† | 1.004NS | 1.010£ | 0.999NS | 1.091‡ | 0.981NS | 1.030£ | 1.756† | 1.503‡ | --- | 3666.994 | 0.4339 |
| 9 | 0.508£ | 1.003NS | 1.010£ | 0.999NS | 1.095‡ | 0.980 NS | 1.030¥ | 1.730† | --- | 1.670‡ | 3666.759 | 0.9283 |

M=Model; Gast = Gastrectomy; cigs/day = number of cigarettes smoked per day; alcohol=oz of alcohol consumed per month; BMI=body mass index; SF-Tri-skinfolds triceps; SF-Sub=skinfold subscapular; CHD Prev=Prevalence of coronary heart disease, indicating this was active at Exam 1; HTN-1-Stage 1 Hypertension; HTB-2=Stage 2 Hypertension; AIC= Akaike's Information Criteria; GOF=Goodness of Fit

NS = not significant; † significant at the < 0.05 level; £ significant at the < 0.01 level;

¥ significant at the < 0.001 level; ‡ significant at the < 0.0001 level

**Metabolic Syndrome (MetS)**

**Prevalence of Metabolic Syndrome (MetS)**

At Exam 1, of the 7,659 NGS patients 1,821 patients (23.78%) met the definition for MetS while 46 of the 347 GS patients (13.26%) met that same definition. This nearly 2-fold difference in MetS at Exam 1 for incoming HHP patients was significantly different, $X^2$=20.5429, p<0.0001. After focusing on those patients who survived to Exam 4, 20.66% of the NGS group (763 of 3693) and 11.18% (17 of 152) of the GS group and met the definition of MetS, ($X^2$=8.1076, p=0.0044) at Exam 1. The prevalence of MetS was a bit lower in the men who survived the 25 years of follow-up, but the difference between the two groups was consistent and remained statistically significant.

**Incidence of Metabolic Syndrome (MetS)**

At Exam 4, the IDF definition of MetS yielded a significant difference between those in the GS group versus those in the NGS group. In the NGS group, 721 of 3590 (20.08%) study participants met the overall IDF criteria while in the GS group, 18 of 149 (12.08%) met the overall IDF criteria. The difference was statistically significant ($X^2$=5.7780, p=0.0154).

Running the same comparison of MetS at Exam 4, but excluding those who met MetS criteria at Exam 1 and including only those study participants surviving to Exam 4, 495 of 2842 (17.42%) NGS patients and 15 of 132 GS patients (11.36%) achieved MetS criteria. This 6.06% difference it was of borderline significance ($X^2$=3.2536, p=0.0713).

Examining this comparison from a slightly different perspective, excluding those patients who were considered to have T2DM at Exam 1, presumably a consequence of MetS, and including only those study participants surviving to Exam 4, produced a significant difference. In the non-GS group, 651 of 3335 (19.52%) study participants met the overall

IDF criteria while in the GS group, 17 of 139 (12.23%) met the overall IDF criteria. The difference was statistically significant ($X^2$=4.5660, p=0.0362).

**Prevalence of Characteristics Comprising MetS at Exam 4.**

In analyzing the available individual MetS factors, the characteristics contributing to the IDF definition of MetS were waist circumference, SBP, DBP, and an elevated glucose. The prevalence of these characteristics at Exam 4 is shown in Table 10. A waist circumference greater than 90 cm was 50% + more common in the NGS than in the GS group and the prevalence of elevated blood glucose or use of diabetic medication was roughly twice as common in the NGS as in the GS group. Interestingly, in this cohort of older men the prevalence of elevated systolic and diastolic blood pressure was higher after gastrectomy than in the non-operated men. Were this not true, the discrepancy in prevalence of MetS at Exam 4 would have been larger.

**Univariate Predictors of MetS at Exam 1 and Exam 4**

Univariate and multivariate logistic regression models were constructed to identify Exam 1 predictors of MetS at Exam 4 (25 years later). See Table 22. As expected, measures of obesity, blood pressure, and glucose intolerance were associated with a higher prevalence of MetS 25 years later. Against this background a prior gastrectomy was protective with an unadjusted odds ratio of 0.61 (p=0.07). Accounting for these influences in a multivariate analysis moves the point estimate for gastrectomy toward the null. Although the protective trend persists in all models tested, gastrectomy was not statistically significant in any of them.

| Table 22: Univariate Logistic Regression Models MetS Regressing Exam 1 and Exam 4 Variables | | | | | | |
|---|---|---|---|---|---|---|
| | Exam 1 | | | Exam 4 | | |
| Variables | Odds ratio | (95% CI) | p | Odds ratio | (95% CI) | p |
| Gastrectomy | 0.608 | 0.352, 1.050 | 0.0741 | --- | --- | --- |
| Age (yrs) | 0.949 | 0.929, 0.970 | **<0.0001** | 0.947 | 0.926, 0.968 | **< 0.0001** |
| Education (yrs) | 0.967 | 0.935, 1.000 | **0.0478** | 0.991 | 0.962, 1.021 | 0.5591 |
| Cigarettes Per Day | 1.009 | 1.002, 1.016 | **0.0134** | 1.019 | 0.979, 1.061 | 0.3529 |
| Cigarettes Per Day (Smokers only) | 1.011 | 1.002, 1.019 | **0.0117** | 1.019 | 0.979, 1.061 | 0.3529 |
| Smoking Status | 1.046 | 0.935, 1.171 | 0.4306 | 0.904 | 0.766, 1.065 | 0.2278 |
| Pack-years | 1.005 | 1.001, 1.009 | **0.0261** | 1.003 | 1.000, 1.006 | **0.0301** |
| Alcohol (oz/month) | 1.002 | 0.998, 1.007 | 0.3036 | 1.003 | 1.001, 1.005 | **0.0061** |
| Hypertension Meds | 1.612 | 1.098, 2.366 | **0.0148** | 1.915 | 1.574, 2.329 | **< 0.0001** |
| Hypertension-Stage 1 | 1.600 | 1.206, 2.121 | **0.0011** | --- | --- | --- |
| Hypertension-Stage 2 | 1.555 | 1.104, 2.190 | **0.0115** | --- | --- | --- |
| Cholesterol meds | 1.176 | 0.783, 1.767 | 0.4356 | 1.089 | 0.803, 1.477 | 0.5831 |
| Weight (lbs) | 1.034 | 1.028, 1.040 | **<0.0001** | 1.050 | 1.044, 1.055 | **<0.0001** |
| Height (in) | 1.116 | 1.069, 1.165 | **<0.0001** | 1.145 | 1.097, 1.194 | **<0.0001** |
| Body Mass Index (BMI) | 1.238 | 1.194, 1.284 | **<0.0001** | 1.379 | 1.328 1.432 | **<0.0001** |
| Skinfold-Tricep (mm) | 1.070 | 1.039, 1.101 | **<0.0001** | 1.127 | 1.101, 1.153 | **<0.0001** |
| Skinfold-Subscapular (mm) | 1.070 | 1.055, 1.086 | **<0.0001** | 1.115 | 1.095, 1.130 | **<0.0001** |
| Physical Activity Index | 1.010 | 0.989, 1.030 | 0.3547 | 0.985 | 0.963, 1.007 | 0.1871 |
| CHD Prevalence | 1.345 | 0.723, 2.505 | 0.3496 | --- | --- | --- |
| CVA Prevalence | 0.967 | 0.211, 4.423 | 0.9650 | --- | --- | --- |
| Cancer Prevalence | 1.116 | 0.317, 3.929 | 0.8648 | --- | --- | --- |
| Chest Depth (cm) | 1.312 | 1.243, 1.386 | **<0.0001** | --- | --- | --- |
| Biacromial Diameter (cm) | 1.189 | 1.129, 1.252 | **<0.0001** | --- | --- | --- |
| Bi-iliac diameter (cm) | 1.207 | 1.148, 1.270 | **<0.0001** | --- | --- | --- |
| Girth-Arm (cm) | 1.015 | 1.011, 1.019 | **<0.0001** | --- | --- | --- |
| Hematocrit (%) | 1.071 | 1.034, 1.108 | **0.0001** | --- | --- | --- |
| Uric Acid (mg/dL) | 1.012 | 1.005, 1.019 | **0.0005** | --- | --- | --- |
| Random Triglyceride (mg/dL) | 1.001 | 1.000, 1.002 | **0.0005** | --- | --- | --- |
| Non-fasting glucose (mg/dL) | 1.005 | 1.003, 1.007 | **<0.0001** | --- | --- | --- |
| Serum cholesterol (mg/dL) | 1.002 | 1.000, 1.005 | 0.0852 | --- | --- | --- |
| Hip Circumference (cm) | --- | --- | --- | 1.167 | 1.146, 1.188 | **<0.0001** |
| Fasting insulin (mg/dL) | --- | --- | --- | 1.019 | 1.012, 1.026 | **<0.0001** |
| Fasting Glucose (mg/dL) | --- | --- | --- | 1.020 | 1.017, 1.023 | **<0.0001** |
| Rate General Health | --- | --- | --- | 1.142 | 0.985, 1.325 | 0.0776 |
| Quality of Life | --- | --- | --- | 0.944 | 0.804, 1.108 | 0.4800 |
| Insulin Resistance | --- | --- | -- | 1.063 | 1.042 1.083 | **<0.0001** |
| Insulin Sensitivity | --- | --- | --- | 0.949 | 0.942, 0.956 | **<0.0001** |
| Disposition Index | --- | --- | --- | 0.279 | 0.153, 0.507 | **<0.0001** |
| Note: Significant values are bolded | | | | | | |

**Multivariate Predictors of MetS**

Multivariate logistic regression, modeling MetS and fitting Exam 1 variables evaluated in the univariate analyses, showed interesting results (see Table 23). In all models, having a gastrectomy did not significantly show any decreased risk of developing MetS. Age across all models showed about a 5% decreased risk of developing MetS at Exam 4. Smoking history and alcohol use when added to the model to control for those variables showed a significant slight (0.5%) increased risk of developing MetS while alcohol did not exhibit either increased or decreased risk. BMI when added to the model showed a 23.2% increased risk of developing MetS at Exam 4, but that risk decreased as other parameters were added to the model ultimately ending with a 15.3% increased risk in the final model. When chest depth and bi-iliac diameter, 2 anthropometric measures were added, they exhibited 9.1% and 10.4% increased risk in the final model. Lastly, when hypertension, both stages 1 and 2 were entered into their respective models, only Stage 1 hypertension exhibited a significant 45.3% increased risk of developing MetS in the final model. After controlling for age, smoking, and alcohol use, obesity as measured independently by BMI, chest depth, and bi-iliac diameter were strong predictors for MetS at Exam 4. But, of all the parameters evaluated, having hypertension at Exam 1, particularly stage 1 hypertension, was shown to be the strongest predictor conferring the greatest risk of developing MetS among Exam 1 variables.

Table 23: Multivariate Logistic Regression Models Showing Odds Ratios of MetS Incidence at Exam 4

| M | Gast | Age | Pack-years | Alc | BMI | Chest Dpth | Bi-iliac | HTN1 | HTN2 | AIC | GOF |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.608$^{NS}$ | --- | --- | --- | --- | --- | --- | --- | --- | 2725.989 | --- |
| 2 | 0.632$^{NS}$ | 0.950$^{‡}$ | --- | --- | --- | --- | --- | --- | --- | 2705.098 | 0.4257 |
| 3 | 0.532$^{NS}$ | 0.948$^{‡}$ | 1.005$^{†}$ | --- | --- | --- | --- | --- | --- | 2643.101 | 0.7541 |
| 4 | 0.536$^{NS}$ | 0.947$^{‡}$ | 1.005$^{†}$ | 1.001$^{NS}$ | --- | --- | --- | --- | --- | 2640.077 | 0.9038 |
| 5 | 0.723$^{NS}$ | 0.959$^{¥}$ | 1.006$^{†}$ | 1.002$^{NS}$ | 1.232$^{‡}$ | --- | --- | --- | --- | 2513.303 | 0.2027 |
| 6 | 0.706$^{NS}$ | 0.958$^{¥}$ | 1.005$^{†}$ | 1.002$^{NS}$ | 1.179$^{‡}$ | 1.109$^{£}$ | --- | --- | --- | 2503.825 | 0.2403 |
| 7 | 0.697$^{NS}$ | 0.954$^{‡}$ | 1.005$^{†}$ | 1.002$^{NS}$ | 1.157$^{‡}$ | 1.093$^{†}$ | 1.106$^{¥}$ | --- | --- | 2493.563 | 0.6434 |
| 8 | 0.697$^{NS}$ | 0.951$^{‡}$ | 1.005$^{†}$ | 1.002$^{NS}$ | 1.152$^{‡}$ | 1.091$^{†}$ | 1.104$^{¥}$ | 1.453$^{†}$ | --- | 2489.885 | 0.3374 |
| 9 | 0.694$^{NS}$ | 0.952$^{‡}$ | 1.005$^{†}$ | 1.002$^{NS}$ | 1.153$^{‡}$ | 1.092$^{†}$ | 1.106$^{¥}$ | ---- | 1.429$^{NS}$ | 2491.995 | 0.5018 |

M=Model; Gast = Gastrectomy; pack-years=number of packs of cigarettes smoked per day multiplied by the number of years smoking; alcohol=oz of alcohol consumed per month; BMI=body mass index; Chest Dpth= Chest Depth; Bi-iliac=Bi-iliac Diameter; HTN-1-Stage 1 Hypertension; HTN2=Stage 2 Hypertension; AIC= Akaike's Information Criteria; GOF=Goodness of Fit;
$^{NS}$ = not significant; $^{†}$ significant at the < 0.05 level; $^{£}$ significant at the < 0.01 level; $^{¥}$ significant at the < 0.001 level; $^{‡}$ significant at the < 0.0001 level

**Insulin Resistance (IR)**

As data to examine IR, particularly fasting insulin and fasting glucose were not available at Exam 1 and were only available at Exam 4, prevalence at study start and incidence were not determined. However, the data at exam 4 allowed for an examination of IR as well as insulin sensitivity, percent (%) β cell function, and disposition index in the context of gastrectomy in a cross-sectional fashion.

**Occurrence of Insulin Resistance**

From the original 8,006 patients entering the HHP at Exam 1, 3,562 patients (3,418 NGS and 144 GS) provided fasting insulin and fasting glucose at Exam 4 from which IR could be calculated (see Table 24).

| Table 24: Number of Patients at Exam 4 for Insulin Resistance Analyses | | | |
|---|---|---|---|
| | **Total** | **NGS** | **GS** |
| All Patients at Exam 1 | 8006 | 7659 | 347 |
| *Excluding diabetics at Exam 1 | 7232 | 6910 | 322 |
| All Patients Contributing Data for IR analyses | 3562 | 3418 | 144 |
| *Excluding diabetics at Exam 1 | 3309 | 3175 | 134 |
| *Excluding diabetics at Exam 1 AND only incident diabetes at Exam 4 | 854 | 837 | 17 |
| *Excluding diabetics at Exam 1 AND only non-diabetics at Exam 4 | 2455 | 2338 | 117 |

Mean HOMA-IR values showed a significant difference between the NGS and GS groups across different patient sub-groups; all patients ($t(1,525.91)=4.43$, $p<0.0001$), excluding diabetics at Exam 1 ($t(1,178.19)=3.82$, $p=0.0002$), and excluding diabetics at Exam 1 and only non-diabetics at Exam 4 ($t(1,132.29) = 3.25$, $p = 0.0015$; see Table 25). For the sub-group excluding diabetics at Exam 1 and only including diabetics at exam 4, the difference was not significant ($t(1,17.721)=0.39$, $p=0.6989$. As those meeting criteria for diabetes already have difficulties with insulin control, this non-significant difference is not surprising.

| Table 25: Mean HOMA-IR Values of Patients at Exam 4 by Gastrectomy Status | | | | |
|---|---|---|---|---|
| | **n** | **NGS** | **GS** | **p-value** |
| All Patients Contributing Data for IR analyses | 3562 | 5.23 (4.68, 5.78) | 3.44 (2.87, 4.01) | **<0.0001** |
| *Excluding diabetics at Exam 1 | 3309 | 4.65 (4.42, 4.89) | 3.40 (2.80, 4.00) | **0.0002** |
| *Excluding diabetics at Exam 1 AND only incident diabetes at Exam 4 | 854 | 8.00 (7.18, 8.83) | 7.27 (3.39, 11.15) | 0.6989 |
| *Excluding diabetics at Exam 1 AND only non-diabetics at Exam 4 | 2455 | 3.45 (3.36, 3.55) | 2.84 (2.48, 3.20) | **0.0015** |
| Note: Significant values are bolded | | | | |

After determining IR using either the broad 2.5 cut-off value or the conservative 1.7 cut-off value, it was clear across all comparisons that there were less insulin resistant patients in the GS group compared to the NGS group (See Table 26).

Table 26: Percentages of Insulin Resistance between GS and NGS Groups Categorized by Two Different Cut-offs and Select Patient Groups

| | | 2.5 Cut-Off[1] | | | 1.7 Cut-Off[2] | | |
|---|---|---|---|---|---|---|---|
| **Patient Data Analyzed** | **n** | **NGS** | **GS** | **p-value** | **NGS** | **GS** | **p-value** |
| All Patients | 3562 | 67.79 | 50.69 | **<0.0001** | 88.21 | 74.31 | **<0.0001** |
| Excluding diabetics at Exam 1 | 3309 | 66.96 | 50.00 | **<0.0001** | 87.91 | 73.88 | **<0.0001** |
| Excluding diabetics at Exam 1 AND incident diabetes at Exam 4 | 854 | 86.26 | 70.59 | 0.0657 | 95.58 | 94.21 | 0.7723 |
| Excluding diabetics at Exam 1 AND non-diabetics at Exam 3 | 2455 | 60.05 | 47.01 | **0.0050** | 85.16 | 70.94 | **<0.0001** |

[1] A 'health associated' reference interval for HOMA-IR of 0.4 to 2.4 was established. HOMA-IR > 2.5 is considered a reasonable indicator of IR in a Japanese population[69]

[2] A 'decision based' reference interval for HOMA-IR for use by clinicians to diagnose or manage patients. The optimal cut-off value for HOMA-IR to discriminate MetS in non-diabetic Japanese subjects is 1.7.[70]

Note: Significant values are bolded

So, regardless of the cut-off threshold for defining IR, there was significantly less IR among GS patients than among NGS patients across all patient sub-groups at Exam 4. Of note, even with the more broad 2.5 cut-off definition of IR, the percentage range among non-diabetic patients either at Exam 1 or Exam 4 went from 47.01% of GS patients up to 66.96% of NGS patients, roughly at least half to two-thirds. When the more conservative 1.7 cut-off definition of IR was applied, that range among those same non-diabetics increased to 70.94% to 87.91%. This suggests that IR is rampant in older age. And since it is so pervasive in older age, IR very well maybe an underlying factor among many chronic diseases.

**Insulin Resistance and its Relationship to Diabetes and Metabolic Syndrome**

In looking at the relationship between diabetes and IR, the odds ratio of having diabetes if one had IR defined at the 2.5 cut-off threshold, was 4.18 (95%CI:3.39,5.15) and the relative risk for having diabetes was 1.34 (95%CI: 1.23,1.39). At the 1.7 IR cut-off threshold, the odds ratio was 3.94 (95%CI: 2.80, 5.56) and the relative risk was 1.27

(95%CI: 1.22,1.32). In either case, there was a significant increase of occurrence of diabetes, at the p <0.0001 levelif IR was present.

Likewise, in looking at the relationship between MetS and IR, the odds of developing MetS if one had IR defined at the 2.5 cut-off threshold, was 4.93 (95%CI: 3.73,6.53) and the relative risk of developing MetS was 1.24 (95%CI: 1.20,1.27). At the 1.7 IR cut-off threshold, the odds ratio was 5.77 (95%CI: 3.46,9.60) and the relative risk was 1.20 (95%CI: 1.16,1.23). In either case, there was a significant increase of occurrence of MetS at the p<0.0001 level in the presence of IR.

**Logistic Regression: Univariate Predictors of Insulin Resistance**

Table 27 [Logistic Regression Models for Insulin Resistance] shows the details of variables at Exam 4 when regressed against the IR variable (Yes or No) using the 2.5 cut-off level. Univariate predictors showed a 50.7% protection from IR with gastrectomy while stage 1 hypertension and stage 2 hypertension showed a 74.1% and 90.0% increased risk of IR, respectively. More modest effects showed significant increased risk of IR from subscapular skinfold (17.5%), triceps skinfold (16.3%), hip circumference (15.6%), waist circumference (12.6%), weight (10.9%), armspan (1.6%), diastolic blood pressure (1.6%), and systolic blood pressure (0.7%). And, there were even some significant small to modest decreases in risk of IR with quality of life (15.6%), age, (4.5%), and PAI (2.2%).

When the more conservative 1.7 cut-off was applied, the pattern remained the same but the percentages for increased risk or increased protection grew. Univariate predictors showed 61.1% protection from IR with gastrectomy with body fat, stage 1 hypertension, and stage 2 hypertension showing a 2.41 fold (1.41%), 97%, and 2.18 fold (1.18%) increased risk of IR, respectively. The previously significant, modest increases in risk of

IR from the 2.5 cut-off became more prominent with subscapular skinfold (25.6%), triceps skinfold (24.2%), hip circumference (19.6%), waist circumference (14.7%), weight (13.4%), arm span (1.7%), diastolic pressure (2.2%), and systolic blood pressure (1.0%). And, there were small to moderate decreases in risk of IR with quality of life (21.0%) and age (4.5%). At the 1.7 cut-off for IR, PAI became non-significant.

| Table 27: Univariate Logistic Regression Models for Insulin Resistance Exam 1 Variables 2.5 and 1.7 Cut-Off Thresholds | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Model (IR at Exam 4 = )** | **2.5 Cut-Off Threshold** | | | | | **1.7 Cut-Off Threshold** | | | | |
| | **OR** | **(95% CI)** | **p** | **AIC** | **GOF (p)** | **OR** | **(95% CI)** | **p** | **AIC** | **GOF (p)** |
| Gastrectomy | 0.493 | 0.349, 0.698 | **<0.0001** | 4218.566 | --- | 0.389 | 0.261, 0.580 | **<0.0001** | 2499.814 | --- |
| Age | 0.952 | 0.938, 0.967 | **<0.0001** | 4194.392 | 0.8551 | 0.956 | 0.936, 0.976 | **<0.0001** | 2500.814 | 0.5842 |
| Education | 0.993 | 0.969, 1.018 | 0.5769 | 4233.110 | 0.4234 | 1.017 | 0.981, 1.054 | 0.3550 | 2517.173 | 0.5261 |
| Cigarettes per Day | 1.003 | 0.998, 1.009 | 0.2345 | 4225.706 | 0.7637 | 0.998 | 0.990, 1.006 | 0.6123 | 2512.292 | 0.1283 |
| Cigarettes per day (smokers only) | 1.004 | 0.997, 1.010 | 0.2691 | 2736.742 | 0.8029 | 0.998 | 0.989, 1.007 | 0.6306 | 1638.714 | 0.3207 |
| Smoking Status | 1.025 | 0.941 1.116 | 0.5752 | 4233.106 | 0.9887 | 0.955 | 0.846, 1.078 | 0.4539 | 2517.472 | 0.3142 |
| Pack-years | 1.000 | 0.997, 1.003 | 0.9328 | 4177.769 | 0.3606 | 0.997 | 0.993, 1.002 | 0.2423 | 2489.589 | 0.5289 |
| Alcohol | 0.994 | 0.991, 0.997 | **0.0004** | 4217.887 | 0.6761 | 0.995 | 0.990, 0.999 | **0.0147** | 2511.967 | 0.0789 |
| Hypertension Meds | 1.691 | 1.239, 2.310 | **0.0009** | 4208.805 | --- | 1.783 | 1.090, 2.917 | **0.0213** | 2505.591 | --- |
| Hypertension-Stage 1 | 1.777 | 1.466, 2.154 | **<0.0001** | 4197.791 | --- | 1.834 | 1.362, 2.468 | **<0.0001** | 2500.296 | --- |
| Hypertension-Stage 2 | 1.829 | 1.416, 2.363 | **<0.0001** | 4211.084 | --- | 1.837 | 1.232, 2.740 | **0.0029** | 2508.031 | --- |
| Cholesterol Meds | 1.327 | 0.839, 2.098 | 0.2261 | 4231.180 | --- | 1.092 | 0.676, 1.764 | 0.7197 | 2517.880 | --- |
| Weight | 1.032 | 1.028, 1.037 | **<0.0001** | 3984.785 | 0.0760 | 1.038 | 1.032, 1.045 | **<0.0001** | 2348.362 | 0.4021 |
| Height | 1.061 | 1.027, 1.096 | **0.0004** | 4220.722 | 0.1794 | 1.060 | 1.013, 1.110 | **0.0127** | 2511.802 | 0.1631 |
| Body Mass Index | 1.246 | 1.211, 1.282 | **<0.0001** | 3976.023 | 0.6973 | 1.302 | 1.250, 1.355 | **<0.0001** | 2334.823 | 0.7076 |
| Skinfold Tricep | 1.135 | 1.107, 1.165 | **<0.0001** | 4131.053 | 0.2919 | 1.197 | 1.149, 1.246 | **<0.0001** | 2430.010 | 0.3288 |
| Skinfold-Subscapular | 1.102 | 1.088, 1.116 | **<0.0001** | 3987.909 | **0.0258** | 1.132 | 1.110, 1.156 | **<0.0001** | 2342.151 | **0.0036** |
| Systolic Blood Pressure | 1.016 | 1.012, 1.020 | **<0.0001** | 4176.428 | 0.1061 | 1.018 | 1.012, 1.025 | **<0.0001** | 2482.053 | 0.1248 |
| Diastolic Blood Pressure | 1.033 | 1.026, 1.041 | **<0.0001** | 4144.381 | 0.1020 | 1.039 | 1.028, 1.050 | **<0.0001** | 2460.019 | 0.2564 |
| Physical Activity Index | 0.975 | 0.960, 0.990 | **0.0012** | 4207.480 | 0.6040 | 0.958 | 0.939, 0.977 | **<0.0001** | 2493.875 | 0.7363 |
| CHD Prevalence | 2.183 | 1.187, 4.012 | **0.0120** | 4226.954 | --- | 1.845 | 0.738, 4.614 | 0.1902 | 2516.267 | --- |
| CVA Prevalence | 0.225 | 0.069, 0.733 | **0.0133** | 4227.407 | --- | 1.743 | 0.226, 13.438 | 0.5940 | 2517.971 | --- |
| Cancer Prevalence | 0.677 | 0.234, 1.957 | 0.4717 | 4233.738 | --- | 0.360 | 0.112, 1.154 | 0.0856 | 2515.802 | --- |
| Chest Depth | 1.291 | 1.237, 1.348 | **<0.0001** | 4082.660 | 0.2240 | 1.333 | 1.255, 1.416 | **<0.0001** | 2424.405 | 0.9166 |
| Biacromial Diameter | 1.113 | 1.072, 1.157 | **<0.0001** | 4200.654 | 0.6862 | 1.111 | 1.053, 1.172 | **0.0001** | 2502.468 | 0.4443 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Bi-iliac diameter | 1.119 | 1.078, 1.162 | **<0.0001** | 4197.848 | 0.0589 | 1.152 | 1.093, 1.214 | **<0.0001** | 2490.054 | 0.3729 |
| Girth-Arm | 1.018 | 1.015, 1.021 | **<0.0001** | 4084.569 | 0.4941 | 1.022 | 1.018, 1.027 | **<0.0001** | 2399.807 | 0.9084 |
| Hematocrit | 1.101 | 1.072 1.131 | **<0.0001** | 4153.415 | 0.7710 | 1.093 | 1.053, 1.134 | **<0.0001** | 2468.121 | 0.9192 |
| Uric Acid | 1.020 | 1.014, 1.025 | **<0.0001** | 4158.788 | 0.0581 | 1.023 | 1.015, 1.031 | **<0.0001** | 2467.227 | 0.0572 |
| Random Triglyceride | 1.003 | 1.002, 1.003 | **<0.0001** | 3955.823 | **0.0014** | 1.003 | 1.002, 1.004 | **<0.0001** | 2355.491 | **0.0397** |
| Non-fasting glucose | 1.002 | 1.001, 1.004 | **0.0115** | 4212.748 | 0.4188 | 1.001 | 0.998, 1.003 | 0.4610 | 2503.451 | 0.1946 |
| Serum cholesterol | 1.004 | 1.002, 1.006 | **0.0006** | 4198.020 | 0.5892 | 1.005 | 1.002, 1.008 | **0.0005** | 2489.442 | 0.1682 |

**Univariate Logistic Regression Models for Insulin Resistance Exam 4 Variables 2.5 and 1.7 Cut-Off Thresholds**

| **Model (IR at Exam 4 = )** | **2.5 Cut-Off Threshold** | | | | | **1.7 Cut-Off Threshold** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Odds ratio** | **(95% CI)** | **p** | **AIC** | **GOF (p)** | **Odds ratio** | **(95% CI)** | **p** | **AIC** | **GOF (p)** |
| Gastrectomy | 0.493 | 0.349, 0.698 | **<0.0001** | 4218.566 | --- | 0.389 | 0.261, 0.580 | **<0.0001** | 2499.814 | --- |
| Age | 0.955 | 0.935, 0.975 | **<0.0001** | 2500.329 | 0.7869 | 0.955 | 0.935, 0.975 | **<0.0001** | 2500.329 | 0.7869 |
| Education | 1.007 | 0.984 1.030 | 0.5492 | 4233.883 | 0.3111 | 1.018 | 0.986, 1.051 | 0.2814 | 2517.136 | 0.5135 |
| Cigarettes per Day | 1.004 | 0.998, 1.011 | 0.1929 | 2117.541 | 0.6756 | 1.003 | 0.993, 1.013 | 0.5564 | 1181.569 | 0.5006 |
| Cigarettes per day (smokers only) | 1.004 | 0.998, 1.011 | 0.1929 | 2117.541 | 0.6756 | 1.003 | 0.993, 1.013 | 0.5564 | 1181.569 | 0.5006 |
| Smoking Status | 1.032 | 0.911, 1.169 | 0.6211 | 3960.138 | **0.0032** | 0.856 | 0.717, 1.021 | **0.0846** | 2343.110 | **<.0001** |
| Pack-years | 1.002 | 1.000, 1.004 | 0.0639 | 3872.049 | 0.4834 | 1.002 | 0.999, 1.005 | 0.2663 | 2280.196 | 0.3046 |
| Alcohol | 0.999 | 0.997, 1.001 | 0.3505 | 3901.927 | **0.0013** | 0.999 | 0.997, 1.002 | 0.6191 | 2320.207 | **0.0081** |
| Hypertension Meds | 1.940 | 1.657, 2.270 | **<0.0001** | 4126.407 | --- | 2.007 | 1.583, 2.544 | **<0.0001** | 2454.817 | --- |
| Cholesterol Meds | 1.189 | 0.936, 1.510 | 0.1558 | 4181.801 | --- | 1.155 | 0.817, 1.633 | 0.4154 | 2485.308 | --- |
| Weight | 1.109 | 1.098, 1.120 | **<0.0001** | 3610.746 | 0.6241 | 1.134 | 1.117, 1.150 | **<0.0001** | 2062.361 | 0.6429 |
| Height | 1.085 | 1.051 1.121 | **<0.0001** | 4075.840 | 0.7913 | 1.093 | 1.044, 1.144 | **0.0001** | 2396.434 | 0.8110 |
| Body Mass Index | 1.388 | 1.345, 1.432 | **<0.0001** | 3533.487 | 0.3031 | 1.487 | 1.422, 1.555 | **<0.0001** | 1997.788 | 0.1292 |
| Skinfold Tricep | 1.163 | 1.137, 1.190 | **<0.0001** | 3976.393 | **0.0008** | 1.242 | 1.197, 1.289 | **<0.0001** | 2302.212 | **0.0003** |
| Skinfold-Subscapular | 1.175 | 1.155, 1.195 | **<0.0001** | 3680.843 | **<.0001** | 1.256 | 1.222, 1.291 | **<0.0001** | 2081.789 | **<.0001** |
| Systolic Blood Pressure | 1.007 | 1.003, 1.010 | **<0.0001** | 4215.802 | 0.0766 | 1.010 | 1.005, 1.014 | **<0.0001** | 2500.116 | **0.0365** |
| Diastolic Blood Pressure | 1.016 | 1.010, 1.023 | **<0.0001** | 4205.059 | 0.2558 | 1.022 | 1.013, 1.031 | **<0.0001** | 2495.459 | 0.2815 |
| Physical Activity Index | 0.978 | 0.963, 0.993 | **0.0050** | 3940.854 | **0.0153** | 0.981 | 0.960, 1.002 | 0.0762 | 2336.210 | 0.1942 |
| Waist Circumference | 1.126 | 1.114, 1.139 | **<0.0001** | 3589.665 | 0.4018 | 1.147 | 1.130, 1.164 | **<0.0001** | 2057.833 | 0.6261 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Hip Circumference | 1.156 | 1.139, 1.173 | **<0.0001** | 3687.015 | 0.2172 | 1.196 | 1.172, 1.222 | **<0.0001** | 2098.031 | 0.0650 |
| Waist to Hip Ratio | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Stage 1 Hypertension | 1.741 | 1.484, 2.042 | **<0.0001** | 4188.454 | --- | 1.970 | 1.590, 2.440 | **<0.0001** | 2481.395 | --- |
| Stage 2 Hypertension | 1.900 | 1.642, 2.199 | **<0.0001** | 4158.930 | --- | 2.182 | 1.766, 2.696 | **<0.0001** | 2464.109 | --- |
| Rate General Health | 1.075 | 0.959, 1.205 | 0.2155 | 3737.528 | 0.0638 | 1.017 | 0.863, 1.199 | 0.8390 | 2168.683 | 0.7536 |
| Satisfied Quality of Life | 0.844 | 0.747, 0.953 | **0.0063** | 3732.427 | 0.5855 | 0.790 | 0.664, 0.939 | **0.0077** | 2161.944 | 0.7425 |
| Armspan | 1.016 | 1.005, 1.026 | **0.0027** | 4092.141 | 0.8657 | 1.017 | 1.003, 1.032 | **0.0181** | 2405.427 | 0.9446 |
| OR=Odds Ratio; AIC= Akaike's Information Criteria; GOF=Goodness of Fit; Note: Significant values are bolded | | | | | | | | | | |

So, a number of variables appear to be related to insulin resistance. Interestingly, neither smoking nor alcohol consumption appeared to be contributors to insulin resistance at either the 2.5 or the 1.7 insulin resistance cut-off/threshold.

**Logistic Regression: Multivariate Predictors of Insulin Resistance**

Based on the results from the univariate analyses, multivariate models were constructed at both the 2.5 and 1.7 IR cut-off levels. Using the AIC and Hosmer-Lemeshow goodness of fit tests, a sequence of models were generated resulting in the final models shown in Table 28 below.

Focusing on Exam 1 variables, at the 2.5 IR cut-off, controlling for age, smoking, and alcohol, gastrectomy showed a 32.8% protection from IR, an 18.1% difference from the 1.7 IR cut-off. Age and alcohol use were slightly protective 4.5% and 0.8%, respectively while, smoking in the form of pack-years increased the risk slightly (0.4%). CHD prevalence showed a 212% (2.1-fold) increased risk of IR. CVA prevalence showed an 88.5% decreased risk of IR. BMI, skinfold-triceps, and chest depth showed 17.1%, 3.9%, and 6.4% increased risk of IR, respectively. Stage 1 and Stage 2 hypertension showed a 47.5% and 63.6% increased risk of IR, respectively.

At the 1.7 IR cut-off, an even stronger 50.9% protection was seen with gastrectomy after controlling for age, smoking, and alcohol. This effect was significant at the $p<0.001$ level. Age and alcohol were slightly protective 4.2% and 0.5% decreased risk. Smoking, in the form of pack years was not statistically significant. Skinfold triceps and chest depth showed increased risk of 12.6% and 22.0%, respectively. Stage1 and Stage 2 hypertension exhibited a 58.0% and 62.8% increased risk of IR.

The 2.5 cut-off which was considered a broad, reasonable threshold for classifying IR encompassed more variables that contributed to IR and highlighted strong increased and decreased risk with CHD and CVA prevalence, respectively. When the 1.7 more conservative IR cut-off was applied, while holding the sample control factors (age, smoking alcohol), gastrectomy became even more protective and BMI fell out of the model, elevating the effects of skinfold-triceps and chest depth. Hypertension (Stage 1 and Stage 2) at both cut-off levels showed the strong and consistent increased risk of developing IR. The results at both cutoffs demonstrate the roles both hypertension and obesity play in the development of IR.

Table 28: Multivariate Logistic Regression Models for Insulin Resistance

| | **2.5** | | | **1.7** | | |
|---|---|---|---|---|---|---|
| **Predictors** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| Gastrectomy | 0.672 | 0.462, 0.979 | **0.0385** | 0.491 | 0.322, 0.750 | **0.0010** |
| Age | 0.955 | 0.939, 0.970 | **<0.0001** | 0.958 | 0.938, 0.979 | **0.0001** |
| Pack-years | 1.004 | 1.000, 1.008 | **0.0351** | 1.001 | 0.995, 1.006 | 0.8279 |
| Alcohol | 0.992 | 0.989, 0.996 | **<0.0001** | 0.995 | 0.990, 0.999 | **0.0220** |
| BMI | 1.171 | 1.123, 1.221 | **<0.0001** | --- | --- | --- |
| CHD Prevalence | 2.121 | 1.129, 3.985 | **0.0194** | --- | --- | --- |
| CVA Prevalence | 0.115 | 0.033, 0.402 | **0.0007** | --- | --- | --- |
| Skinfold-Tricep | 1.039 | 1.008, 1.071 | **0.0126** | 1.126 | 1.079, 1.176 | **<0.0001** |
| Chest Depth | 1.064 | 1.004, 1.128 | **0.0375** | 1.220 | 1.142, 1.304 | **<0.0001** |
| Stage 1 Hypertension* | 1.475 | 1.197, 1.818 | **0.0003** | 1.580 | 1.157, 2.158 | **0.0040** |
| Stage 2 Hypertension* | 1.636 | 1.239, 2.159 | **0.0005** | 1.628 | 1.073, 2.471 | **0.0220** |

* As Stage 1 and Stage 2 Hypertension are highly correlated, each was evaluated in a separate model with the preceding 9 covariates and the ORs reported here.
Note: Significant values are bolded

**Homeostasis Model Assessment (HOMA) Measures by Gastrectomy Status**

Insulin resistance is one of a few measures assessed with HOMA. As noted before, insulin sensitivity (IS) is the reciprocal of IR and represents how sensitive one is to insulin; lower IS leads to worse metabolic outcomes. As expected, IS and IR are moderately, but significantly inversely correlated ($r= -0.3977$, $p<0.0001$). (See Table 29). With HOMA %Beta estimating the percentage of working β-cells producing insulin, it was also expected that IR would be positively correlated ($r=0.3402$, $p<0.0001$) as more β-

cells would need to work to keep up with insulin demand, and that IS would be inversely correlated (r= -0.1505, p<0.0001) as greater IS means less cells have to work, or work as hard. With the DI measuring the ability of β-cells to compensate for insulin resistance, it was also anticipated that the correlation would be negative with IR as β-cells would be struggling to compensate with IR (r=-0.0922 and have decreased functionality, p<0.0001) and positive with IS as there would be less of struggle to compensate (r=0.1286, p<0.0001). Lastly, with HOMA %Beta and DI capturing the amount of working cells and how they are working, it is no surprise that these 2 measures were highly correlated (r=0.78675, p<0.0001).

Table 29: Pearson Correlation Coefficients of HOMA-IR Variables

| | HOMA-IR | HOMA-IS | HOMA-% Beta | HOMA-DI |
|---|---|---|---|---|
| HOMA-IR | 1.00000 | --- | --- | --- |
| HOMA-IS | -0.39769<br>**p < 0.0001** | 1.00000 | --- | --- |
| HOMA-% Beta | 0.34023<br>**p < 0.0001** | -0.15045<br>**p < 0.0001** | 1.00000 | --- |
| HOMA-DI | -0.09216<br>**p < 0.0001** | 0.12859<br>**p < 0.0001** | 0.78675<br>**p < 0.0001** | 1.00000 |

HOMA-IR = Homeostatic Model Assessment of Insulin Resistance
HOMA-IS = Homeostatic Model Assessment of Insulin Sensitivity
HOMA-%Beta = Homeostatic Model Assessment % of functioning Beta cells
HOMA-DI = Homeostatic Model Assessment of Disposition Index
Note: Significant values are bolded

From the results in Table 26, there was less insulin resistance among GS patients compared to NGS patients. It was predicted that GS patients at Exam 4 were more sensitive to insulin compared to NGS patients (50.66 vs. 39.28, p=0.0003; see Table 30). In examining percent β cell function, there appeared to be greater β cell function among GS patients compared to NGS patients based on the mean values. However, the difference was not statistically significant (p=0.7504). Of note, both means were in excess of 100% meaning the β cells in both GS and NGS patients were functioning beyond normal capacity to support insulin production and homeostasis. With the disposition index measuring the ability of the β cells to compensate for insulin resistance

and being thought of as a measure of β cell functionality, the greater index value of 0.4956 in the GS group compared to the index value of 0.3945 in the NGS group suggests the β cells in the GS group may be compensating better for insulin resistance and that β cells are functioning better than the β cells in the NGS group. The difference was not significant (p=0.2984), however, similar to % β cell function meaning there may not truly be a difference.

Table 30: Homeostasis Model Assessment (HOMA) Measures: Means and 95%CIs

| | n | NGS (n = 2338) | GS (n = 117) | p** |
|---|---|---|---|---|
| **HOMA-Insulin Resistance** | 2455 | 3.45 (3.36, 3.55) | 2.84 (2.48, 3.20) | **0.0015** |
| **HOMA-Insulin Sensitivity** | 2455 | 39.28 (38.31, 40.24) | 50.66 (44.63, 56.69) | **0.0003** |
| **HOMA-% β Cell Function** | 2455 | 126.90 (123.40, 130.30) | 138.90 (64.25, 213.60) | 0.7504 |
| **HOMA-Disposition Index** | 2455 | 0.3945 (0.3866, 0.4024) | 0.4956 (0.3040, 0.6872) | 0.2984 |

*Excluding diabetics at Exam 1 AND only non-diabetics at Exam 4
** p-value determine via independent samples t-tests
Note: Significant values are bolded

**Is the Protective Effect in the Gastrectomy Group Independent of Obesity?**

In a univariate logistic regression, gastrectomy showed an odds ratio predicting T2DM of 0.427 (95%CI: 0.258, 0.705) that was significant (p=0.0009) suggesting a 57.3% reduction of risk of developing T2DM. In the final multivariate model, the odds ratio of gastrectomy protecting from diabetes was 0.511 (95%CI: 0.307, 0.852) that was also significant (p=0.0101). Taking all relevant variables into consideration, there was still a 48.9% reduction of risk of developing T2DM. Obesity in the form of BMI was controlled for in the final model and was highly significant (OR=1.134, 95%CI: 1.102, 1.168, p<0.0001). But, to see what extent obesity was impacting gastrectomy status in the context of predicting T2DM, a multivariate regression was conducted saturating the model with obesity variables from all study visits. Starting from a 57.3% reduction, the reduction of risk fluctuated slightly reducing the protection to as little as 43.9% reduction

in risk, ending at 53.3% reduction of risk when all obesity variables were entered; a difference of only 4%. So, the effects of gastrectomy appeared independent of the effects of obesity in predicting T2DM.

As gastrectomy did not demonstrate a statistically significant protective effect against developing MetS, gastrectomy and obesity were not evaluated in this fashion.

There appeared to be at least a partial effect of obesity on gastrectomy in predicting IR. Following the same multivariate regression, constructing a model and saturating it with obesity variables did reduce the protective effect of gastrectomy on IR. At the 2.5 IR cut-off, adding the obesity variables diminished the protective effect of gastrectomy to the point of becoming non-significant. Starting at a 50.7% ($p<0.0001$) reduction in risk of developing IR from the univariate model, the effect diminished to 19.8% at its zenith, but became non-significant around 35% reduced risk. When the cut-off was set to 1.7, gastrectomy remained significantly protective after saturation with obesity variables. Starting from the univariate analysis looking at gastrectomy alone predicting IR at the 1.7 cut-off, there was 61.1% ($p<0.0001$) reduced risk. At its zenith, that protection was diminished to as little as 40.3% reduced risk. Although the reduced risk after saturating the model remained significant, the almost 21% difference suggests obesity does impact the effect gastrectomy has on reducing the risk of developing IR. The thresholds of a 2.5 cut-off or a 1.7 cut-off for the definition of IR are arbitrary, but represent the extreme boundaries of cut-offs used by previous studies in the literature evaluating IR.

**Discussion (Diabetes, Metabolic Syndrome, Insulin Resistance)**

Although at Exam 1 the GS men weighed less, had lower anthropometric evidence of adiposity and lower blood glucose levels, they had only a modestly (non-significant) lower prevalence rate of T2DM (7.20%) compared to the NGS group (9.55%). After excluding these prevalent cases and focusing on those men who survived to and contributed data to Exam 4, the incidence of T2DM in the GS group at Exam 4 was about 50% lower than in the non-operated men: 13.33% (18 of 135) versus 26.51% (845 of 3188), respectively. After adding other predictors of T2DM, such as BMI, prevalent coronary heart disease, and hypertension, the risk of developing T2DM was decreased to 48.9 % among those entering HHP with a gastrectomy ($p<0.001$). Over the course of the 25+ years from study entry, those who had a gastrectomy prior to entering the study saw significant protection from developing T2DM. And, the protection provided by gastrectomy was independent of obesity.

There was also evidence that the GS men were more likely to have MetS at baseline or to develop MetS by the 25 year follow-up. Focusing on those patients surviving to and contributing data to Exam 4, 11.18% (17 of 152) of GS patients and 20.66% (765 of 3693) of NGS patients aligned with MetS criteria. This demonstrated that from study entry, the GS group had fewer cases of MetS than the NGS group with this difference continuing through to Exam 4 where 11.36% (15 of 132) of GS patients and 17.42% (495 of 2842) of NGS patients achieved MetS criteria. Excluding those who had diabetes at Exam 1, this difference in MetS was significant. Components of MetS such as blood pressure, weight, cholesterol, and particularly triglycerides which are key to the definition of MetS were all lower in GS patients and align with previous findings from Glober et al[15] and Stemmerman et al.[16] These results support the observation that patients who had a

gastrectomy remained less likely to develop MetS later in life compared to those who did not undergo a gastrectomy.

The estimate of insulin resistance that we derived from fasting values of glucose and insulin at the 25 year exam was significantly less (and insulin sensitivity greater) in patients who had a gastrectomy 25-40 years earlier. Whether categorizing IR based on a sensitive cut-off criterion of 1.7 or a more conservative (specific) cut-off of 2.5, the pattern remained the same where the GS group consistently had less IR than the NGS group overall and across multiple sub-groups. Over the follow-up years, systolic blood pressure increased more in the GS group than in other men. In multivariate regression, hypertension raised the risk of IR 50-60% while gastrectomy provided about a 49% to 67% protection from IR, depending on which cut-off was used. Overall the GS patients had less insulin resistance and greater insulin sensitivity than their NGS counterparts, but IR was common in both groups.

Over the 25 years of follow-up the difference in weight and BMI between the GS and NGS groups remained essentially constant. Between the six year exam and the 25 year exam both weight and height decreased, and in more than half of both groups BMI fell under the lower limit of normal, 18.5. An increase in skinfolds over this period suggested that a substantial part of the weight loss was lean tissue, and if expressed as a percentage, the weight loss in the GS group was slightly larger. The decrease in height was also greater in the GS group. Being underweight also brings its own set of complications. But, those complications may manifest themselves in areas of health other than T2DM, MetS, and IR.

There are some limitations to this study. First, as this study was conducted in Japanese-American men, these findings may not be generalizable to non-Japanese populations or

to women. Second, the baseline examination did not include several variables that are relevant to glucose metabolism such as fasting blood sugar and insulin and waist circumference. Third, non-participation (selection bias) may distort some of the risk estimates. The initial cohort of 8,006 men were respondents from an estimated 14,000 men on the island of Oahu, and it is known that participants had slightly lower disease rates than non-participants.[71] It is likely that the differences in mortality and participation over the years add some further minor biases, but they would have to differ substantially between GS and NGS men and also be related to the endpoints under discussion for them to have a major influence on the associations found.

In summary, in these Japanese-American men, partial gastrectomy was associated with a life-long decrement in body weight, a 50% decrease in the subsequent incidence of T2DM, less insulin resistance (assessed after 25 years of follow-up), and a suggestive decrease in metabolic syndrome. Simultaneous adjustment for multiple measurements of adiposity did not explain the striking effects on diabetes incidence or glucose metabolism, so the data provide a *prima facie* case for metabolic effects of gastrectomy that operate through other mechanisms.

## CHAPTER 2: THE IMPACT OF GASTRECTOMY ON SURVIVAL, CORONARY HEART DISEASE, AND STROKE


### Abstract

#### Background/Purpose

Gastrectomy (GS) is a major surgical procedure in which part or all of the stomach is removed. Gastrectomy typically addresses a near term health issue such as a stomach ulcer or removal of cancer. But, the long-term consequences of gastrectomy for health in old age are not well documented. This study examined the long-term impacts of gastrectomy on overall survival as well as development of coronary heart disease (CHD) and stroke (CVA).

#### Methods

Three-hundred forty-seven men of Japanese ancestry participating in the Honolulu Heart Program (HHP) who had a partial gastrectomy prior to entering the study were compared to the remaining 7,659 HHP participants who did not have a gastrectomy and their outcomes regarding survival, stroke, and development of coronary heart disease were examined. Means, 95% confidence intervals, and independent samples t-tests were used to characterize continuous variables, while two by k contingency tables and chi-square analyses were used to evaluate frequency data. Time to event data (e.g. death, coronary heart disease, and stroke) were analyzed using life table analysis and Cox regression models, with both univariate and multivariate modeling.

#### Results/Findings

As described in Chapter 1, gastrectomy (GS) participants differed from their peers at baseline in 1965-1968 having lower body weight, serum cholesterol, and blood pressure than non-gastrectomy (NGS) participants. However, they smoked more and drank more

alcohol. Another worrisome finding was that over the years, systolic blood pressure rose more in the GS than in the NGS participants.

Over an average of 33 years of follow-up 74.3% of the operated men vs 63.5% of the non-operated men died ($p < 0.0001$). The difference in mortality was largely explained by elevated relative risks of death from smoking realted caused-lung cancer (2.23), and emphysema (1.94) in the GS group. However, there were also excess stroke deaths in the GS group, both ischemic (1.91), and hemorrhagic (1.74). All of these increases were statistically significant. Despite the excess stroke mortality, GS patients had lower relative risk for death from dementias (0.76, NS).

Stroke incidence was also elevated in the GS group, 18.77% compared to 12.22% of the NGS group ($p=0.0004$). This was corroborated with the finding from the cumulative incidence function showing increased incidence of stroke over time for the GS group ($p=0.0003$). After controlling for age, smoking, alcohol consumption, and BMI, those with hypertension or diabetes, at study entry had an increased risk of developing stroke of 38.8% ($p=0.0012$), and 22.7% ($p=0.0472$), respectively. Age, alcohol, and obesity all significantly increased the risk of stroke, but surprisingly, smoking did not.

In univariate analyses, there were no differences between GS and NGS groups regarding the frequency of developing CHD during the study period (GS: 25.1% vs NGS: 27.1%, ($p=0.4135$).This was echoed in the cumulative incidence function where CHD occurred at about the same rate over time ($p=0.3397$). After controlling for age, smoking, alcohol, and obesity, having a gastrectomy at study entry still had no impact on the development of CHD, while drinking, smoking, and being obese did have an impact. Previous history of stroke, hypertension, and diabetes at study entry increased the

hazard of developing CHD by 43.2% (p=0.0437), 27.9% (p=0.0009), and 22.7% (p=0.0090), respectively.

**Conclusions/Implications**

This group of men with a history of peptic ulcer disease treated by partial gastrectomy included many who were heavy smokers. Although their surgery was associated with favorable changes in several coronary risk factors, they experienced a high rate of mortality from smoking related causes, especially lung cancer and emphysema. However, their CHD rates, which might also have been affected by smoking, were not elevated, supporting an earlier suggestion that they were protected by the favorable changes in weight, serum cholesterol, diabetes and mid-life blood pressure levels. As noted in Chapter 1, blood pressure rose more rapidly over subsequent years in the GS group than the NGS group, so that by the 25 year follow-up exam, systolic blood pressure was actually higher in the GS group. Over this period the incidence of stroke was 50% higher in the GS group than in other cohort members and stroke mortality was almost twice as high. The reasons for this unexpected increase in blood pressure and cerebrovascular disease is uncertain, but it suggests the possibility that persons having partial gastrectomy to induce weight loss or for other reasons might be at similar risk. Further studies of long term survivors of stomach surgery are warranted.

**Introduction/Background**

**Gastrectomy**

Gastrectomy is a major surgical procedure involving partial or complete removal of the stomach. A gastrectomy may be recommended by a physician to treat: gastric and duodenal ulcers, stomach cancer, benign tumors, bleeding, inflammation, or perforations or trauma to the stomach wall. Some types of gastrectomy are also used to treat obesity by making the stomach smaller so that it fills more quickly and satiates faster. These

procedures, termed bariatric surgery, are coming into widespread use, but are only appropriate to treat obesity that has been resistant to other options such as diet, exercise, medication, and counseling.[72,73]

In 1974, Glober et al.[15] published a paper from the Honolulu Heart Program (HHP) titled "Long-Term Results of Gastrectomy with Respect to Blood Lipids, Blood Pressure, Weight and Living Habits" in which a sample of ambulant Japanese-American men aged 45-69 was divided into those having a previous partial gastrectomy and those who did not (a control, non-gastrectomy population). They identified 347 men with a history of partial gastrectomy for a benign condition (nearly all peptic ulcer disease), and found that they weighed less and had lower values for serum cholesterol, triglycerides, and blood pressure than did the control population of 7,598 men.

Ten years later, Stemmerman, et al.[16] published a paper following up on the gastrectomy patients in the HHP in a paper titled "Late Mortality after Partial Gastrectomy". The 10-year prospective study showed that "the age-adjusted mortality rates in men with partial gastrectomy were slightly higher than in those with an intact stomach, but the difference failed to achieve statistical significance." The excess of mortality was believed, to be due to excess smoking by men who had a history of peptic ulcer. They also found that "in men with an intact stomach death from coronary heart disease, an illness with a substantial association with smoking, was less frequent in men with gastrectomy, but the difference was not statistically significant". The authors surmised that men with partial gastrectomy had other characteristics that weakened the impact of smoking upon coronary disease risk: low blood pressure, low serum cholesterol, low body weight and increased alcohol consumption.[16]

There have been quite a number of studies examining the short-term consequences of gastrectomy for gastro-intestinal side effects, weight loss and associated metabolic changes. A recent article by Juodeikis, et al.[74] described a review of 20 studies examining the post-operative effects of sleeve gastrectomy; 14 studies had 5 years of follow-up, while 2 studies had 6 years of follow up, and 3 had 8 years of follow-up. The remaining study had 11 years of follow up. Samples sized ranged from 26 in one study upwards to 175 in another, with the largest sample size being 1395 with only 859 reaching the 5 year follow up mark out of a total of 8 years. Another review paper published in JAMA by Puzziferri, et al[75] examined the long-term effects of various types of bariatric surgery and multiple outcomes. In all, 29 studies were included in that review with almost all providing 3–5 years of follow up post-surgery. Among the studies examined, outcomes observed included significant weight loss, remission of T2DM, improvement or remission of hypertension, improvement or remission of hyperlipidemia, and 'late' complications of the surgery including incisional hernia, treatment failure requiring operative revision, gastroesophageal reflux, and death.

In contrast to the extensive information on short term effects, only a few studies have provided follow-up information beyond 15 years, and most of these have lacked standardized measurements of important risk factors for other chronic diseases. A notable set of interventional studies by Sjostrom and colleagues[76,77,78,79] related to the long-term effects of gastrectomy examined whether bariatric surgery and weight loss induced from bariatric surgery were associated with lower mortality compared with the death rates during conventional treatment in contemporaneously matched, obese control subjects. The study also looked at the effects of bariatric surgery and weight loss on cardiovascular disease (myocardial infarction, stroke, claudication, angina pectoris and hypertension) diabetes, biliary disease, health related quality of life and cost-efficiency.

Patient follow-up continues, but as of the publication the range of follow up was between 12 and 25 years. Key results in the long-term follow-up period compared to controls included decreased mortality, diabetes remission, diabetes prevention (the effects of which markedly diminished after 10-15 years), and lower numbers of cardiovascular events like myocardial infarction or stroke, particularly in patients who had diabetes at the beginning of the study.

This analysis takes advantage of the long follow-up that was implemented for participants of the HHP and examines the effects of gastrectomy on the incidence of coronary heart disease (CHD) and stroke (CVA), as well as overall survival over a period exceeding 25 years.

To our knowledge, this will be the first paper to examine the putative effect of gastrectomy on long-term mortality/survival, development of CHD, and development/occurrence of stroke in old age.

## Methods

### Study Design

### Data Source-Honolulu Heart Program

In the 1950's, it was observed by Tavia Gordon that while overall mortality rates for men in the United States were similar, the incidence of CHD and cerebrovascular accidents (CVA) was significantly lower in Japan.[58] To explore this phenomenon, the Honolulu Heart Program (HHP), along with 2 other studies, was initiated in Hawaii, and plans were made to compare its findings to cohorts of Japanese men in Japan and California. The purpose of this effort was to assess formally the magnitude of the difference in the incidence of CHD and mortality between Japanese living in Japan and those living in Hawaii who were of Japanese ancestry.

The target participants for the Hawaii study were “non-institutionalized men of Japanese ancestry, born 1900-1919,… {and} resident on the island of Oahu.”[59] To identify these individuals, a retired Japanese school teacher inspected 165,000 selective service registry cards from World War II, looking for birthdates between 1900 and 1919 and Japanese last names or a notation of Japanese national origin.[59] Of the 22,892 names that met these criteria, 12,417 had an apparent mailing address on Oahu. A letter introducing these individuals to the study and inviting them to participate in the HHP was sent with a preliminary questionnaire in 1965. After appropriate follow-up, 1,269 questionnaires were returned unopened by the post office, and 1,270 addresses did not return a questionnaire. Of the remaining 9,878 potential participants, 1,692 refused examination and 180 died before the study could begin. From October 1965 to 1968 the 9,878 questionnaire respondents were sequentially invited to participate in a baseline interview and health examination. Of these, 8,006 men ultimately participated and became the HHP study population.[59]

The interview at the first examination included informed consent procedures and captured family and personal history of illness, sociological history, smoking status, dietary habits, and physical activity level. As part of a full physical examination, electrocardiogram (ECG) and urinalysis were performed, and measurements of weight, height, skinfold thickness, blood pressure and serum cholesterol were taken.[60] Surveillance was conducted in cooperation with Oahu hospitals, which recorded the "diagnosis of any type of heart disease, CVA, or pulmonary embolus" and "abnormal electrocardiograms."[60] All events were adjudicated by a panel of physicians not associated with the HHP. Participants were also periodically mailed questionnaires on illnesses "suggestive of cerebrovascular disease or CHD."[60] Mortality was measured by daily reviews of death certificates filed at the Hawaii State Health Department and the

obituary section of local newspapers.[59] Cancer surveillance was followed via the state cancer registry.

HHP participants returned to complete follow-up examinations collecting information similar to that from the initial exam (Exam1) during the years: Exam 2 (1967-1970), Exam 3 (1971-1974), and Exam 4 (1991-1993). Additionally, a small, subset of HHP participants came back for additional follow-up visits as part of a sub-study on lipids at Lipoprotein Exam 1 (1970-1972), Lipoprotein Exam 2 (1975-1978), and Lipoprotein Exam 3 (1980-1982).

## Study Participants

### Gastrectomy Group (GS)

All 347 men who entered the HHP with a documented history of previous partial gastrectomy (GS) for peptic ulcer disease will comprise the GS group. Of these, 171 (49.3%) had gastroduodenal anastomosis (Billroth I), 169 (48.7%) had gastrojejunal anastomoses (Billroth II), and 7 (2%) had a reconstruction that could not be determined by medical records (Table 31). Within this same set of patients, 113 (33.7%) were diagnosed with a duodenal ulcer, 202 (58.2%) were diagnosed with a gastric ulcer, 15 (4.3%) were diagnosed with both a duodenal ulcer and a gastric ulcer, and 13 (3.7%) had a diagnosis of either ‘other’ or ‘unknown’ (Table 32). Regarding vagotomy, 267 (77.0%) patients did not have a vagotomy, 65 (18.7%) patients did have a vagotomy, and 15 (4.3%) patients had a vagotomy status that was unknown (Table 33). From the gastrectomies, 1 (0.3%) patient had 1-25 % of their stomach removed, 51 (14.7%) patients had 26-50% of their stomach removed, 167 (48.1%) patients had 51-75% of their stomach removed, 15 (4.3%) patients had 76-99% of their stomach removed, and 113 (32.6%) patients did not have a value documented indicating how much stomach was removed (Table 34).

Table 31: Summary of Gastrectomy Reconstructions in GS Group

| Operation | Frequency | Percent of Total |
|---|---|---|
| Billroth I | 171 | 49.28% |
| Billroth II | 169 | 48.70% |
| Pyloroplasty | 0 | 0.00% |
| Unknown | 7 | 2.02% |
| Total | 347 | 100.00% |

Table 32: Summary of Diagnoses Leading to Gastrectomy in GS Group

| Diagnosis | Frequency | Percent of Total |
|---|---|---|
| Duodenal Ulcer | 117 | 33.72% |
| Gastric Ulcer | 202 | 58.21% |
| Both Duodenal and Gastric Ulcers | 15 | 4.32% |
| Other | 11 | 3.17% |
| Unknown | 2 | 0.58% |
| Total | 347 | 100.00% |

Table 33: Summary of Vagotomy Status in GS Group

| Vagotomy Status | Frequency | Percent of Total |
|---|---|---|
| No | 267 | 76.95% |
| Yes | 65 | 18.73% |
| Unknown | 15 | 4.32% |
| Total | 347 | 100.00% |

Table 34: Percent of Stomach Removed Among GS Group

| % Stomach Removed | Frequency | Percent of Total |
|---|---|---|
| None | 0 | 0% |
| 1 -25% | 1 | 0.29% |
| 26-40% | 9 | 2.59% |
| 41-50% | 42 | 12.10% |
| 51-66% | 89 | 25.65% |
| 67-75% | 78 | 22.48% |
| 76-90% | 12 | 3.46% |
| 91-99% | 3 | 0.86% |
| Unknown | 113 | 32.56% |
| Total | 347 | 100.00% |

This group of 347 will be the same group of subjects identified by Glober et al.[15] in 1974 and followed by Stemmerman et al.[16] These men were questioned specifically about any past history of gastric surgery, and an attempt was made to review hospital records for each of the positive responses. Cases excluded by Glober et al. are likewise excluded from the present study and include those for whom hospital records could not be located, a malignancy was diagnosed, or no gastric tissue was removed. For incidence tabulations, cases already having the conditions of interest at the baseline examination were additionally excluded.

### Non-Gastrectomy Group (NGS)

Subjects who gave no history of gastric surgery (e.g. gastrectomy, bariatric surgery) at the time of study entry (Exam 1 of the HHP) and were free of the conditions under investigation (CHD and CVA) will comprise the non-NGS group.

## Study Endpoints/Definitions

### Mortality/Survival

Month and year of death were captured from death certificates beginning at Exam 1 in 1965 through 2013. As day of the month is considered private health information (PHI) and not extracted from the database for the present study, days for all dates of death will be assumed to be the 1$^{st}$ of the month (e.g. 01JAN1990). Survival or time to death was calculated as the time in years from the Exam 1 date until the date of death.

### Prevalence and Incidence of Coronary Heart Disease (CHD)

At Exam 1, study participants were asked if they had been diagnosed with coronary heart disease. For affirmative answers attempts were made to retrieve relevant medical records and these were reviewed in conjunction with heart study electrocardiograms to identify prevalent cases. For CHD incidence, a systematic hospital surveillance program

was instituted in 1965 and maintained through 1999 to capture incidence cases of myocardial infarction. This involved reviewing hospital records for all CHD admissions of Japanese men born in 1900-1919 to any acute care civilian hospital on the Island of Oahu. Hospital admission notes, progress notes, cardiac enzyme levels and hospital electrocardiograms were abstracted and the resulting information was reviewed by a committee of three physicians with training in internal medicine to arrive at a consensus judgment as to whether an MI had occurred. In addition all death certificates of Japanese men in the appropriate age groups resident on Oahu were reviewed in conjunction with relevant hospital records to produce a consensus identification of CHD deaths. These consensus events were captured in a surveillance file and analyzed by month and year of diagnosis of myocardial infarction and CHD death. To protect subject identity, day of the month was not retained and all events occurring in a given month were assigned to the 1$^{st}$ of the month (e.g. 01JAN1990). Time to development of CHD was calculated as the time in years from the Exam 1 date until the date of development of CHD.

### Prevalence and Incidence of Stroke/Cerebrovascular Accidents (CVA)

The identification of strokes was carried out in parallel with the identification of CHD. Study participants were asked at Exam 1 whether they had experienced symptoms suggestive of a cerebrovascular accident (CVA) or stroke prior to that visit. A brief neurologic exam was conducted to look for sequelae of stroke, and a positive history led to a review and abstracting of pertinent medical records. The exam findings and the medical records were reviewed by committee to yield a consensus on the determination for both prevalent cases of stroke at the baseline examination and for subsequent incident cases.

### Physical Activity Index (PAI)

Physical activity was evaluated at the baseline exam and at Exam 4 using a physical activity index (PAI). This was a summary measure obtained by asking subjects the number of hours spent in a 24 hour period they usually conducted physical activity in each of five different activity level categories: basal (e.g. sleeping or reclining), slight (causal walking), moderate (carpentry or gardening), and heavy (lifting or snow shoveling). The estimate of physical activity was calculated by multiplying the number of hours spent in each activity by a weighting factor that was based on the estimated amount of oxygen consumed (in liters per minute) that was needed to perform the activities at each of the five levels. To arrive at the overall PAI score, the weighted estimates across the five activity levels were summed.[62]

### Weight/Body Mass Index (BMI)

Weight was measured in pounds without shoes using a standardized scale and standardized procedures. Height was measured with a standard stadiometer. BMI, calculated as the ratio of weight in kilograms to the square of the height in meters is a global metric used to measure and classify levels of adiposity and associated obesity-related chronic disease risk among adults.[1] BMI was calculated for Exam 1, 2, 3, and 4. For classification purposes, the 'International Classification of adult underweight, overweight and obesity according to BMI' table created by the WHO was utilized.[63] See Table 35.

Table 35: The International Classification of adult underweight, overweight and obesity according to BMI

| Classification | BMI [kg/m$^2$] | |
|---|---|---|
| | **Principal cut-off points** | **Additional Cut-off points** |
| **Underweight** | < 18.50 | <18.50 |
| Severe thinness | <16.00 | <16.00 |
| Moderate Thinness | 16.00 – 16.99 | 16.00 - 16.99 |
| Mild thinness | 17.00 – 18.49 | 17.00 – 18.49 |
| **Normal range** | 18.50 - 24.99 | 18.50 – 22.99 |
| | | 23.00 - 24.99 |
| **Overweight** | ≥ 25.00 | ≥ 25.00 |
| Pre-obese | 25.00 – 29.99 | 25.00 – 27.49 |
| | | 27.50 – 29.99 |
| **Obese** | ≥ 30.00 | ≥ 30.00 |
| Obese Class I | 30.00 – 34.99 | 30.00 – 32.49 |
| | | 32.50 – 34.99 |
| Obese Class II | 35.00 – 39.99 | 35.00 – 37.49 |
| | | 37.50 – 39.99 |
| Obese Class III | ≥ 40.00 | ≥ 40.00 |

In addition to height and weight, adiposity was also estimated using triceps and subscapular skinfold thickness, which was measured by trained technicians using calipers designed for these purposes. Even though BMI is widely accepted as a useful obesity metric, it is not a perfect measure as it does not directly measure body fat or body fat distribution. We therefore have supplemented BMI by tabulating the skinfold data directly.

### Blood Pressure

Blood pressure was collected in the sitting position after the subject had been in the clinic for some time, Mercury manometers were used for examination 1, 2, and 3 and attention was paid to slow release of cuff pressure. Wide cuffs were available for obese subjects. Interpretation of blood pressure followed the American Heart Association healthy and unhealthy blood pressure ranges[65] as depicted in Table 36 below:

Table 36: Table of Blood Pressure Categories

| Blood Pressure Category | Systolic (mmHg) | | Diastolic (mmHg) |
|---|---|---|---|
| Normal | < 120 | And | < 80 |
| Prehypertension | 120-139 | Or | 80-89 |
| High Blood Pressure (Hypertension) Stage 1 | 140-159 | Or | 90-99 |
| High Blood Pressure (Hypertension) Stage 2 | ≥ 160 | Or | ≥ 100 |
| Hypertensive Crisis (Emergency care needed) | > 180 | Or | > 110 |

### Smoking/ Alcohol

Complete smoking history and current alcohol consumption were measured at Exam 1 and Exam 4. Current smoking was determined at each examination by capturing the number of cigarettes per day each participant reported smoking at that time. Smoking was also estimated in pack-years by multiplying the number of packs of cigarettes a person has smoked per day by the number of years that same person has smoked. Participants were also categorized at each examination as ‘never smoked’, ‘former smoker’, or ‘current smoker’. Alcohol consumption was measured as number of ounces of alcoholic beverages consumed per month. Wine, beer, and liquor were weighted by 0.1, 0.037, and 0.38 units per ounce of beverage, respectively, to reflect their approximate alcohol content.

### Glucose/Cholesterol/Triglyceride

At Exam 1, blood was collected without overnight fasting approximately 2 hours after an oral 50 gram glucose load. Glucose in mg/dL, serum cholesterol in mg/dL, and random triglycerides in mg/dL were collected at Exam 1 and Exam 2 via blood sample collection. Glucose was measured approximately 2 hours after ingestion of 50 grams of a standard oral glucose solution. The rationale was that ingestion of a standard glucose load prior to testing would provide all patients with a similar starting point regardless of when the last

meal was ingested. Non-fasting serum cholesterol and triglycerides were measured by standard methods as part of a complete medical history and physical examination.

### Hypertension and Cholesterol Medication

Use of anti-hypertensive medication, as well as lipid-lowering agents, were recorded at Exam 1. Patients were categorized as either users or non-users based on their interview responses.

### Age, Weight, Height, Education

At each examination, age was captured in years, weight was captured in pounds (lbs), height was captured in inches, and education was captured as years of school completed. For the purposes of calculating BMI, weight and height were also converted to kilograms and meters.

## Study Oversight

This analysis was approved by the Kuakini Medical Center as well as the Rutgers University Institutional Review Boards. The authors vouch for the completeness and accuracy of the data and analyses.

## Statistical Analyses

### Summary Statistics

Means and 95% confidence intervals for all continuous variables, and frequencies and percentages for all categorical variables, were reported by Exam, outcome group, and gastrectomy status.

### Patients Evaluable at Each Visit

As is to be expected with long-term follow-up studies, over the course of the study, participants exit the study for a variety of reasons including death, illness or disability,

loss of interest, and inability to contact. As such, the number of participants contributing data decreases with each exam. To determine if this decrease differs by gastrectomy status, participant counts were made at each examination and tests for trend were applied to indicate if there was a difference in rate of decreased participation at each visit. This was examined for the entire group, the CHD subset (where those positive for CHD at Exam 1 are excluded), and the CVA sub-set (where those positive for CVA at Exam 1 are excluded).

**Individual Variable Analyses**

To examine individual variables from Exam 1 through Exam 4 between the GS and NGS groups, independent samples t-tests and repeated measures ANOVA models were constructed. Variables were examined at all visits from Exams 1 through 4 that had data at those visits. For variables where only partial data were available, meaning data at only two or three of the Exams existed, the repeated measures ANOVA models reported on the Exam data that were present. For variables that appear at a singular Exam (e.g. waist circumference), a standard t-test was utilized. Differences between the GS and NGS groups were analyzed using the independent samples t-tests and ANOVA models while differences in frequencies were analyzed using chi-square analysis on 2 x k tables.

**Time to Event (e.g. Death, CHD, CVA)**

Time to event data were analyzed starting from Exam 1 (study entry) until the event being examined, (e.g. time to death, time to development of CHD, and time to occurrence of first (CVA)/stroke). Due to the long-term follow-up nature of the study, time to event was captured in years. Time to event was calculated by taking the difference in date between the event occurrence (e.g. date of death) and date of Exam 1. That difference was rounded to the nearest year. Those participants not achieving the event of interest were censored at the cut-off point when data stopped being available

(December 2013 for mortality/death and December 1999 for CHD and CVA) and the time they had contributed was accounted for in the censoring variable. For the CHD and CVA outcomes, competing risks were also taken into consideration as it was possible that a participant could have died during the study period, prior to the occurrence of CHD or CVA and before the cut-off point when data stopped being available.

**Life-Tables**

To better understand the survivor function underlying mortality in this large HHP dataset, a survival curve was constructed to provide a visual representation. To examine differences between the survivor functions, log-rank, as well as Wilcoxon statistics were computed, testing the null hypothesis that survivor functions were identical between the two study groups, NGS and GS. For the CHD and CVA outcomes, cumulative incidence function figures were constructed to compare NGS versus GS participants taking into account the competing risk of death. In addition, the Gray's test of equality of cumulative incidence functions was applied to test if the differences in the cumulative incidence functions were statistically significant.[80]

**Cox-Regression**

To examine factors impacting time to event, Cox regression models were constructed. Cox regression is a semi-parametric method in contrast to traditional linear or logistic regression as it does not require that one chooses some particular probability distribution to represent survival times. More importantly, Cox regression in contrast to Cox proportional hazards models, lends itself to incorporating time-dependent covariates, or covariates that may change in value over the course of the observation period. With patients providing data at multiple study examinations over the course of the observation period, this feature of Cox regression is quite useful. Additional features of Cox regression that were useful in these analyses were that it: 1) allows a kind of stratified

analysis which is effective in controlling for confounders, 2) makes it easy to adjust for periods of time when an individual is not at risk of an event, and 3) can easily accommodate both discrete and continuous measurement of event times.[81] For the CHD and CVA outcomes, competing risks methods were applied to the analysis to account for the circumstance where death may have preceded and thereby prevented either CHD or CVA from occurring.[82]

Utilizing Cox regression models, univariate models predicting the time to event outcomes of death, CHD, and CVA were constructed. Based on the impact of each variable in the univariate analyses on the particular time to event, multivariate models were constructed to represent the contributions of the various variables in predicting time to death, CHD, or CVA.

## Results

### Patients Evaluable at Each Visit

At Exam 1, 8,006 study participants eligible for evaluation in the HHP entered the study. Table 37 outlines the study participants providing study data at the follow-up examinations through Exam 4, whether examining survival/mortality (all participants), incident coronary heart disease (excluding CHD at Exam 1), or incident cerebrovascular accident (excluding CVA at Exam 1).

| Table 37: Count and Change from Exam 1 of HHP Study Participants by Gastrectomy Group (Mortality, CHD, and CVA/Stroke) | | | | | | |
|---|---|---|---|---|---|---|
| **Survival/Mortality (All HHP Participants)** | | | | | | |
| | Total | % change from Exam 1 (All) | NGS | % change from Exam 1 (Non-GS) | GS | % change from Exam 1 (GS) |
| Exam 1 | 8006 | --- | 7659 | --- | 347 | --- |
| Exam 2 | 7498 | -6.35 | 7170 | -6.38 | 328 | -5.48 |
| Exam 3 | 6860 | -14.31 | 6569 | -14.23 | 291 | -16.14 |
| Exam 4 | 3845 | -52.00 | 3693 | -51.78 | 152 | -56.20 |
| Mantel Haenszel Chi-Square Test for Trend = 0.8303 df=1, p=0.3622 | | | | | | |
| **All HHP Participants Excluding Prevalent Coronary Heart Disease (CHD)** | | | | | | |
| | Total | % change from Exam 1 (All) | NGS | % change from Exam 1 (Non-GS) | GS | % change from Exam 1 (GS) |
| Exam 1 | 7681 | --- | 7342 | --- | 339 | --- |
| Exam 2 | 7210 | -6.13 | 6889 | -6.17 | 321 | -5.31 |
| Exam 3 | 6618 | -13.84 | 6332 | -13.76 | 286 | -15.63 |
| Exam 4 | 3768 | -50.94 | 3617 | -50.74 | 151 | -55.46 |
| Mantel Haenszel Chi-Square Test for Trend = 0.8857. df=1, p=0.3466 | | | | | | |
| **All HHP Participants Excluding Prevalent Cerebrovascular Accident (CVA)/Stroke** | | | | | | |
| | Total | % change from Exam 1 (All) | NGS | % change from Exam 1 (Non-GS) | GS | % change from Exam 1 (GS) |
| Exam 1 | 7893 | --- | 7552 | --- | 341 | --- |
| Exam 2 | 7399 | -6.26 | 7077 | -6.29 | 322 | -5.57 |
| Exam 3 | 6788 | -14.00 | 6502 | -13.90 | 286 | -16.13 |
| Exam 4 | 3828 | -51.50 | 3676 | -51.32 | 152 | -55.43 |
| Mantel Haenszel Chi-Square Test for Trend = 0.7493. df=1, p=0.3867 | | | | | | |

| Table 38: Baseline (Exam 1) Characteristics of All Study Participants | | |
|---|---|---|
| | EXAM 1-All Study Participants | |
| | Non-GS | GS |
| | n = 7659 | n = 347 |
| | Mean<br>95% CI | Mean<br>95% CI |
| Age | 54.86<br>54.73, 54.98 | 55.81<br>55.22 56.39 |
| Pr > \|t\| | **p = 0.0020** | |
| Weight (lbs) | 140.10<br>139.60, 140.50 | 128.80<br>126.60, 131.00 |
| Pr > \|t\| | **p < 0.0001** | |
| Height (in) | 64.09<br>64.04, 64.14 | 64.31<br>64.06, 64.56 |
| Pr > \|t\| | p = 0.0779 | |
| BMI | 23.94<br>23.87, 24.01 | 21.85<br>21.53, 22.17 |
| Pr > \|t\| | **p < 0.0001** | |
| BMI-Underweight | 3.21% | 12.68% |
| BMI-Normal Weight | 61.38% | 70.03% |
| BMI-Overweight | 32.34% | 16.71% |
| BMI-Obese | 3.00% | 0.58% |
| BMI-MIssing | 0.07% | 0.00% |
| Pr > \|$X^2$\| | **p < 0.0001** | |
| Education | 10.34<br>10.28, 10.41 | 10.20<br>9.91, 10.49 |
| Pr > \|t\| | p = 0.3780 | |
| Cigarettes per day | 10.13<br>9.82, 10.44 | 14.27<br>12.83, 15.72 |
| Pr > \|t\| | **p < 0.0001** | |
| Cigarettes per day (Excl.never smoked) | 14.68<br>14.28, 15.07 | 16.29<br>14.78, 17.81 |
| Pr > \|t\| | **p = 0.0431** | |
| Cigarettes per day (current smokers only) | 23.66<br>23.26, 24.06 | 23.36<br>22.06, 24.67 |
| Pr > \|t\| | p = 0.6661 | |
| Never Smoked (%) | 30.90% | 12.39% |
| Former Smoker (%) | 26.14% | 26.51% |
| Current Smoker (%) | 42.96% | 61.10% |
| Pr > \|$X^2$\| | **p < 0.0001** | |
| Pack-years | 23.53<br>22.98, 24.09 | 33.64<br>31.30, 35.99 |
| Pr > \|t\| | **p < 0.0001** | |
| Pack-years (Excl. never smoked) | 34.32<br>33.71, 34.94 | 38.43<br>36.24, 40.63 |
| Pr > \|t\| | **p = 0.0004** | |

| | | |
|---|---|---|
| Pack-years (current smokers only) | 39.29<br>38.56, 40.02 | 40.93<br>38.54, 43.31 |
| Pr > \|t\| | p = 0.1966 | |
| Alcohol (oz/mo) | 13.63<br>13.08, 14.18 | 15.81<br>13.25, 18.36 |
| Pr > \|t\| | p = 0.1051 | |
| Systolic blood pressure | 134.30<br>133.90, 134.80 | 129.00<br>126.80, 131.20 |
| Pr > \|t\| | **p < 0.0001** | |
| Diastolic blood pressure | 82.45<br>82.19, 82.71 | 77.37<br>76.07 78.68 |
| Pr > \|t\| | **p < 0.0001** | |
| HTN-Normal | 22.21% | 34.87% |
| HTN-Prehypertension | 38.32% | 34.58% |
| HTN-Stage 1 Hypertension | 25.15% | 22.77% |
| HTN-Stage 2 Hypertension | 10.18% | 6.34% |
| HTN-Hypertension Crisis | 4.14% | 1.44% |
| HTN-Missing | 0.00% | 0.00% |
| Pr > $\|X^2\|$ | **p < 0.0001** | |
| Prevalent CHD – Yes | 4.14% | 2.31% |
| Prevalent CHD - No | 95.86% | 97.69% |
| Pr > $\|X^2\|$ | p = 0.0905 | |
| Prevalent CVA – Yes | 1.40% | 1.73% |
| Prevalent CVA - No | 98.60% | 98.27% |
| Pr > $\|X^2\|$ | p = 0.6080 | |
| Prevalent Cancer – Yes | 1.04% | 0.58% |
| Prevalent Cancer- No | 98.96% | 99.42% |
| Pr > $\|X^2\|$ | p = 0.3969 | |
| Prevalent Diabetes – Yes | 9.55% | 7.20% |
| Prevalent Diabetes- No | 90.45% | 92.80% |
| Pr > $\|X^2\|$ | p = 0.1433 | |
| Blood Glucose (non-fasting) | 162.40<br>161.10, 163.70 | 144.00<br>137.70, 150.20 |
| Pr > \|t\| | **p < 0.0001** | |
| Serum cholesterol | 219.00<br>218.10, 219.80 | 204.60<br>200.80, 208.40 |
| Pr > \|t\| | **p < 0.0001** | |
| Random Triglyceride | 238.40<br>233.70, 243.10 | 188.80<br>173.40, 204.30 |
| Pr > \|t\| | **p < 0.0001** | |
| Uric acid | 59.98<br>59.64, 60.32 | 59.12<br>57.44, 60.80 |
| Pr > \|t\| | p = 0.3060 | |
| Physical Activity Index | 32.82<br>32.72, 32.92 | 32.50<br>32.02, 32.97 |
| Pr > \|t\| | p = 0.2008 | |

| | | |
|---|---|---|
| Biacromial Diameter (cm) | 38.03<br>37.99, 38.08 | 37.77<br>37.55, 38.00 |
| Pr > \|t\| | **p = 0.0177** | |
| Bi-iliac diameter (cm) | 28.90<br>28.85, 28.94 | 28.69<br>28.47, 28.91 |
| Pr > \|t\| | p = 0.0556 | |
| Skinfold-left triceps (mm) | 8.03<br>7.95, 8.10 | 6.63<br>6.28, 6.97 |
| Pr > \|t\| | **p < 0.0001** | |
| Skinfold left-subscapular (mm) | 16.63<br>16.48, 16.78 | 13.09<br>12.40, 13.78 |
| Pr > \|t\| | **p < 0.0001** | |
| Girth-Left upper arm | 279.70<br>279.00, 280.30 | 265.00<br>261.90, 268.10 |
| Pr > \|t\| | **p < 0.0001** | |
| Chest Depth | 19.34<br>19.30, 19.39 | 18.61<br>18.42, 18.80 |
| Pr > \|t\| | **p < 0.0001** | |
| Hematocrit | 44.73<br>44.66, 44.80 | 44.04<br>43.70, 44.37 |
| Pr > \|t\| | **p < 0.0001** | |

Over the course of the study through Exam 4, due to death and lost to follow-up, the total number of study participants examined decreased at very similar rates among the GS and NGS groups.

**Baseline Characteristics and Follow-Up**

Mean values by NGS and GS groups with associated 95% confidence intervals were constructed and t-tests were conducted to examine the group means between the NGS and GS groups for each variable at Exam 1 or study entry. For categorical variables, percentages by level in the NGS and GS groups were calculated and chi-square analyses were conducted to determine unexpected differences. Table 38 details those analyses for all HHP participants. Results for analyses either excluding CHD participants or CVA participants were not included as they were almost identical to the results observed in the ‘all study participants’ comparison of NGS versus GS participants.

**Age, Education, Physical Activity, and Alcohol**

Mean age of GS participants tended to be about 1 year greater than their NGS counterparts. This difference was significant across all outcome groups ($p<0.01$). With education, both GS and NGS participants across outcome groups had a mean of just over 10 years of education. There was no difference. With physical activity in the form of the physical activity index (PAI) the GS group had a slightly lower PAI score compared to the NGS participants, which was not statistically significant. On average and across outcome groups, GS participants consumed about 2 to 3 oz of alcohol per month more than their NGS counterparts. This difference though, was also not significant in any of the outcome groups.

**Smoking (Cigarettes/Day, Pack-years, Smoking Status)**

A remarkable 88% of the GS group were present or former smokers, compared with 69% for the NGS group. About 26% of each group were past smokers, which represents a lower quit rate in the GS group (26/88=29.5%) than in the others (26/69=37.7%). This left 61% of the GS men still smoking at the first exam compared to 43% of the comparison group. Among current smokers there was very little difference in the number of cigarettes smoked per day, but the number of pack-years was 41% greater in the GS group. Smoking is a well-established risk factor for peptic ulcer disease, which was the principal indication for stomach surgery in the GS group, and presumably accounts for their excess of smoking. The lower quit rate among those who (ever) smoked suggests that the GS men were more addicted to cigarettes than other smokers, which may also have contributed to their needing surgery to deal with their ulcer disease.

**Systolic Blood Pressure, Diastolic Blood Pressure, Hypertension**

Across all outcome groups, the mean systolic blood pressure at baseline was consistently about 5 mmHg lower in the GS group than the NGS group (~129 mmHg versus ~134 mmHg). This difference was significant at the $p<0.0001$ level. Likewise, mean diastolic blood pressure was about 5 mmHg lower in the GS group compared to the NGS group (~77 mmHg versus ~82 mmHg). This difference was also significant at the $p<0.0001$ level.

After categorizing blood pressure following the American Heart Association definitions for hypertension (see Table 36 above), into Normal, Prehypertension, Stage 1 Hypertension, Stage 2 Hypertension, and Hypertension Crisis, the pattern remained the same across outcome groups where there were greater percentages of GS participants in the 'Normal' blood pressure category (~35% in the GS group versus ~22% in the NGS group) and smaller percentages of GS participants, in each hypertension category ranging from Pre-hypertension to Hypertension Crisis. The differences were significant at the $p<0.0001$ level and supported the pattern seen with the individual systolic and diastolic blood pressures. So, at Exam 1, blood pressure was lower and more likely to be in the normal range for GS participants compared to their NGS counterparts.

**Obesity Related Measures (Weight, Height, BMI, Anthropometric Measures)**

At Exam 1, GS participants had a mean weight roughly 11 pounds less than the mean weight of the NGS group (~129 lbs vs. 140 lbs, $p<0.0001$). The mean height of GS and NGS participants was essentially the same at about 64 inches. So, it is no surprise that the mean BMI for GS participants was 2 units lower than for NGS participants (~22 versus ~24, $p<0.0001$).

After categorizing BMI following the WHO definitions for obesity (see Table 35 above) into Underweight, Normal Weight, Overweight, and Obese, GS participants were four

times more likely to be underweight than the NGS men, half as likely to be overweight and only one-fifth as likely to be obese in both the CHD and CVA cohorts. The BMI differences were significant at the $p<0.0001$ level.

Skinfold measurements were available over the triceps on the back of the upper arm and below the scapula on the back. These were reduced by 18% and 21%, respectively, in the GS men implying that a substantial proportion of the BMI difference was related to loss of adipose tissue after gastrectomy. Upper arm girth was also consistent being 1.5 cm less in the GS group ($p<0.0001$). Other anthropometric measurements differed only slightly between the two groups.

Taken together, the body of evidence suggests that the GS participants at baseline/study entry were already lighter and leaner than their NGS counterparts.

**Laboratory Values (Non-fasting Glucose, Cholesterol, Triglycerides, Hematocrit, and Uric Acid)**

Various measurements were ascertained from blood samples collected via venipuncture. Non-fasting glucose was about 18 mg/dL lower for GS compared to NGS (~144 mg/dL vs. ~162 mg/dL). Serum cholesterol was about 15 mg/dL lower for GS compared to NGS (~204 mg/dL vs. ~219 mg/dL)/ Random triglycerides were about 50 mg/dL lower for GS compared to NGS (~188 mg/dL versus ~238 mg/dL) And, hematocrit was about 0.7% lower for GS compared to NGS (~44.70 mg/dL vs. ~44.60 mg/dL). All of these differences were significant at the $p<0.0001$ level. There was a roughly 0.1 mg/dL difference for uric acid (~59 mg/dL vs ~60mg/dL), but this difference was not significant. Taken together, these findings suggest that GS participants had better glucose and lipid profiles coming into the HHP, echoing the findings of Glober et al.[15]

**Prevalent Conditions (CHD, CVA, Cancer)**

In examining the prevalent conditions of CHD, CVA, diabetes, and cancer at baseline across outcome categories, there appeared to be about 2% less cases of CHD in the GS group (~2% vs. ~4%), about 0.5% more cases of CVA in the GS (~1.7% vs. ~1.4%), about 2.5% less cases of diabetes (~7.0% vs. 9.5%), and about 0.5% less cases of cancer in the GS group (~0.5% vs. ~1.0%) as compared to the NGS counterparts. All of these differences though were not statistically significant.

**Mortality/Surveillance**

Of all 8006 patients at Exam 1, 7659 were NGS and 347 were GS. From 1965 to 1999, the study surveillance period, there were 5,124 deaths (4,866 in the NGS group and 258 in the GS group). These deaths comprised 63.53% of the NGS group and 74.35% of the GS group. This 10.82% difference in deaths observed was significant ($p<0.0001$). So, during the study period, there was a greater proportion of deaths within the GS group compared to the number of deaths within the NGS group.

Underlying causes of death characterized by ICD-9 codes, and deaths over the surveillance period are expressed as percent deceased for the two groups in Table 39. Only causes comprising at least 2% of deaths were tabulated. Causes of death closely related to smoking (lung cancer and emphysema) and both ischemic and hemorrhagic stroke deaths were substantially more common in the GS group as seen in the differences between GS observed and expected values in the chi-square analysis shown in Table 40. All other causes of death contributed at least 2% of deaths within the NGS or GS categories. These causes appeared to be less common in GS patients: stomach cancer (27% lower), dementias (24% lower), complications of medical care not elsewhere classified (19% lower), acute myocardial infarction (17% lower), late effects of stroke (13% lower), colon/rectum cancer (12% lower), prostate cancer (5% lower), and

old myocardial infarction (6% higher). However, none of these differences were statistically significant.

Even though it did not meet the 2% cut-off utilized for the causes mentioned above, chronic liver disease and cirrhosis was noted to differ substantially between NGS and GS groups, accounting for 1.07% of the NGS group deaths and 1.94% of the GS group deaths.

Table 39: Proportional Mortality by Underlying Cause in Men With and Without Gastrectomy Prior to First Examination (Cause of Death)

| | NGS | | | GS | | | Risk Difference & Risk Ratio | |
|---|---|---|---|---|---|---|---|---|
| | Population at Risk n = 7659 | | | Population at Risk n = 347 | | | | |
| Cause of Death | Freq | % of Deaths | Rate | Freq | % of Deaths | Rate | Risk Diff | Risk Ratio |
| All Deaths | 4866 | 100 | 0.64 | 258 | 100 | 0.74 | 0.10 | 1.17 |
| Lung Cancer | 356 | 7.32 | 0.05 | 36 | 14.00 | 0.10 | 0.05 | 2.23 |
| Emphysema | 182 | 3.74 | 0.02 | 16 | 6.20 | 0.05 | 0.03 | 1.94 |
| Ischemic Stroke | 104 | 2.14 | 0.01 | 9 | 3.49 | 0.03 | 0.02 | 1.91 |
| Hemorrhagic stroke | 127 | 2.61 | 0.02 | 10 | 3.88 | 0.03 | 0.01 | 1.74 |
| Old Myocardial Infarction | 208 | 4.27 | 0.03 | 10 | 3.88 | 0.03 | 0.00 | 1.06 |
| Prostate Cancer | 163 | 3.35 | 0.02 | 7 | 2.71 | 0.02 | -0.00 | 0.95 |
| Colon/Rectum Cancer | 201 | 4.13 | 0.02 | 8 | 3.10 | 0.02 | -0.00 | 0.88 |
| Late Effects of stroke | 178 | 3.66 | 0.02 | 7 | 2.71 | 0.02 | -0.00 | 0.87 |
| Acute Myocardial Infarction | 477 | 9.8 | 0.06 | 18 | 6.98 | 0.05 | -0.01 | 0.83 |
| Dementia | 145 | 2.98 | 0.0 | 5 | 1.94 | 0.01 | -0.01 | 0.76 |
| Stomach Cancer | 241 | 4.95 | 0.03 | 8 | 3.10 | 0.02 | -0.01 | 0.73 |
| Complications Med Care | 735 | 15.10 | 0.10 | 27 | 10.47 | 0.08 | -0.02 | 0.81 |
| All other | | | 0.23 | | | 0.28 | 0.05 | 1.22 |

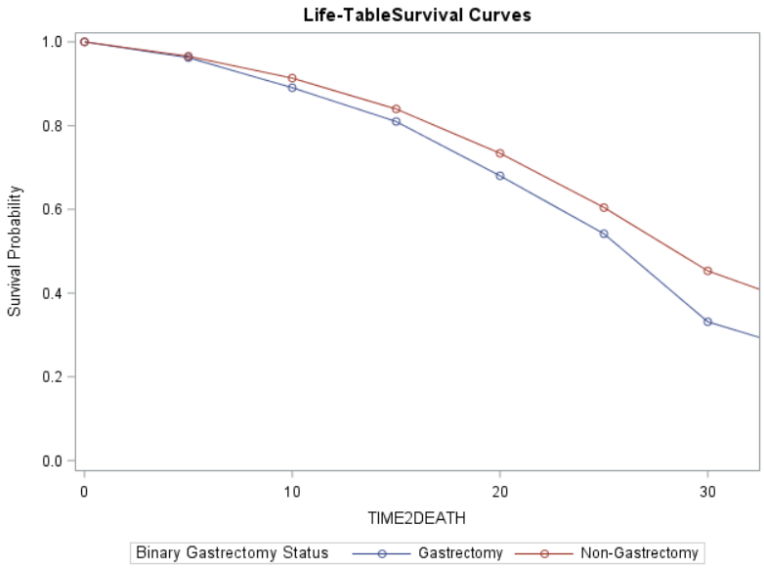
NGS=Non-Gastrectomy; GS=Gastrectomy; Pop=population; Freq=Frequency; Rate=Rate as a proportion of population at risk; Complications Med Care = Complications of medical care not elsewhere classified

| Table 40: Observed Vs Expected Deaths in the Gastrectomy Group For Selected Causes | | | | |
|---|---|---|---|---|
| | | | | |
| | NGS Observed | GS Observed | GS Expected | p-value |
| CHD (Old Myocardial Infarction + Acute Myocardial infarction) | 685 | 28 | 30.90 | NS |
| Stroke (Ischemic + Hemorrhagic) | 231 | 19 | 10.84 | **< 0.05** |
| Lung Cancer | 356 | 36 | 16.99 | **<0.0001** |
| Prostate Cancer | 163 | 7 | 7.37 | NS |
| Colon/Rectum Cancer | 201 | 8 | 9.06 | NS |
| Stomach Cancer | 241 | 8 | 10.80 | NS |
| Emphysema | 182 | 16 | 8.58 | **<0.05** |
| Dementia | 145 | 5 | 6.50 | NS |
| Late Effects of Stroke | 178 | 7 | 8.02 | NS |
| Complications Med Care | 735 | 27 | 33.03 | NS |
| NGS = Non-Gastrectomy; GS = Gastrectomy; Complications Med Care = Complications of medical care not elsewhere classified<br>Note: Significant values are bolded | | | | |

**Life Table-Mortality/Survival**

Figure 14 is a Life Table – survival curve comparing time to death in years, between the GS and the NGS groups. From the figure, it is apparent that the curves diverge beginning about 10 years after entry into the study suggesting that between the GS and NGS groups, the time to death was sooner for GS participants compared to NGS participants. Tests of equality over strata revealed significant differences between the GS and NGS group (Log-Rank Chi-Square = 19.83, p=<0.0001; Wilcoxon Chi-Square=15.89, p<0.0001).

Figure 14: Time to Death Life-Table Survival Curve by Gastrectomy Status




## Cox-Regression-Mortality/Survival

### Mortality/Survival - Multivariate Regression

Cox-regression models were constructed to examine the factors driving time to death, specifically focusing on the effect of gastrectomy. A priori potential confounders of age, alcohol, and smoking, in the forms of ounces of alcohol per month and smoking status (e.g. pack-years at Exam 1) were controlled for in the model. See Table 41. Older age and increased smoking in the GS group appeared to account for most of their excess mortality risk, but there remained a 12.9% excess hazard even after controlling for these confounders (not statistically significant). With the addition of BMI to control for obesity in the model, the hazard statistic for death increased slightly to 16.1%. This is consistent with the idea that weight loss is a salutary effect of partial gastrectomy, and that when you remove this effect by statistical adjustment, unfavorable associations become more obvious. These could be negative physiologic effects of the surgery, sequelae of previous peptic ulcer disease, or lifestyle associations as evidenced by the excess smoking and drinking in the GS group.

In each model shown in Table 41, age consistently showed about an 11% increased risk per year (p<0.0001). Consumption of alcohol at Exam 1 was associated with a slight increase in risk of death, about 0.3% to 0.5% per ounce of alcohol (p<0.0001). Smoking at Exam 1 in the models where smoking was included increased risk of death consistently about 0.9% for every pack-year. BMIs contribution to the model revealed a significant 1.4% increase in risk for each unit of BMI.

Table 41: Multivariate Cox Regression Models Showing Hazard Ratios Predicting Mortality – Focusing on Gastrectomy and Confounding Factors (N = 7848)

| Model | Gastrectomy | Age | Alcohol | Smoking (Pack-years) | Body Mass Index (BMI) | Alcohol$^2$ |
|---|---|---|---|---|---|---|
| 1 | 1.329 ‡ | --- | --- | --- | --- | |
| 2 | 1.235 ¥ | 1.109 ‡ | --- | --- | --- | |
| 3 | 1.231 ¥ | 1.110 ‡ | 1.005 ‡ | --- | --- | |
| 4 | 1.129 NS | 1.108 ‡ | 1.003 ‡ | 1.009 ‡ | --- | |
| 5 | 1.161 † | 1.109 ‡ | 1.003 ‡ | 1.009 ‡ | 1.014 £ | |
| 6 | 1.130 NS | 1.108 ‡ | --- | 1.010 ‡ | --- | 1.000 † |

NS = not significant; † significant at the < 0.05 level; £ significant at the < 0.01 level; ¥ significant at the < 0.001 level; ‡ significant at the < 0.0001 level

After CHD, CVA and cancer prevalence were added to the model, hazard ratios for age, alcohol consumption, and smoking essentially remained the same. Similar to what was observed in the univariate analyses, these prevalent conditions at study entry showed significant increased risk of death. Prevalent CHD, CVA, and cancer, conveyed 113%, 129%, and 49% increased risk of death, respectively. With these diseases added to the model, the mortality hazard associated with gastrectomy was 1.143, p=0.0414, see Table 42.

| Table 42: FINAL Multivariate Cox Regression Model - Mortality (N=7853) | | | |
|---|---|---|---|
| Model | Hazard ratio | (95%9 CI) | p |
| Gastrectomy | 1.143 | 1.005 1.299 | **0.0414** |
| Age | 1.106 | 1.101 1.112 | **<0.0001** |
| Alcohol | 1.003 | 1.002 1.004 | **<0.0001** |
| Smoking (Pack-years) | 1.009 | 1.008 1.010 | **<0.0001** |
| CHD Prevalence | 2.134 | 1.831 2.487 | **<0.0001** |
| CVA Prevalence | 2.293 | 1.776 2.959 | **<0.0001** |
| Cancer Prevalence | 1.493 | 1.063 2.097 | **0.0207** |

**Coronary Heart Disease**

Of the original 8006 participants of the HHP, 325 study participants (317 NGS, 8 GS) entered Exam 1 with CHD. The prevalence of CHD at Exam 1 among NGS and GS patients was 4.14% and 2.31%, respectively. The difference was not statistically different (p=0.0905), but appeared to differ in the expected direction based on differences in blood pressure and serum cholesterol (but not smoking).

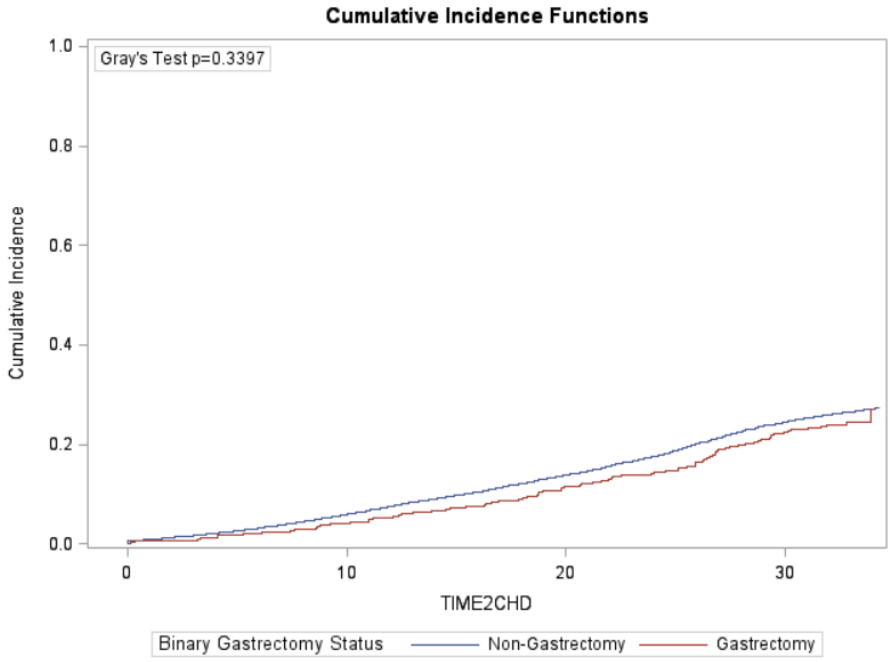
After excluding study participants who had CHD from the analysis of incidence after Exam 1, 7681 patients remained; 7342 NGS and 339 GS. Coronary heart disease incidence was assessed in these men by the hospital surveillance program described above and by the clinical examinations conducted at 2, 6, and 25 years of follow-up. Only MI and CHD were counted as incident cases. Over the course of follow-up, up to December 1999, 27.09% of the NGS participants developed CHD, while 25.07% of GS participants developed CHD. This 2.0% difference was not significantly different (p=0.4135). The percentages of patients as a group developing CHD were essentially the same between the NGS and GS groups during the study period.

**Cumulative Incidence of Coronary Heart Disease**

Figure 15 depicts life-table cumulative incidence function curves comparing the time to event data, of CHD, between the GS and the NGS group. From the cumulative

incidence function curves, it appears that the NGS and GS curves show a relatively parallel separation over time suggesting a slightly lower incidence of CHD in the GS group. The separation between the GS and NGS group, however was not statistically significant confirming no difference in cumulative incidence of CHD (Gray's Test for Equality of Cumulative Incidence Functions, p = 0.3397)

Figure 15: Cumulative Incidence Function Curves for Coronary Heart Disease by Gastrectomy Status




## Cox Regression-Coronary Heart Disease

### Coronary Heart Disease – Multivariate Regression

Cox-regression models were constructed to examine whether there was any evidence of a potential effect of gastrectomy on the incidence of CHD when taking other CHD risk factors into account. A priori potential confounders of alcohol and smoking, in the forms of ounces of alcohol per month and pack-years of cigarettes, were controlled for in the models focusing on the impact of gastrectomy on CHD.

Table 43: Multivariate Cox Regression Models Showing Hazard Ratios Predicting CHD– Focusing on Gastrectomy and Controlling Factors and Accounting for Competing Risks (N=7983)

| Model | Gastrectomy | Age | Alcohol | Smoking (Pack-years) | Body Mass Index (BMI) | Current Smoker |
|---|---|---|---|---|---|---|
| 1 | 0.901 [NS] | --- | --- | --- | --- | |
| 2 | 0.899 [NS] | 1.002 [NS] | --- | --- | --- | |
| 3 | 0.912 [NS] | 1.001 [NS] | 0.994 [‡] | --- | --- | |
| 4 | 0.878 [NS] | 1.001 [NS] | 0.993 [‡] | 1.003 [¥] | --- | |
| 5 | 1.009 [NS] | 1.006 [NS] | 0.994 [‡] | 1.003 [‡] | 1.075 [‡] | |
| 6 | 1.005 [NS] | 1.008 [†] | 0.994 [‡] | --- | 1.078 [‡] | 1.296 [‡] |

[NS] = not significant; [†] significant at the < 0.05 level; [£] significant at the < 0.01 level; [¥] significant at the < 0.001 level; [‡] significant at the < 0.0001 level

CHD incidence was slightly lower in the gastrectomy group as shown by the hazard ratio of 0.9 in the first line of Table 43, but the difference was not statistically significant. After controlling for age, smoking, and alcohol, gastrectomy continued to have no significant effect on the risk of developing CHD. Adding BMI to the model to account for obesity changed the sign on the gastrectomy hazard coefficient from decreased to increased risk, suggesting, as with total mortality, that the weight loss associated with stomach surgery may help to offset the risks of surgery, smoking and lifestyle associated with peptic ulcer disease. However, none of these coefficients were statistically significant. Alcohol intake per month consistently showed a 0.6% decreased risk per ounce per month of developing CHD across models, while smoking consistently showed a 0.3% increase in risk per pack-year accumulated before first exam. When pack-years was replaced by ‘current smoker’, a variable that strongly predicted CHD in univariate analyses, ‘current smoker’ revealed a 29.6% increased risk of CHD and age increased the hazard to 0.8% making age now significant in the model. Alcohol remained the same, BMI stayed about the same, and the hazard ratio for gastrectomy decreased slightly to 1.005 and still not significant. BMI appeared to significantly increase the risk of CHD about 7.5%.

When other variables that individually predicted CHD strongly in the univariate models were added culminating in a final model (Table 44), the effects of gastrectomy, age, smoking, alcohol, and BMI seemed to settle similar to how they did in the focused model with gastrectomy and age still non-significant, alcohol slightly protective, and smoking and BMI slightly increasing risk of CHD. Additionally, increased risk was seen with prevalent CVA (43.2%), prevalent diabetes (22.7%), and prevalent controlled hypertension (27.9%), as seen with the use of hypertensive medications. Lastly, triglycerides, non-fasting glucose, and serum cholesterol showed small, but significant increases in risk of developing CHD. Taken together, these results suggest gastrectomy, either alone or in concert with other predictors provided neither protection nor increased risk of CHD.

Table 44: FINAL Multivariate Cox Regression Model – CHD – Accounting for Competing Risks

| Model | Hazard ratio | (95%9 CI) | p |
|---|---|---|---|
| Gastrectomy | 1.048 | 0.831 1.323 | 0.6916 |
| Age | 1.002 | 0.993 1.010 | 0.6764 |
| Alcohol | 0.994 | 0.991 0.996 | **<0.0001** |
| Smoking (Pack-years) | 1.004 | 1.002 1.005 | **<0.0001** |
| BMI | 1.054 | 1.039 1.069 | **<0.0001** |
| CVA Prevalence | 1.432 | 1.010 2.029 | **0.0437** |
| Cancer Prevalence | 0.693 | 0.396 1.214 | 0.2001 |
| Diabetes Prevalence | 1.227 | 1.053 1.431 | **0.0090** |
| Triglycerides | 1.000 | 1.000 1.000 | **0.0054** |
| Non-Fasting Glucose | 1.002 | 1.001 1.003 | **<0.0001** |
| Cholesterol | 1.005 | 1.004 1.006 | **<0.0001** |
| Hypertension Meds | 1.279 | 1.106 1.479 | **0.0009** |

**Cerebrovascular Accident (CVA)/Stroke**

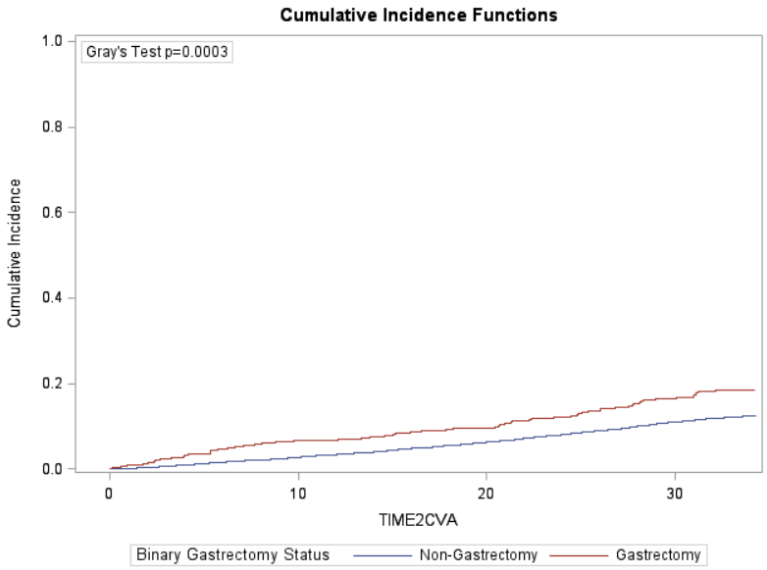
Of the original 8006 participants of the HHP, 113 study participants (107 NGS, 6 GS) entered Exam 1 having previously had a CVA. The prevalence of CVA at Exam 1 between NGS and GS patients was 1.40% and 1.73%, respectively. The difference was not statistically different (p=0.6081).

After excluding patients who had a CVA prior to Exam 1, the total number of participants examined in the CVA analysis was 7893; 7522 NGS and 341 GS. In the NGS group, 12.22% experienced their first CVA, while in the GS group 18.77% experienced their first CVA. This 6.5% difference was highly significant (p=0.0004). There was a higher rate of experiencing first CVA within the GS group compared to the NGS group during the study period.

**Cumulative Incidence of CVA/Stroke**

Figure 16 shows the cumulative incidence of stroke for the GS and the NGS groups. The excess stroke incidence in the GS group is apparent practically from the outset and the curves remain separated through the end of follow-up in December 1999. This separation was confirmed by Gray's Test. (p=0.0003)

Figure 16: CVA/Stroke Cumulative Incidence Function Curves by Gastrectomy Status




## Cox Regression-CVA/Stroke

### Cerebrovascular Accident (CVA)/Stroke – Univariate Analyses

Variables at Exam 1 were individually modeled to their association with the occurrence of cerebrovascular accident (CVA)/stroke. Table 45 below shows the resulting hazard ratios with their corresponding 95% confidence intervals and p-values.

| Table 45: Univariate Cox Regression Models for Cerebrovascular Accident Regressing Exam 1 Variables-Accounting for Competing Risk of Death | | | |
|---|---|---|---|
| Model Variables | Hazard Ratio | (95% CI) | p-value |
| Gastrectomy | 1.599 | 1.239, 2.064 | **0.0003** |
| Age | 1.038 | 1.027, 1.049 | **<0.0001** |
| Education | 0.976 | 0.954, 0.998 | **0.0330** |
| Cigarettes Per Day | 1.006 | 1.002, 1.010 | **0.0051** |
| Cigarettes Per Day (Smokers only) | 1.007 | 1.003, 1.012 | **0.0021** |
| Smoking Status - Never Smoked | 0.980 | 0.856, 1.122 | 0.7722 |
| Smoking Status - Past Smoker | 0.780 | 0.670, 0.907 | **0.0012** |
| Smoking Status - Current Smoker | 1.223 | 1.079, 1.386 | **0.0016** |
| Pack-years | 1.003 | 1.000, 1.005 | **0.0409** |
| Alcohol | 1.002 | 1.000, 1.005 | **0.0449** |
| Hypertension Meds | 1.584 | 1.312, 1.911 | **<0.0001** |
| Stage 1 Hypertension | 1.684 | 1.477, 1.920 | **<0.0001** |
| Stage 2 Hypertension | 1.710 | 1.466, 1.996 | **<0.0001** |
| Cholesterol meds | 0.714 | 0.440, 1.159 | 0.1732 |
| CHD Prevalence | 1.335 | 1.003, 1.777 | **0.0473** |
| CVA Prevalence | --- | --- | --- |
| Cancer prevalence | 0.583 | 0.259, 1.311 | 0.1917 |
| Diabetes Prevalence | 1.343 | 1.104, 1.634 | **0.0032** |
| Weight | 1.001 | 0.999, 1.004 | 0.3241 |
| Height | 0.959 | 0.934, 0.985 | **0.0021** |
| Body Mass Index (BMI) | 1.029 | 1.009, 1.049 | **0.0046** |
| Chest Depth | 1.066 | 1.033, 1.100 | **<0.0001** |
| Biacromial Diameter | 0.979 | 0.948, 1.011 | 0.1905 |
| Bi-iliac diameter | 1.009 | 0.978, 1.041 | 0.5883 |
| Skinfold-Tricep | 1.029 | 1.012, 1.047 | **0.0008** |
| Skinfold-Subscapular | 1.015 | 1.006, 1.024 | **0.0008** |
| Girth-Arm | 1.001 | 0.998, 1.003 | 0.5932 |
| Hematocrit | 1.017 | 0.995, 1.040 | 0.1252 |
| Uric Acid | 1.004 | 1.000, 1.009 | **0.0452** |
| Random Triglyceride | 1.000 | 1.000, 1.000 | 0.1753 |
| Non-fasting glucose | 1.002 | 1.001, 1.003 | **<0.0001** |
| Serum cholesterol | 1.000 | 0.998, 1.001 | 0.6949 |
| Systolic Blood Pressure | 1.015 | 1.012, 1.017 | **<0.0001** |
| Diastolic Blood Pressure | 1.025 | 1.019, 1.030 | **<0.0001** |
| Physical Activity Index | 1.000 | 0.986, 1.013 | 0.9613 |
| Note: Significant p-values are bolded | | | |

Gastrectomy status did show a significant impact on developing CVA, suggesting a 59.9% increase in risk of developing CVA. Age increased risk 3.8% for every increase in year, while alcohol also increased risk 0.2% for every ounce of alcohol consumed per month. Education showed a significant 2.4% decreased risk of CVA for every year of school, while physical activity in the form of the Physical Activity Index, was not predictive.

Most of the obesity variables showed an impact on CVA development. BMI showed a 2.9% increased risk per unit increase. Chest depth, skinfold triceps, and skinfold-subscapular showed a 6.6%, 2.9%, and 1.5% increase in risk of development of CVA. Weight, biacromial diameter, bi-iliac diameter and arm girth did not show any impact on the development of CVA.

Variables capturing smoking showed significant contribution to increased risk of CVA. Those participants who never smoked saw neither increase nor decrease in risk of CVA. However, participants at study entry who previously smoked were 22% less likely to develop CVA, while current smokers were 22.3% more likely to develop CVA later in life. Number of cigarettes smoked per day showed a 0.6% increased risk for every cigarette smoked while pack-years echoed that sentiment revealing 0.3% increased risk for every pack-year.

Cancer, as well as the use of cholesterol medications (suggesting dyslipidemia at study entry), were not associated with CVA risk. However, diabetes and CHD revealed a 34.3% and 33.5% significant increase in CVA risk, respectively.

With laboratory tests, uric acid and non-fasting glucose slightly increased the risk of CVA by 0.4% and 0.2%, respectively. No other laboratory measurements, including cholesterol triglycerides, and hematocrit were significant in predicting CVA.

Lastly, all blood pressure variables were highly predictive of CVA. Medications to treat hypertension increased the risk of CVA later in life 58.4% while Stage 1 hypertension and Stage 2 hypertension significantly increased the risk by 68.4% and 71.0%, respectively. Looking at individual components of blood pressure, systolic and diastolic blood pressure at study entry increased risk of CVA by 1.5% and 2.5%, respectively for every mmHg increase of each.

### Cerebrovascular Accident (CVA)/Stroke – Multivariate Analyses

Cox-regression models were constructed to examine the factors driving time to occurrence of CVA or stroke. Table 46 below shows multiple regression models adding variables that were significant univariate predictors, culminating in a final model predicting CVA.

Gastrectomy as a univariate predictor and as a co-variate in multivariate models showed significant increase in the risk of developing CVA. Focusing on gastrectomy as a single predictor, gastrectomy increased risk of CVA by 59.9%. The risk decreased slightly when age, smoking and alcohol were added. But, when BMI was added the risk further increased to 66.1%. When age was added to any model, a consistent 4% increased risk of CVA per year of age was observed. Alcohol across models increased risk of CVA 2% to 3%. Surprisingly, smoking in the form of pack-years across all models did not increase the risk of CVA.

When pack-years was replaced in the multivariate model with ‘current smoker’, participants who were smokers and had a gastrectomy by study entry had a 26.9% and 62.1% increased risk of stroke, respectively. BMI increased to 5.0% increased risk and alcohol decreased just enough to become non-significant, while the effect of age remained unchanged. Lastly, when ‘current smoker’ was replaced with ‘former smoker’

in the multivariate model, quitting smoking had a change in direction of the hazard ratio to 0.760 or a 24% decrease in risk of stroke while the risk of gastrectomy increased to 68.6%. The hazard ratio for alcohol increased slightly to 0.3%, but enough to make the estimate significant at the p <0.05 level. BMI returned to the 4.7% increased risk, while the risk associated with age remained about the same at 4.2%. These substitutions and subsequent changing coefficients underscore the risk of stroke associated with smoking and how quitting smoking greatly reduces that risk. Also, this provides a truer sense of the risk of gastrectomy as the risk first decreased when switching pack-years for current smokers then increased after switching current smokers to former smokers.

Table 46: Multivariate Cox Regression Models Showing Hazard Ratios Predicting CVA– Focusing on Gastrectomy and Controlling Factors and Accounting for Competing Risks (N=7963)

| Model | Gastrectomy | Age | Alcohol | Smoking (Pack-years) | Body Mass Index (BMI) | Current Smoker | Former Smoker |
|---|---|---|---|---|---|---|---|
| 1 | 1.599 ¥ | --- | --- | --- | --- | --- | --- |
| 2 | 1.551 ¥ | 1.037 ‡ | --- | --- | --- | --- | --- |
| 3 | 1.518 £ | 1.038 ‡ | 1.003 † | --- | --- | --- | --- |
| 4 | 1.502 £ | 1.040 ‡ | 1.002 NS | 1.001 NS | --- | --- | --- |
| 5 | 1.661 ¥ | 1.043 ‡ | 1.002 † | 1.002 NS | 1.047 ‡ | --- | --- |
| 6 | 1.621 ¥ | 1.043 ‡ | 1.002 NS | --- | 1.050 ‡ | 1.269 ¥ | --- |
| 7 | 1.686 ¥ | 1.042 ‡ | 1.003 † | --- | 1.047 ‡ | --- | 0.760 ¥ |

NS = not significant; † significant at the < 0.05 level; £ significant at the < 0.01 level
¥ significant at the < 0.001 level; ‡ significant at the < 0.0001 level

After adding variables significant in the univariate analyses to the model focusing on gastrectomy (eg. gastrectomy, age, alcohol, smoking, and BMI), a few variables continued to show predictive properties in the final model in the development of CVA. See Table 47. Diabetes and CHD at study entry increased risk of CVA 22.7% and 16.2%, respectively. Cancer prevalence was not predictive of CVA. When hypertension variables were added, correlations with other variables in the model obscured some of the effects. Seeing that medications to treat hypertension had the lowest correlation, and

thus the least impact on other variables, this variable, also implying controlled hypertension, increased risk of CVA development 38.8%. Taken together, it appears that of all of the exam 1 variables predictive of CVA/stroke, gastrectomy conferred the greatest risk, followed by prevalent controlled hypertension, and prevalent diabetes. Age and BMI were highly significant in the model with alcohol also contributing. Surprisingly, smoking in the form of pack-years was not significant suggesting the larger effects of other highly predictive variables overshadowed the risk of CVA due to smoking.

When pack-years was replaced with current smokers and then again by former smokers, the effect of smoking status was associated with a significant increase in the risk of CVA/stroke by 29.5% for current smokers and decrease in risk by 25.2% for former smokers. CHD at study entry risk increased to 23.3% and 26.7%, respectively, while gastrectomy status changed to 61.4% and 68.6%, respectively. All other variables remained about the same, see Table 47.

Table 47: FINAL Multivariate Cox Regression Models – CVA – Accounting for Competing Risks

| | Gast | Age | Alcohol | BMI | CHD Prev | Cancer Prev | Diab Prev | Hyp Drug | Pack Years | Current Smoker | Former Smoker |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | 1.654 ¥ | 1.040‡ | 1.003† | 1.041‡ | 1.162 NS | 0.510 NS | 1.227† | 1.388£ | 1.002 NS | --- | --- |
| 9 | 1.614 ¥ | 1.040‡ | 1.003† | 1.043‡ | 1.233 NS | 0.506 NS | 1.238† | 1.418¥ | --- | 1.295‡ | --- |
| 10 | 1.686‡ | 1.039‡ | 1.003¥ | 1.040‡ | 1.267 NS | 0.512 NS | 1.233† | 1.406¥ | --- | --- | 0.748¥ |

NS = not significant; † significant at the < 0.05 level; £ significant at the < 0.01 level
¥ significant at the < 0.001 level; ‡ significant at the < 0.0001 level

**Discussion (Survival/Mortality, CHD, CVA/Stroke)**

Gastrectomy is a major surgical procedure with well-documented short-term consequences but less well studied long-term effects. The earlier findings of Glober et al. [15] and Stemmerman et al.[16] in the HHP cohort of Japanese American men suggested that the subjects with a previous gastrectomy might have done quite well, in terms of CHD, as they aged, despite their relatively heavy smoking, because they were closer to ideal weight, and had lower blood pressure and serum cholesterol than other cohort members. We have documented in Chapter 1 that the lower weight and cholesterol persisted into old age, and that the incidence of diabetes after gastrectomy was reduced by half. A surprising finding, however, was that systolic blood pressure had risen more with aging among men who underwent a gastrectomy than it did in the men who did not.

The increase in stroke incidence of more than 50% to a cumulative proportion of 18.77% in men who survived 25 years after enrollment (average of 23.6 years after gastrectomy) is highly significant, both clinically and statistically. This finding is supported by a slightly higher prevalence of stroke at enrollment and by a relative risk for stroke mortality of 1.9. Stroke deaths were quite evenly divided between ischemic and hemorrhagic strokes with the relative risks being 2.0 and 1.8, respectively. Presumably the non-fatal strokes would be mainly ischemic.

Although smoking rates dropped by half in the surviving men who were examined after 25 years, the men with partial gastrectomy have nevertheless experienced higher overall mortality. This is mainly explained by mortality from lung cancer and emphysema with rates that were, respectively, 2.2 and 1.9 times higher in the gastrectomy group than in other cohort men. Increased stroke mortality also contributed. Coronary disease rates have not differed much from the rest of the cohort, so the favorable effects on weight

and coronary risk factors in the early years may truly have afforded some protection from the excessive smoking in that regard.

There are some limitations to this study. First, as this study was conducted in Japanese-American men, these findings may not be generalizable to non-Japanese populations or to women. Second, as the HHP was conducted and completed in the past, the present study is limited by the data items selected for study by the initial HHP study authors. For example, waist circumference was not collected at Exam 1 although a number of anthropomorphic variables were collected. Third, non-participation (selection bias) may play a role in the study's findings. The initial cohort of 8,006 men included respondents from an estimated 14,000 men on the island of Oahu. It cannot be assumed that those who chose to participate had the same prevalence of exposures, nor incidence of disease as those who did not participate. It is always possible that there may be a difference in rates of disease between those who participated in the HHP and those who did not. Likewise, the number of gastrectomy patients among those who would have been eligible to participate in HHP, but chose not to participate is unknown. Another limitation of the study is that the follow-up data giving time of death, time to developing CHD and time to experiencing CVA goes beyond the confines of the original HHP study which ended at Exam 4. This additional follow-up allowed us to examine the survival or time to event curves more completely. But, there were no study visits or follow-up information to provide additional information on health status proximal to death. While we have assumed that all original participants were followed for mortality and incidence of CHD and stroke, it is likely that a few men moved away or were otherwise lost to follow-up. Since all of these participants were long-time residents of Hawaii and since newspaper obituaries were regularly scanned for deaths, it is unlikely that many deaths

were missed. But, non-hospitalized events after Exam 4 or hospitalizations outside Hawaii could have been missed.

In sum, despite their excess smoking, the men undergoing gastrectomy appeared not to have an elevated rate of coronary heart disease, supporting the suggestion of Stemmerman et al.[16] that they were protected by the favorable effects of their surgery on body weight, serum cholesterol, and, in the early years, blood pressure. However, there was a clear excess of total mortality in the gastrectomy group that was largely explained by the main smoking-related causes, namely,- lung cancer and emphysema, but was also exacerbated by excess stroke deaths, both hemorrhagic and ischemic types. The incidence of non-fatal stroke was also elevated over that of non-operated men by about 50% with more than one in six men having a stroke over an average of 33 years of average follow-up.

## CHAPTER 3: THE IMPACT OF GASTRECTOMY ON CANCER: LUNG, PROSTATE, COLORECTAL, AND STOMACH


### Abstract

#### Background/Purpose

Cancers, particularly prostate and colon, are more frequently diagnosed in people who are obese. Bariatric surgery, or surgical intervention for weight loss, has been shown to improve cancer outcomes in some morbidly obese patients.[83,84] Follow-up on these patients however, has typically been short in duration. Gastrectomy is a surgical procedure similar to bariatric surgery where a part of the stomach is removed. Typically, significant weight loss is observed post procedure. This study examined the long-term impacts of gastrectomy on the development of cancer, particularly lung, prostate, colorectal and stomach cancer.

#### Methods

Three-hundred forty-five men of Japanese ancestry participating in the Honolulu Heart Program (HHP) who had a partial gastrectomy and were free of cancer upon entering the study were compared to 7,579 HHP participants who did not have a gastrectomy and were also cancer free, and their development of cancers in the decades to follow, particularly lung, prostate, colorectal, and stomach cancer were examined. Means, 95% confidence intervals, and independent samples t-tests were used to characterize continuous variables, while two by k contingency tables and chi-square analyses were undertaken to evaluate frequency data. Time to cancer data were analyzed using Life Table Analysis and Cox regression models, with both univariate and multivariate modeling.

#### Results/Findings

Gastrectomy patients smoked more and were less obese, less hypertensive, and had better lipid and glucose values compared to non-gastrectomy patients. GS participants

had a greater cumulative incidence of lung cancer compared to the NGS participants (p=0.0421), but this became non-signifcant when the excess smoking of the gastrectomy subjects was taken into account. In multivariate Cox regression models, gastrectomy appeared to decrease the risk of stomach cancer by 46.7% (p=0.0437). Gastrectomy had no impact on the development of lung, prostate, or colorectal cancer. Age and smoking proved to be consistent sources of risks across all cancers.

**Conclusions/Implications**

There were substantial differences in smoking, obesity and risk factors correlated with obesity between the GS and NGS groups at study start. Over the decades of long-term follow up though, gastrectomy conferred no advantage for cancer incidence except for significant protection from stomach cancer.

**Introduction/Background**

**Gastrectomy**

Obesity is a well-established risk factor for several types of cancer, and because of the increasing use of gastric surgery to treat obese individuals, it is logical to examine the effect of surgery itself on cancer incidence and mortality. Many cancers are believed to have a pathogenesis that develops over decades, but there are few studies that provide this long of a follow-up after bariatric or other stomach surgery. Therefore, we believed that the assessment of cancer incidence and mortality in a group of 347 men with a history of gastrectomy who were part of a large prospective study of cardiovascular disease and cancer would be of interest. Detailed information about lifestyle, height, weight, other anthropometric measurements, medical history, and limited physiological variables were available for these men and for the other 7,659 participants who were enrolled in the Honolulu Heart Program in the years 1965-68. In this Chapter we examine cancer incidence and mortality overall as well as separately for the most

common cancers: lung, colorectal, prostate and stomach. Because of the heavy smoking by the GS participants we expected to find that lung cancer incidence would be elevated. We also hypothesized that stomach cancer rates might be elevated because "remnant" stomach cancers are a recognized late complication of gastrectomy[85] and because there also is evidence that smoking increases the risk of stomach cancer. Prostate and colorectal cancers have been associated with obesity, so it seemed possible that their incidence might be decreased in men in the GS group.

## Methods

### Study Participants

#### Gastrectomy Group (GS)

All 347 men who entered the HHP with a documented history of previous partial gastrectomy (GS), for peptic ulcer disease comprised the GS group. This is the same group of subjects identified by Glober et al.[15] in 1974. These men were questioned specifically about any past history of gastric surgery, and an attempt was made to review hospital records for each of the positive responses. Only cases where a partial gastrectomy was verified by review of medical records were included. The surgical note was abstracted in nearly all cases. Cases excluded by Glober et al.[15] include those for whom hospital records could not be located, a malignancy was diagnosed, or no gastric tissue was removed.

Among the 347 men, 171 (49.3%) had gastroduodenal anastomoses (Billroth I), 169 (48.7%) had gastrojejunal anastomoses (Billroth II), and 7 (2%) had a reconstruction that could not be determined by medical records (Table 48). Within this same set of patients, 113 (33.7%) were diagnosed with a duodenal ulcer, 202 (58.2%) were diagnosed with a gastric ulcer, 15 (4.3%) were diagnosed with both a duodenal ulcer and a gastric ulcer, and 13 (3.7%) had a diagnosis of either 'other' or 'unknown' (Table 49). Regarding

vagotomy, 267 (77.0%) patients did not have a vagotomy, 65 (18.7%) patients did have a vagotomy, and 15 (4.3%) patients had a vagotomy status that was unknown (Table 50). From the gastrectomies, 1 (0.3%) patient had 1-25 % of their stomach removed, 51 (14.7%) patients had 26-50% of their stomach removed, 167 (48.1%) patients had 51-75% of their stomach removed, 15 (4.3%) patients had 76-99% of their stomach removed, and 113 (32.6%) patients did not have a value documented indicating how much stomach was removed (Table 51).

Table 48: Summary of Gastrectomy Reconstructions in GS Group

| Operation | Frequency | Percent of Total |
|---|---|---|
| Billroth I | 171 | 49.28% |
| Billroth II | 169 | 48.70% |
| Pyloroplasty | 0 | 0.00% |
| Unknown | 7 | 2.02% |
| Total | 347 | 100.00% |

Table 49: Summary of Diagnoses Leading to Gastrectomy in GS Group

| Diagnosis | Frequency | Percent of Total |
|---|---|---|
| Duodenal Ulcer | 117 | 33.72% |
| Gastric Ulcer | 202 | 58.21% |
| Both Duodenal and Gastric Ulcers | 15 | 4.32% |
| Other | 11 | 3.17% |
| Unknown | 2 | 0.58% |
| Total | 347 | 100.00% |

Table 50: Summary of Vagotomy Status in GS Group

| Vagotomy Status | Frequency | Percent of Total |
|---|---|---|
| No | 267 | 76.95% |
| Yes | 65 | 18.73% |
| Unknown | 15 | 4.32% |
| Total | 347 | 100.00% |

Table 51: Percent of Stomach Removed Among GS Group

| % Stomach Removed | Frequency | Percent of Total |
|---|---|---|
| None | 0 | 0% |
| 1 -25% | 1 | 0.29% |
| 26-40% | 9 | 2.59% |

| | | |
|---|---|---|
| 41-50% | 42 | 12.10% |
| 51-66% | 89 | 25.65% |
| 67-75% | 78 | 22.48% |
| 76-90% | 12 | 3.46% |
| 91-99% | 3 | 0.86% |
| Unknown | 113 | 32.56% |
| Total | 347 | 100.00% |

**Non-Gastrectomy Group (NGS)**

Subjects who gave no history of gastric surgery (e.g. gastrectomy, bariatric surgery) at the time of study entry (Exam 1 of the HHP) and were free of the conditions under investigation (e.g. cancer) comprised the non-GS group.

**Prevalence and incidence of Cancer**

At Exam 1, study participants were asked if they had been diagnosed with cancer. Affirmative answers were compiled to determine the prevalence of cancer in the HHP study population. For cancer incidence, study participants were matched to the Hawaii Tumor Registry, which is part of the SEER cancer registry system supported by the National Cancer Institute. Cancer site, month and year of diagnosis, and month and year of death were captured. Time to development of cancer was calculated in years from the Exam 1 date until the date of development of cancer. Prevalent cases were excluded from incidence tabulations.

**Variables Collected at Baseline and Subsequent Examinations**

All of the examination variables used in this Chapter have been previously defined in Chapters 1 and 2.

## Statistical Analyses

### Summary Statistics/Baseline Characteristics

Means and 95% confidence intervals for all continuous variables and frequencies and percentages for all categorical variables were reported at Exam 1, by outcome group (i.e. each individual cancer), and by gastrectomy status as either a gastrectomy (GS) patient or a non-gastrectomy patient (NGS). Comparisons of NGS versus GS group for each individual continuous variable were made using independent samples t-tests. For comparisons of categorical variables between NGS and GS groups, chi-square analyses were performed after construction of 2 x K tables.

### Prevalence of Cancer

Cancers reported at Exam 1 were tabulated by cancer site (e.g. lung, prostate, colorectal, or stomach) and by gastrectomy group. Chi-square analyses and Fisher's Exact Tests, where appropriate, were utilized to see if there was a difference between the prevalence of cancer between the NGS and GS groups at Exam 1.

### Incidence of Cancer

After excluding participants reporting cancer at Exam 1, cancers occurring during the course of the study through 2013, when collection of cancer reports ended, were tabulated by cancer site and gastrectomy group. Differences in frequencies were examined using chi-square analyses. Mean age when cancer developed was calculated by gastrectomy group for all cancers as a single group as well as individual cancers. Independent samples t-tests were run to examine the differences between the NGS and GS group.

### Cause of Death for Incident Cancers

Major causes of death by cancer site and gastrectomy group were tallied and frequencies calculated. As noted previously, a binary variable was created to indicate

whether a participant had a gastrectomy prior to entering the HHP or not. Causes of death were extracted from death certificates.

**Time to Cancer (e.g. All Cancer, Lung, Prostate, Colorectal, and Stomach Cancer)**

Time to event data were analyzed starting from Exam 1 (study entry) until the event being examined, e.g. time to development of cancer any, lung, prostate, colorectal, and stomach cancer). Due to the long-term follow up nature of the study, considering the follow-up from Exam 1 can be decades, time to event was captured in years. Time to event in years for all cancers was calculated by taking the difference in date between the event occurrence (e.g. cancer date) and date of Exam 1. That difference, represented in days, was divided by 30.417 to determine time to death in months and that result divided by 12 to attain the time in years.

**Life-Tables**

Life tables were constructed taking into account the competing risk of death during the study. In particular, cumulative incidence function figures were constructed to assess the difference in incidence rates between GS and NGS participants. The Gray's test for equality of cumulative incidence functions was utilized, testing the null hypothesis that the cumulative incidence functions are identical between the two study groups, NGS and GS.[86]

**Cox-Regression**

To examine factors impacting time to cancer, Cox regression models were constructed. Cox regression is a semi-parametric method in contrast to traditional linear or logistic regression as it does not require that one chooses some particular probability distribution to represent survival times. Utilizing Cox regression models, univariate models predicting the time to event outcomes of the cancers were constructed. Based on the impact of each variable in the univariate analyses on the particular cancer, multivariate models

were constructed to represent the contributions of the various variables in predicting each cancer. As with the life tables, competing risks analysis taking into account death occurring before cancer was implemented.

## Results

### All Cancer

#### Baseline Characteristics

Mean values by NGS and GS groups with associated 95% confidence intervals were generated and t-tests were constructed to examine the group means between the NGS and GS groups for each variable at Exam 1 or study entry. For categorical variables, percentages by level and gastrectomy group are shown with p-values from chi-square analyses. Table 52 summarizes the results of these analyses focusing on all participants in the HHP, excluding those who had cancer at study entry.

| Table 52: Baseline (Exam 1) Characteristics of Study Participants – Excluding Prevalent Cancer | | | |
|---|---|---|---|
| | Non-GS | GS | |
| | n = 7579 | n = 345 | |
| | Mean<br>95%CI or % | Mean<br>95%CI or % | p-value |
| Age (years) | 54.81<br>54.69, 54.94 | 55.81<br>55.22, 56.39 | **p = 0.0012** |
| Education (years) | 10.35<br>10.28, 10.41 | 10.21<br>9.91, 10.50 | p = 0.3610 |
| Weight (lbs) | 140.10<br>139.60, 140.60 | 128.90<br>126.70, 131.10 | **p < 0.0001** |
| Height (in) | 64.09<br>64.03, 64.14 | 64.32<br>64.08, 64.57 | p = 0.0641 |
| BMI ($kg/m^2$) | 23.94<br>23.87, 24.01 | 21.86<br>21.54, 22.18 | **p < 0.0001** |
| BMI-Underweight | 3.16% | 12.75% | **p < 0.0001** |
| BMI-Normal Weight | 61.43% | 69.86% | |
| BMI-Overweight | 32.35% | 16.81% | |
| BMI-Obese | 3.00% | 0.58% | |
| BMI-Missing | 0.07% | 0.00% | |
| Cigarettes per day (current smokers only) | 23.69<br>23.29, 24.09 | 23.40<br>22.08, 24.71 | p = 0.7171 |
| Never Smoked (%) | 30.96% | 12.46% | **p < 0.0001** |
| Former Smoker (%) | 26.15% | 26.67% | |
| Current Smoker (%) | 42.89% | 60.87% | |
| Pack-years | 23.49<br>22.93, 24.05 | 33.61<br>31.25, 35.96 | **p < 0.0001** |
| Alcohol (ounces/month) | 13.67<br>13.12, 14.22 | 15.77<br>13.21, 18.34 | p = 0.1183 |
| Systolic blood pressure (mmHg) | 134.40<br>133.90, 134.80 | 129.10<br>127.00, 131.30 | **p < 0.0001** |
| Diastolic blood pressure (mmHg) | 82.49<br>82.23, 82.75 | 77.44<br>76.13, 78.75 | **p < 0.0001** |
| HTN-Normal | 22.15% | 34.49% | **p < 0.0001** |
| HTN-Prehypertension | 38.37% | 34.78% | |
| HTN-Stage 1 Hypertension | 25.08% | 22.90% | |
| HTN-Stage 2 Hypertension | 10.23% | 6.38% | |
| HTN-Hypertension Crisis | 4.17% | 1.45% | |
| Prevalent CHD | 4.10% | 2.32% | p = 0.0991 |
| Prevalent CVA | 1.39% | 1.74% | p = 0.5846 |
| Prevalent Diabetes | 9.54% | 6.96% | p = 0.1088 |
| Hypertension Medications | 9.15% | 8.72% | p = 0.7888 |
| Cholesterol Medication | 1.52% | 0.87% | p = 0.5543 |

| | | | |
|---|---|---|---|
| Blood Glucose (non-fasting) (mg/dL) | 162.40<br>161.10, 163.70 | 144.00<br>137.60, 150.30 | **p < 0.0001** |
| Serum cholesterol(mg/dL) | 219.10<br>218.20, 219.90 | 204.60<br>200.80, 208.50 | **p < 0.0001** |
| Serum cholesterol-Desirable | 30.97% | 45.51% | **p < 0.0001** |
| Serum cholesterol-Borderline High | 42.10% | 38.26% | |
| Serum cholesterol-High | 26.93% | 16.23% | |
| Random Triglyceride(mg/dL) | 238.60<br>233.90, 243.30 | 189.00<br>173.50, 204.60 | **p < 0.0001** |
| Random Triglyceride-Desirable | 37.26% | 53.62% | **p < 0.0001** |
| Random Triglyceride-Borderline High | 19.04% | 18.84% | |
| Random Triglyceride-High | 43.70% | 27.54% | |
| Uric acid (mg/dL) | 60.00<br>59.66, 60.34 | 59.09<br>57.40, 60.78 | p = 0.2787 |
| Physical Activity Index | 32.82<br>32.72, 32.92 | 32.51<br>32.03, 32.98 | p = 0.2114 |
| Biacromial Diameter (cm) | 38.03<br>37.99, 38.08 | 37.78<br>37.56, 38.01 | **p = 0.0214** |
| Bi-iliac diameter (cm) | 28.89<br>28.85, 28.94 | 28.70<br>28.48, 28.92 | p = 0.0791 |
| Skinfold-left triceps (mm) | 8.03<br>7.95, 8.10 | 6.64<br>6.30, 6.99 | **p < 0.0001** |
| Skinfold left-subscapular (mm) | 16.65<br>16.50, 16.80 | 13.10<br>12.41, 13.80 | **p < 0.0001** |
| Girth-Left upper arm (mm) | 279.70<br>279.10, 280.30 | 265.10<br>262.00, 268.20 | **p < 0.0001** |
| Chest Depth (cm) | 19.35<br>19.30, 19.39 | 18.61<br>18.42, 18.80 | **p < 0.0001** |
| Hematocrit (%) | 44.73<br>44.67, 44.80 | 44.04<br>43.70, 44.37 | **p < 0.0001** |

### Age and Education

At study entry, GS participants had a mean age 1 year older than the NGS participants (55.81 year for GS vs. 54.81 for NGS). This difference was statistically significant (p=0.0012). In contrast, both the GS and NGS groups had about the same education (10.21 years for GS vs. 10.35 years for NGS, p=0.3610).

### Smoking and Alcohol

The GS men had a history of peptic ulcer disease that was (presumably) resistant to medical therapy, perhaps because they were unsuccessful at giving up cigarettes. At study entry they were much more likely to have ever smoked and to be current smokers

than their non-operated peers. Among those who smoked, the number of cigarettes used per day was similar in the two groups. GS participants had an average of 10 more pack-years than the NGS group (33.61 years for GS vs. 23.49 years for NGS, $p<0.0001$). Average alcohol consumption was quite similar in the two groups.

### Obesity (Height, Weight, BMI, Physical Activity)

There was an 11.2 pound mean weight difference between the two groups, and mean BMI was 2.08 $kg/m^2$ lower for GS compared to NGS participants ($p<0.0001$). Height was similar in the two groups, but other body measurements (which may be influenced by the amount adipose tissue), were systematically smaller in the GS group. When categorizing BMI following the WHO guidance for obesity, a greater percentage of GS compared to NGS participants were underweight (12.75% vs. 3.16%) and normal weight (69.86% vs. 61.43%). In contrast, a greater percentage of NGS compared to GS participants were overweight (32.35% vs. 16.81%) and obese (3.00% vs. 0.58%). Both groups showed about the same level of physical activity as assessed by the physical activity index described in previous chapters.

### Laboratory Measurements

From blood samples collected at Exam 1/study entry, laboratory values clearly indicated a highly significant difference at the $p<0.0001$ between the GS and NGS groups. Mean, non-fasting blood glucose was 18.4 mg/dL lower for the GS group (144.00 mg/dL vs. 162.40 mg/dL). Mean serum cholesterol was 14.5 mg/dL lower for the GS group (204.60 mg/dL vs. 219.10 mg/dL). Mean random triglycerides were 48.7 mg/dL lower for the GS group (189.00 mg/dL vs. 238.60 mg/dL), and mean hematocrit was 0.7% lower for the GS group (44.04% vs. 44.73%), although results for each group fall within normal limits of the test. There was no difference in uric acid results ($p=0.2878$).

## Prevalence of Cancer

There were 82 patients indicating a history of cancer at Exam 1, 80 in the NGS group and 2 in the GS group. Of the 80 NGS cancers reported at Exam 1: 1 (1.25%) was lung, 8 (10.00%) were prostate, 36 (45.00%) were colorectal, 17 (21.25%) were stomach and 18 (22.50%) were cancers that were either not specified or missing. With the 2 cancers amongst the GS group, 1 was lung cancer and the other was an unspecified cancer. A chi-square analysis exploring the differences in percentages of cancer by gastrectomy group reveal there was no difference in rate at Exam 1 (p=0.5857). Of the 8006 patients entering HHP, 7659 were NGS and 347 were GS. Excluding those with cancer at Exam 1, 7579 NGS and 345 GS patients were cancer free at Exam 1; see Table 53.

| Table 53: Prevalence of Cancer | | | |
|---|---|---|---|
| Cancers identified at Exam 1 | | | |
| | **All** | **NGS** | **GS** |
| All Patients | 8006 | 7659 | 347 |
| All Patients who were cancer free at Exam 1 | 7924 (98.98%) | 7579 (98.96%) | 345 (99.42%) |
| Patients with Cancer at Exam 1 | 82 (1.02% | 80 (1.04%) | 2 (0.58%) |
| $X^2$= 0.7177, p = 0.3969; Fisher's Exact test p=0.5857 | | | |

**Incidence of Cancer**
**Cancer Types That Developed During the Study**

A total of 2918 participants (36.8%) out of the 7924 patients who were cancer free at exam 1 developed a cancer during the course of the follow-up period, 133 (38.0%) in the GS group and 2787 (36.8%) in the NGS group. This difference was not statistically significant. (p=0.6518; see Table 54).

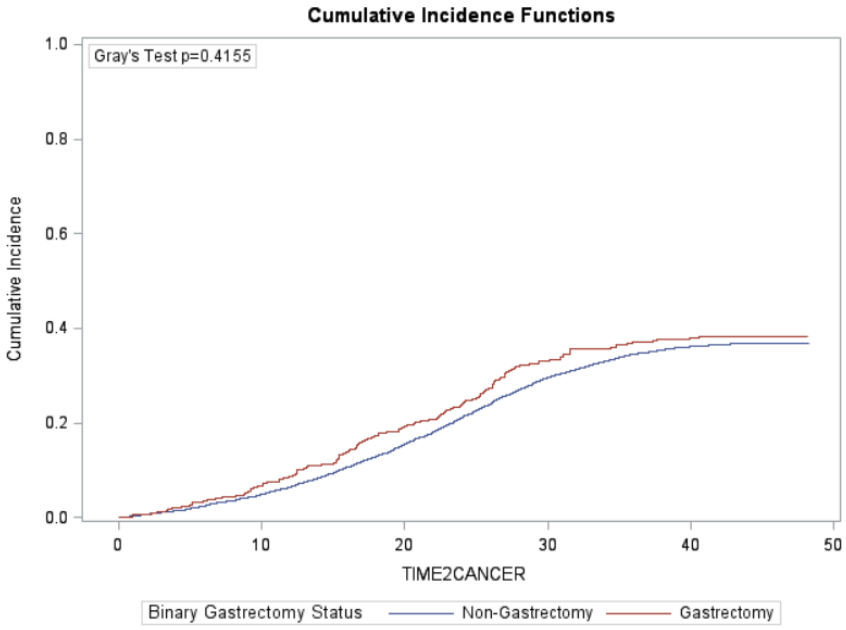
| Table 54: Cancers that developed during the course of the study | | | | |
|---|---|---|---|---|
| | All | NGS | GS | |
| All Patients free of Cancer at Exam 1 | 7924 (100.0%) | 7579 (100.0%) | 345 (100.0%) | p = 0.6518 |
| No Cancer | 5006 (63.2%) | 4792 (63.2%) | 214 (62.0%) | |
| All Cancers | 2918 (36.8%) | 2787 (36.8%) | 133 (38.0%) | |
| → Lung | 375 (12.9%) | 352 (12.6%) | 23 (17.6%) | p = 0.0907 |
| → Prostate | 816 (28.0%) | 781 (28.0%) | 35 (26.7%) | p = 0.9850 |
| → Colorectal | 617 (21.1%) | 590 (21.2%) | 27 (20.6%) | p = 0.9068 |
| → Stomach | 417 (14.3%) | 406 (14.6%) | 11 (8.4%) | p = 0.1073 |
| → Cancer-Non-Specific | 693 (23.8%) | 658 (23.6%) | 35 (26.72%) | p = 0.3492 |

The numbers of specific cancers in the GS group were too small to generate much statistical power, and none of the differences reached statistical significance. Nevertheless, there is a suggestion of an increase in lung cancer incidence in the GS men compared to the NGS men which is consistent with the much heavier smoking history in that group. There was also a suggestion of a decrease in stomach cancer incidence. There was no evidence of an effect of gastrectomy on rates of prostate cancer or colorectal cancer incidence.

**Life-Table - All Cancer**

Figure 17 is a life table cumulative incidence function (CIF) comparing the time to development of cancer for all cancers including lung cancer, prostate cancer, colorectal cancer, and stomach cancer, between the GS and the NGS groups. From the CIF figure, the curves are parallel, but relatively close, showing development of cancer, all cancers, might have been about the same for both GS and NGS groups. Gray's test for equality for cumulative incidence functions showed no difference (p=0.4155) So, across all cancers, there was no difference in incidence.

Figure 17: Time to Development of Cancer Cumulative Incidence Function by Gastrectomy Status

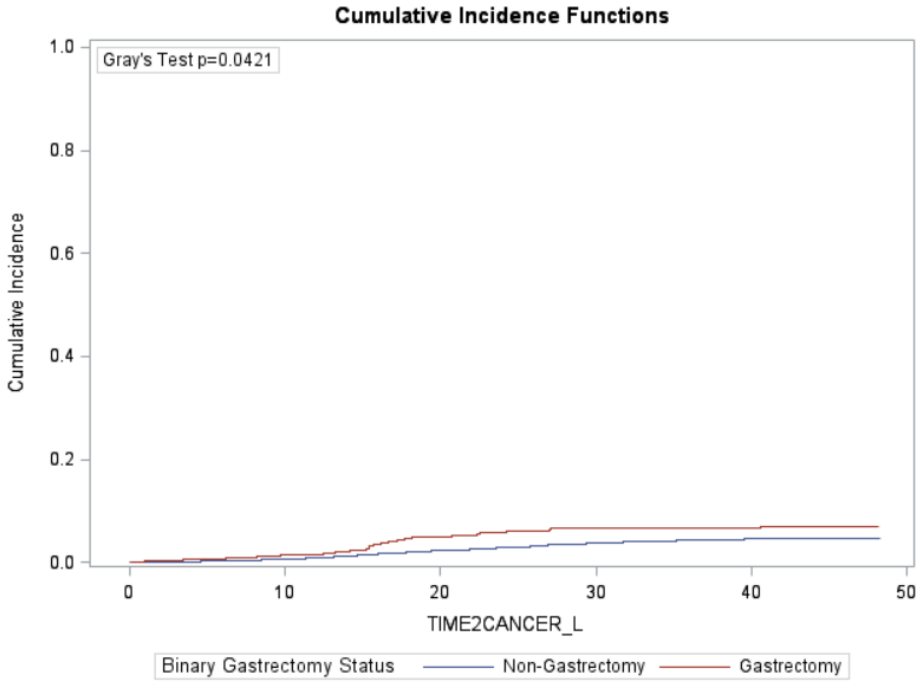



**Lung Cancer**

**Life-Table – Lung Cancer**

Figure 18 depicts a life-table CIF curve comparing the time to development of lung cancer between the GS and the NGS group. From the CIF curve, there is clear separation between the NGS and GS curves beginning around 15 years after study entry with the GS groups showing greater cumulative incidence. This continues through the end of available data. Gray's Test for Equality of CIF confirmed the difference between the GS and NGS groups in CIF returning a, p=0.0421, indicating a significant difference.

Figure 18: Time to Development of Lung Cancer Cumulative Incidence Function By Gastrectomy Status




**Cox Regression – Multivariate Analyses – Lung Cancer**

Table 53 shows the hazard ratio for lung cancer associated with gastrectomy as a single variable in the top line and shows how the HR changes as selected confounders are added to the model. In the univariate analyses, having had a gastrectomy at study start appeared to increase the risk of developing lung cancer by 53.6%. When age, and monthly alcohol consumption were controlled for in the multivariate model, those risk estimates increased slightly and gastrectomy remained significantly predictive in the model. However, as noted earlier, the GS men smoked substantially more than the NGS men and when pack-years was entered into the model, the gastrectomy risk dropped to 37.1% and became statistically non-significant. Presumably, if other smoking covariates were added, the gastrectomy HR might have moved still closer to the null. A curious

finding was that BMI was somewhat protective against lung cancer and when it was added to the model it diminished the putative effect of gastrectomy a bit more. This may have resulted from the negative association between BMI and smoking. Overall, it appears that the excess smoking in the GS group is sufficient to explain the significant association between gastrectomy and lung cancer incidence, see Table 55 below, models 1 through 5. The final model is shown in Table 56 below.

| Table 55: Multivariate Cox Regression Models for Time to Cancer Exam 1 – Base Models with Competing Risks Assessment | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Lung Cancer | | | Prostate Cancer | | | Colorectal Cancer | | | Stomach Cancer | | |
| **Model** | **HR** | **95% CI** | **p** | **HR** | **95% CI** | **p** | **HR** | **95% CI** | **p** | **HR** | **95% CI** | **p** |
| **Model 1** | | | | | | | | | | | | |
| Gastrectomy | 1.536 | 1.013, 2.330 | **0.0433** | 0.997 | 0.708, 1.404 | 0.9878 | 1.006 | 0.682, 1.482 | 0.9768 | 0.586 | 0.322, 1.066 | 0.0799 |
| **Model 2** | | | | | | | | | | | | |
| Gastrectomy | 1.574 | 1.039, 2.385 | **0.0323** | 1.018 | 0.723, 1.433 | 0.9192 | 1.011 | 0.686, 1.490 | 0.9566 | 0.584 | 0.321, 1.064 | 0.0788 |
| Age | 0.973 | 0.955, 0.991 | **0.0042** | 0.979 | 0.966, 0.991 | **0.0009** | 0.995 | 0.981, 1.009 | 0.4742 | 1.003 | 0.986, 1.021 | 0.6991 |
| **Model 3** | | | | | | | | | | | | |
| Gastrectomy | 1.561 | 1.030, 2.365 | **0.0358** | 1.034 | 0.734, 1.456 | 0.8475 | 1.004 | 0.681, 1.481 | 0.9827 | 0.583 | 0.320, 1.063 | 0.0782 |
| Age | 0.976 | 0.958, 0.994 | **0.0108** | 0.977 | 0.965, 0.990 | **0.0004** | 0.996 | 0.982, 1.010 | 0.5358 | 1.004 | 0.986, 1.022 | 0.6606 |
| Alcohol | 1.007 | 1.004, 1.010 | **<0.0001** | 0.993 | 0.990, 0.997 | **<0.0001** | 1.006 | 1.003, 1.008 | **<0.0001** | 1.002 | 0.998, 1.005 | 0.3070 |
| **Model 4** | | | | | | | | | | | | |
| Gastrectomy | 1.371 | 0.904, 2.080 | 0.1380 | 1.102 | 0.778, 1.560 | 0.5848 | 1.020 | 0.691, 1.504 | 0.9221 | 0.566 | 0.310, 1.034 | 0.0640 |
| Age | 0.965 | 0.946, 0.984 | **0.0004** | 0.979 | 0.967, 0.992 | **0.0015** | 0.992 | 0.978, 1.006 | 0.2800 | 1.004 | 0.986, 1.022 | 0.6484 |
| Alcohol | 1.003 | 0.999, 1.006 | 0.1050 | 0.996 | 0.992, 0.999 | **0.0072** | 1.006 | 1.003, 1.008 | **<0.0001** | 1.001 | 0.997, 1.004 | 0.7125 |
| Smoking (Pack-years) | 1.022 | 1.019, 1.025 | **<0.0001** | 0.991 | 0.987, 0.994 | **<0.0001** | 1.000 | 0.997, 1.004 | 0.8506 | 1.004 | 1.001, 1.007 | **0.0237** |
| **Model 5** | | | | | | | | | | | | |
| Gastrectomy | 1.245 | 0.816, 1.898 | 0.3093 | 1.098 | 0.772, 1.563 | 0.6028 | 1.087 | 0.735, 1.607 | 0.6761 | 0.540 | 0.293, 0.994 | **0.0476** |
| Age | 0.961 | 0.942, 0.980 | **<0.0001** | 0.979 | 0.967, 0.992 | **0.0018** | 0.994 | 0.980, 1.009 | 0.4487 | 1.003 | 0.985, 1.021 | 0.7708 |
| Alcohol | 1.002 | 0.999, 1.006 | 0.1910 | 0.996 | 0.992, 0.999 | **0.0072** | 1.006 | 1.003, 1.008 | **<0.0001** | 1.001 | 0.997, 1.004 | 0.7566 |
| Smoking (Pack-years) | 1.022 | 1.019, 1.025 | **<0.0001** | 0.991 | 0.987, 0.994 | **<0.0001** | 1.001 | 0.997, 1.004 | 0.7456 | 1.004 | 1.000, 1.007 | **0.0290** |
| Body Mass Index (BMI) | 0.952 | 0.918, 0.987 | **0.0071** | 0.999 | 0.978, 1.020 | 0.9008 | 1.033 | 1.006, 1.059 | **0.0146** | 0.977 | 0.944, 1.011 | 0.1794 |
| HR=Hazard Ratio; 95% CI=95% Confidence Interval | | | | | | | | | | | | |

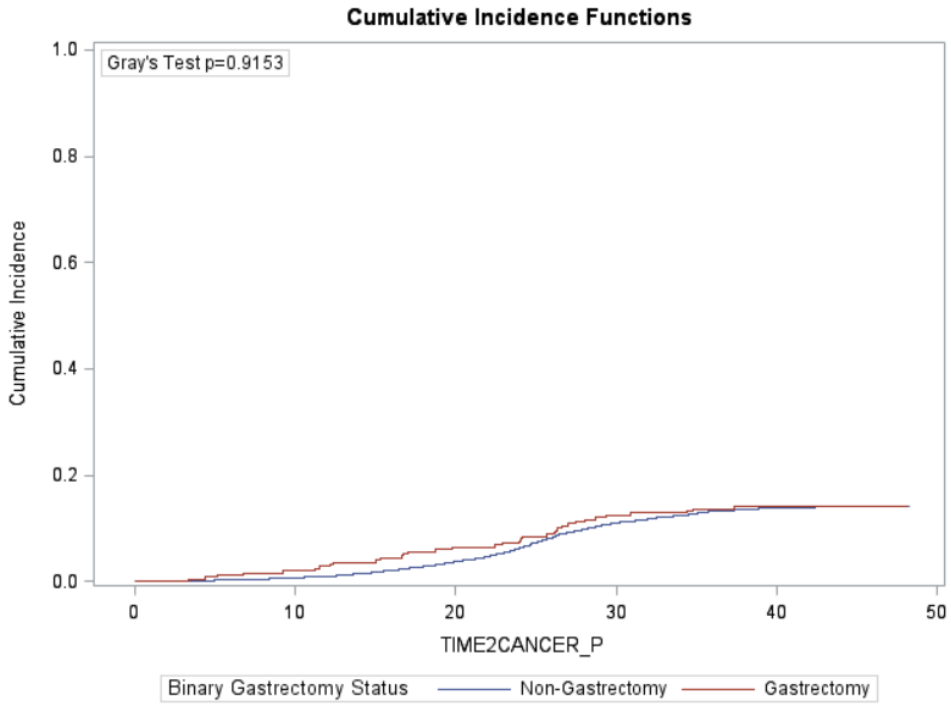
| Table 56: FINAL Multivariate Cox Regression Model – Lung Cancer – Accounting for Competing Risks | | | |
|---|---|---|---|
| Model | Hazard ratio | (95%9 CI) | p |
| Gastrectomy | 1.242 | 0.814 1.896 | 0.3143 |
| Age | 0.964 | 0.945 0.984 | **0.0004** |
| Alcohol | 1.002 | 0.999 1.006 | 0.1641 |
| Smoking (Pack-years) | 1.022 | 1.019 1.025 | **<0.0001** |
| BMI | 0.960 | 0.925 0.995 | **0.0267** |
| Stage 2 Hypertension | 0.639 | 0.439 0.928 | **0.0188** |

**Prostate Cancer**

**Life-Table – Prostate Cancer**

Figure 19 is a life table CIF curve, examining the cumulative incidence of prostate cancer, between the GS and the NGS groups. From the CIF figure, it appears that the curves remained very close to each other for the duration of the follow-up period, suggesting the cumulative incidence of prostate cancer was very similar for men with and without a gastrectomy. Gray's Test for Equality of Cumulative Incidence Functions confirmed that there was no significant difference, p=0.9153.

Figure 19: Time to Development of Prostate Cancer Life-Table Survival Curve by Gastrectomy Status




**Cox Regression – Multivariate Analyses – Prostate Cancer**

In the multivariate model shown in Table 55, neither gastrectomy nor BMI appeared to have any substantial effect on prostate cancer incidence. Age, alcohol use, and smoking were protective in the models shown, but these findings are hard to interpret because of the substantial effect prostate specific antigen (PSA) screening had on incidence. This screening was unavailable until the end of the 1980's, but had come into widespread use in the US by the mid 1990's. Presumably the gentle S-shaped curve in Figure 17, best seen in the more numerous NGS men, reflects this development with the steepest increase in cumulative incidence occurring about 25 years after the baseline exam, i.e. about 1992. A significant number of the oldest men had died by that time and may not have had much opportunity to have prostate cancer diagnosed through PSA screening. Since age is well known to be a very strong risk factor for clinically important prostate

cancer, the protective coefficient in the multivariate model is almost certainly due to confounding.

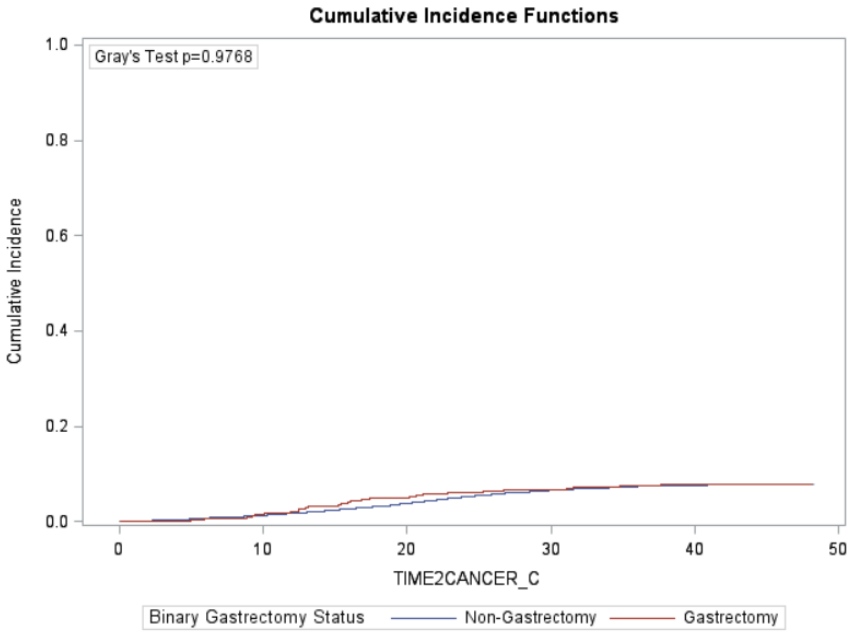
The protective effect of smoking and alcohol use is harder to explain; perhaps men inured to taking health risks were less likely to be screened.

**Colorectal Cancer**

**Life-Table – Colorectal Cancer**

Figure 20 is a life table CIF curve showing the incidence of colorectal cancer, between the GS and the NGS groups over the course of the HHP follow-up period. From the CIF figure, it appears that the cumulative incidence was very similar between the GS and NGS groups. There was an increase beginning around 10 years after study entry, plateauing at around 25 years. Gray's Test for Equality of Cumulative Incidence Function confirmed there was no significant difference between the curves, p=0.9768.

Figure 20: Time to Development of Colorectal Cancer Life-Table Cumulative Incidence Function by Gastrectomy Status



**Cox Regression – Multivariate Analyses – Colorectal Cancer**

Referencing Table 55, having a gastrectomy prior to entering the HHP showed neither an increased nor decreased risk of developing prostate cancer. After age, ounces of alcohol consumed per month, smoking (in the form of pack-years), and BMI were added to the multivariate model, previous gastrectomy still bore no relation to the risk of developing colorectal cancer. Alcohol and BMI showed increased risk when added to the model and the estimates remained constant from model to model. Both of these attributes have been reported to be predictors of colorectal cancer in other prospective studies. Colorectal cancer shares with prostate cancer the important influence of screening on incidence rates. However, the frequency and efficacy of colorectal cancer screening has not changed as sharply through time as did PSA screening. See Table 57 for the final multivariate model.

Table 57: FINAL Multivariate Cox Regression Model – Colorectal Cancer – Accounting for Competing Risks

| Model | Hazard ratio | (95%9 CI) | p |
|---|---|---|---|
| Gastrectomy | 1.062 | 0.717 1.571 | 0.7648 |
| Age | 0.995 | 0.981 1.010 | 0.5433 |
| Alcohol | 1.005 | 1.003 1.008 | **<0.0001** |
| Smoking (Pack-years) | 1.001 | 0.998 1.004 | 0.5378 |
| BMI | 1.029 | 1.003 1.056 | **0.0314** |
| CHD Prevalence | 0.491 | 0.276 0.876 | **0.0161** |
| CVA Prevalence | 0.355 | 0.112 1.118 | 0.0768 |
| Diabetes Prevalence | 0.886 | 0.661 1.187 | 0.4177 |
| Hypertension Medications | 1.385 | 1.065 1.800 | **0.0150** |

**Stomach Cancer**

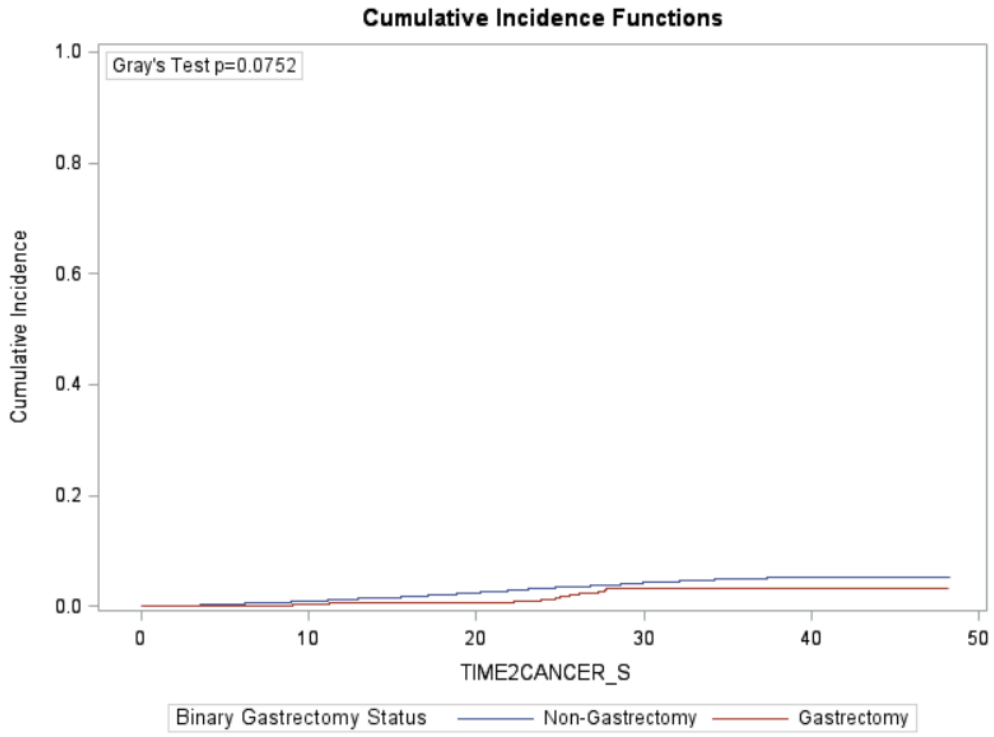
**Life-Table – Stomach Cancer**

There has been substantial concern and a considerable literature focused on the risk of gastric cancer after partial gastrectomy for benign conditions. A recent review summarized the epidemiological data as favoring an increased risk in European

populations, but a decreased risk in Japan.[87] This could be explained by the higher rates of gastric cancer in Japan where the endemic rate in non-operated individuals may have exceeded the rate of remnant cancers in those with a previous gastrectomy.

Figure 21 is a life table CIF curve showing the cumulative incidence of stomach cancer, between the GS and the NGS groups. The CIF curves did show separation between the two groups. Gray's Test for Equality of Cumulative Incidence Function provided a p-value of p=0.075 which was suggestive of a protective effect. Certainly there was no evidence of substantial increased risk for gastric cancer in either group.

Figure 21: Time to Development of Stomach Cancer Life-Table Cumulative Incidence Function By Gastrectomy Status



**Cox Regression – Multivariate Analyses – Stomach Cancer**

Referencing Table 55, having a gastrectomy prior to entering the HHP was associated with an approximate 41% decrease in the risk of gastric cancer. Before adjustment for confounders this did not attain statistical significance (p=0.0799). However, after adjustment for other differences between the GS and NGS men, especially smoking and BMI, the calculated level of protection increased slightly to 46% and was statistically significant (HR =0.0476. with a p-value of 0.048). See Table 58 for the final model controlling from age, alcohol, smoking, BMI and significant univariate predictors.

Table 58: FINAL Multivariate Cox Regression Model –Stomach Cancer – Accounting for Competing Risks

| Model | Hazard ratio | (95%9 CI) | p |
|---|---|---|---|
| Gastrectomy | 0.533 | 0.290 0.982 | **0.0437** |
| Age | 1.008 | 0.989 1.027 | 0.4080 |
| Alcohol | 1.000 | 0.997 1.004 | 0.7871 |
| Smoking (Pack-years) | 1.004 | 1.001 1.008 | **0.0222** |
| BMI | 0.989 | 0.955 1.023 | 0.5099 |
| CHD Prevalence | 0.684 | 0.375 1.247 | 0.2150 |
| CVA Prevalence | 0.205 | 0.029 1.468 | 0.1145 |
| Diabetes Prevalence | 0.692 | 0.467 1.024 | 0.0657 |
| Stage 1 Hypertension | 0.772 | 0.605 0.987 | **0.0390** |

**Discussion (Lung, Prostate, Colorectal, and Stomach Cancer)**

At baseline/Exam 1 there were substantial differences between the GS and NGS participants. GS participants were one year older and substantially thinner than their NGS counterparts. They weighed 11 pounds less on average and had lower BMI and skinfold values. In addition, their blood pressures were lower and their levels of non-fasting glucose, cholesterol, and triglycerides were lower as compared to their NGS counterparts. However, this group of post-gastrectomy men all had a history of peptic ulcer disease - a condition that is associated with smoking – and cigarette smoking was substantially more common and persistent in the GS men than in their non-operated peers. Indeed, it seems likely that some of these men may have gone to surgery because they were unable to quit smoking despite their ulcer disease.

As expected from their high smoking rates, the men in the gastrectomy group had a substantially higher risk of lung cancer than other men (many of whom were also smokers). That this excess was mainly due to smoking rather than to stomach surgery can be inferred from the prior literature on smoking and lung cancer and is indicated here in the Multivariate Cox Regression models which show a hazard ratio of 1.54 for gastrectomy before smoking is even put in the model, which drops to 1.37 and becomes non-significant when smoking is added. It is interesting that BMI is a significant protective factor in this model and further decreases the apparent importance of gastrectomy. This raises the question as to whether excessive thinness in the older GS men could contribute to cancer incidence.

While we had hypothesized that remnant cancers might lead to an increase in gastric cancer in the GS men, we found no support for this. Indeed, gastric cancer incidence was 41% less common in the GS men than in the rest of the cohort (univariate HR = 0.59, p = 0.08), a finding that became statistically significant when confounders were

added to the model (Table 55 and 58). Of course, a simple but unproven explanation for a 40-50% reduction in gastric cancer incidence in the GS men is that they have, perhaps, fewer gastric epithelial cells at risk of transformation. However, we saw no clear inverse association between percentage of stomach removed and incidence of gastric cancer. It is likely that the overall rate of stomach cancer is higher in these Japanese men than in US Caucasians, so the risk from remnant cancer in this population might not be applicable elsewhere in the US. Remnant cancers have apparently not been elevated in Japanese gastrectomy follow-up studies[87] It is interesting to note that smoking was a predictor of gastric cancer in this cohort, a finding that has been previously reported.[88]

We hypothesized that prostate cancer and colorectal cancer, both of which are reported to be somewhat related to obesity and to occur much more commonly in Western countries than in resource poor environments, might be less common after gastrectomy because of the lower body weight. However, the Cox regression models do not suggest any association between gastrectomy and these two cancers. A somewhat surprising finding was that for these two cancers and for lung cancer, age appeared to be protective in the Cox models. Since increasing age is a well-known risk factor for cancer, the reason for this is not clear. It could be that there is a birth cohort effect in the population such that older men are less Westernized and have more protection against diseases of Western lifestyle; or it could be that the large competing risks in old age are somehow distorting the expected age effect. The introduction of the age variable did not affect the gastrectomy coefficient very much for any of these cancers, so it seems unlikely that it has much impact on the conclusions. Another issue is that incidence rates for both of these diseases can be distorted by screening programs, in which the GS and NGS groups might have had different participation rates. These limitations

notwithstanding, the conclusion that gasterectomy has little effect on either prostate cancer or colorectal cancer incidence is consistent in both the univariate and multivariate models and seems firm.

**Limitations**

There are some limitations to this study that should be considered. The strength of having extensive baseline assessments and a large control group in which all the same assessments were made is counter-balanced by the limited size of the gastrectomy group. Since, the study focused solely on Japanese-American men living in Hawaii, these findings may not be generalizable to populations who are non-Japanese or to women. Also, it cannot be assumed that the rates of cancer observed in Hawaii are reflective of rates in other parts of the US or around the world. Another limitation is that non-participation, a form of selection bias, may have had an influence in the study. At study start, the study samples of 8,006 Japanese-American men were those who responded to the initial inquires of an estimated 14,000 men on the island of Oahu. It cannot be assumed that those who chose to participate had the same prevalence of exposures, nor incidence of disease as those who did not participate. If participants differed from non-participants in both respects, it could distort the findings.

In sum, undergoing a gastrectomy appeared to have a protective effect on the subsequent incidence of stomach cancer but not of any other cancers under study.

**SYNTHESIS/CONCLUSION**

Within the context of a major prospective study of heart disease and cancer incidence in Japanese American men who resided in Oahu, Hawaii, we studied the long term effect of having a prior partial gastrectomy among 347 participants who had undergone surgery for peptic ulcer disease. At study enrollment, there were substantial differences between the GS and NGS participants that reproduced results observed by Glober et al.[15] and Stemmerman et al.[16] GS participants were one year older and weighed 11 pounds less on average than their NGS counterparts. Their BMI, skinfold values, and blood pressures were also lower as were their levels of non-fasting blood glucose, serum cholesterol, and triglycerides. Presumably, because of their selection through a history of peptic ulcer disease, the post-gastrectomy men were much more likely to be current or former smokers than their non-operated peers.[89,90,91] Indeed, it seems likely that some of these men may have gone to surgery because they were unable to quit smoking (Which likely exacerbated their ulcer symptoms) despite their ulcer disease.

Over 25 years of follow-up, study participants lost weight in both groups with aging, but men in the GS group remained substantially thinner on average than their NGS peers. In addition, the GS men had a 50% lower incidence of T2DM, less insulin resistance (assessed at 25 years of follow-up), and a suggestive decrease in incidence of metabolic syndrome. Simultaneous adjustment for multiple measurements of adiposity did not explain the striking effects on diabetes incidence or glucose metabolism, so the data provide a *prima facie* case for metabolic effects of gastrectomy that operate through other mechanisms. The difference in insulin resistance between groups was likewise not explained by the difference in obesity, suggesting that if the surgery, per se, confers protection against development of T2DM, that the mechanism likely operates through protection against insulin resistance.

There was little difference in the incidence or mortality from coronary heart disease between men with and without a gastrectomy, supporting the suggestion of Stemmerman et al.[16] that men in the GS group were protected from the known risk for heart disease associated with smoking by the favorable effects of the surgery on other coronary risk factors. However, they were not protected from the effects of smoking on other outcomes and they experienced much higher mortality from lung cancer and emphysema which drove an overall elevated mortality in the GS group. The excess lung cancer rate was not statistically significant after the difference in smoking was taken into account.

Although the GS group had lower blood pressure than the NGS group at enrollment in the study, this difference disappeared and was even slightly reversed among participants in the 25 year follow-up examination. The erosion of the blood pressure advantage was associated with an excess of stroke deaths in the GS group which involved hemorrhagic and ischemic types. The incidence of non-fatal stroke in GS men was also elevated by 50% over that of NGS men with more than one in six men having a stroke over 33 years average follow-up. Unfortunately, because blood pressure was not systematically re-measured during the 19 year interval between the third and fourth examinations (or subsequently), we do not have a clear picture of how quickly the blood pressures in the two groups converged and crossed, nor do we have measurements that would be needed to explore whether the larger increase in blood pressure with age in the gastrectomy group was sufficient to explain their increase in stroke.

There have been a number of reports of late gastric cancer after gastrectomy (so-called “remnant cancers”), but we found no evidence of any late excess in the operated men studied here. Reports from Japan have suggested that remnant cancers are not a common problem there.[86] In this cohort, gastrectomy appeared to have a *protective*

effect on the subsequent incidence of stomach cancer. The average reduction in incidence was roughly proportional to the average percentage of gastric tissue resected (as estimated from the medical records) suggesting that this protection may have resulted from removing a substantial proportion of the gastric mucosal and epithelial cells available for malignant transformation.

There are substantial differences between the gastric surgery performed in these Japanese-American men and the various bariatric procedures that are being increasingly used in the US and around the world. The HHP men were not obese at the time of their surgery, they all had peptic ulcer disease, and presumably many had residual *Helicobacter Pylori* infections for undefined periods of the follow-up presented here. Because of the differences in weight and the frequency of smoking, no direct comparisons with the bariatric population can be made for survival or for the frequency of smoking-related diseases. There are also substantial differences in the surgical procedures used for ulcer disease in the mid-twentieth century and bariatric surgery done today. Despite these differences, the immediate metabolic effects documented in the HHP cohort are quite similar to the short term effects reported after bariatric procedures. It is notable, also, that we found no differences in these effects according to type of surgical reconstruction or reported amount of stomach removed. Thus, there may be some commonalities associated with all of these forms of partial gastrectomy.

We think that optimistic findings in the HHP that likely apply to bariatric gastrectomies are, the long lasting favorable effects on glucose metabolism and on blood lipid levels. A cautionary note that deserves attention in the growing bariatric population is whether the steeper increase in systolic blood pressure with age is reproduced and whether there is any long term increase in the incidence of stroke. Overall, however, when known

smoking-related health effects are discounted, the geriatric experience of the gastrectomy group in the Honolulu Heart Program is reassuring.

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