Life Cycle Changes in Nutritional Status and Adult Mortality

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This paper was prepared for presentation at the Annual Meetings of the Population Association of America, April 1, 2011.

This research is funded by grant AG-032003 from the National Institute on Aging.

Abstract

The Barker hypothesis has focused attention on the long-term effects of differences between the environment a child experienced in the womb and the environment in which it finds itself living at young ages. However, changes in nutritional status are not limited to the earliest ages. This paper examines whether change in BMI between early adult ages and later ages (45-68) is associated with increased risk of death from seven groups of causes after age 45. The analysis is based on longitudinal data from the Honolulu Heart Program, a study of men of Japanese ancestry born in 1900-1919 living on the island of Oahu in 1965.

Most of the groups of causes of death are associated with BMI at both young adult and older ages. However, only one group of causes is closely associated with changes (generally increases) in BMI. That group of causes is dominated by coronary heart disease and other heart diseases.

The association between various measures of obesity and the risk of death is well established.(McGee and Diverse Populations 2005; Collaboration, Whitlock et al. 2009) Although there are better measures of obesity, clinical practice and many studies have relied on the body-mass indicator, BMI, and the evidence suggests little advantage to the use of more refined measures.(Flegal and Graubard 2009; Taylor, Ebrahim et al. 2010) BMI values greater than 30 measured in middle-age have consistently been shown to be associated with excess risk of death.(Adams, Schatzkin et al. 2006) Very low values, less than 22.5, have also been shown to be associated with excess risk. Many researchers have suggested that the risk associated with low BMI is exaggerated as a result of weight loss resulting from disease processes in the months or years preceding death.

There is also substantial evidence that obesity at young adult ages is associated with increased risk of disease processes associated with the development of heart disease and vascular disease. For example, a study in Sweden showed that BMI measured at ages 18-20 was associated with the risk of the onset of coronary heart disease and stroke at ages 40-55.(Falkstedt, Hemmingsson et al. 2007) Data from the CARDIA study show an association between higher BMI at ages 18-30 and the prevalence of coronary artery calcification 15 years later. (Lee, Jacobs et al. 2007) A study of young adults 15-34 years of age showed an association between BMI and early signs of atherosclerosis.(McGill, McMahan et al. 2002)

Although the basic associations of BMI with mortality are well established, few studies have examined BMI as a measure that changes with age. We know less about the implications of a lifetime of obesity compared to obesity in middle age resulting from weight gains during the adult ages. A study in Norway examined the associations of mortality with BMI measured among adolescents aged 14-19 and at later ages (81% of the measurements at later ages were at 40-54).(Engeland, Bjorge et al. 2004) High adolescent BMI was associated with excess risk of death in the years following the adult measurement of BMI. After adjusting for adult BMI, the association with adolescent BMI was no longer significant in men, but it persisted in women. Janssen, et al. used data from NHANES III on self-reported weight ten years before the survey to examine the effects of long-term obesity on the prevalence of the metabolic syndrome, insulin resistance and type-2 diabetes.(Janssen, Katzmarzyk et al. 2004) Among individuals aged 30-64,

the associations with being overweight were higher in those who reported being overweight ten years earlier than among those who were previously of normal weight.

Most studies of mortality risks include some control for the effects of smoking. However, proper controls for smoking are especially important for studies of obesity and mortality. Several studies suggest an interaction between current smoking and obesity such that the optimal weight for smokers is slightly higher than the optimal for non-smokers. In addition, smokers often have lower BMI. The follow-up of the NIH-AARP Diet Study found that among older men the relative risk of death associated with BMI values greater than 25 were lower among current and former smokers than among never-smokers. However, low levels of BMI were associated with greater excess risk among smokers.(Adams, Schatzkin et al. 2006) A similar pattern was found in an analysis of the Cancer Prevention Study II.(Calle, Thun et al. 1999) Both of these studies relied on self-reported weight. Some of this interaction is probably a result of the fact that higher BMI may be protective against mortality from lung cancer and, in smokers, other tobacco-related cancers.(Leung, Lam et al. 2011)

Methods

The Honolulu Heart Program (HHP) was designed to examine the effects of diet on the risk of heart disease in men in a single ethnic group. It began in 1965 with a sample of 8,006 men of Japanese ancestry born between 1900 and 1919 who were living on the island of Oahu. The sample was drawn from Selective Service exams conducted in 1940-'42 for WWII. The first exam included weight, standing height, sitting height, blood pressure and information about their educational attainment, smoking, diet, and physical activity. The selective service records reported their weight when they were about 20-40 years old. The 1965 baseline also included self-reported weight at age 25. Mortality surveillance continued through 1998.

The analysis is based on Gompertz regressions of the risk of death as a function of BMI and other risk factors. The Gompertz model assumes that log of the hazard function is a linear function of age. These models assumed a gamma distribution of frailty. The applicability of Gompertz regression was confirmed by examining the log of the hazard function derived from Cox regressions.

The BMI reported in the Selective Service records, BMI_{SS}, are probably more accurate than the BMI based on retrospective reports of weight at age 25, BMI_{25}. However, the BMI_{SS} were taken at ages 20-40 and, therefore, are not strictly comparable. The BMI_{25} were used to adjust the BMI_{SS} to reflect BMI age 25. The difference between BMI at later ages and self-reported BMI_{25} was used as an estimate of the rate of change in BMI after age 25. This rate of change was used to adjust BMI_{SS} to age 25. The values of unadjusted BMI_{SS} were used for men 45-49 at baseline who were close to age 25 at the time of their Selective Service exams. The resulting adjusted BMI is an estimate of BMI at early ages, BMI_E. Data from Selective Service Exams were available to only 7,777 men. For 224 additional men, BMI_E was based on self-reported weight at age 25.

A baseline model was developed to examine the relationship between baseline BMI at ages 45-68 ("late BMI" or BMI_L) and mortality during the follow-up. To reduce the chance of reverse causation (disease causing weight loss in the few years preceding death), the first five years of observation were dropped from the analysis. However, dropping the first five years of

observation had no appreciable effect on the results. The analysis was based on a sample of 7653 individuals followed for up to 28 years. There were 4660 deaths.

Each regression included controls for age at baseline which is equivalent to controlling for birth year (cohort). This adjusts for trends in mortality over the follow-up period. Smoking status was controlled using four categories: never-smokers, current smokers and two groups of former smokers. Former smokers were divided into those who reported quitting before age 45 ("early quitters") and those who reporting quitting at a later age ("late quitters"). The early quitters are assumed to provide a better estimate of the effect of quitting smoking permanently. Regressions using this classification found that the coefficient for late quitters was exceedingly close to half of the coefficient for current smokers. Therefore, a single marker identified current smokers with a value of 1 and late quitters with a value of 0.5. Other controls were included for education (two binary markers for high school graduate and at least some college) and a measure of exercise based assumed oxygen consumption rates for a list of activities. These controls were dropped from any regressions in which they were not significant at the 0.10 level.

This model was applied to the 13 most frequent causes of death and to the remaining causes as a group. The data for each cause were also examined separately by smoking status (current-, former-, and never-smokers). In each regression, competing causes were treated as censoring. Causes of death were then combined to form seven groups according to the shape of their association between BMI_L.

The fitted regressions for the seven causes of death groups were then combined to produce an estimate of the relationship between BMI_L and all-cause mortality for smoking groups. This process started by creating estimated life tables for each of the seven causes for five groups defined by smoking and education. For this purpose, the current smokers, who are 43.8% of the sample, were divided into two groups by education attainment: those with less than a high school education and those with high school or more. For each of these five groups, the life tables by cause were combined to get an all-cause life table using standard multiple-decrement life table techniques. The life tables for the five groups were then combined into a single life table by fixing the proportions in each group at age 45.

For the life tables, age was set at 50 to reflect the effects of obesity in the more recent cohorts. The exercise variable was fixed at the overall mean, 328. The mean exercise was not observed to differ by smoking status. The other covariates were fixed at the levels shown in Table 1. For each smoking group, the five regressions were used to estimate the proportion surviving to each age 45-100. A final life table was produced by fixing the distribution by smoking status at age 45 (Table 1).

Once this baseline model was established, early-adult BMI (BMI_E) from the adjusted selective service records was added to the regression models for each group of causes. This analysis began by assuming a quadratic relationship between BMI_E and mortality with BMI_E terms that were not significant being removed. Then the model was expanded to test whether there was an association with changes in BMI between age 25 and later ages.

Results

Table 2 presents the characteristics of the sample.

Figure 1 shows the distribution of BMI_E and BMI_L. At younger ages, the sample was concentrated in the lower portion of the "normal" range with a mean of 21.4. By the later ages, the mean had increased to 23.8 with a concentration around the lower end of the "overweight" category. The small proportion obese (only 3% at the older ages) severely limits what we can learn about obesity. However, these data provide an excellent opportunity to examine the effects of low BMI and to identify the levels of risk associated with BMI in the high "normal" and low "overweight" ranges.

During the follow-up period, there 4,660 deaths after the first five years of follow-up. Five underlying causes were responsible for the majority of deaths (Figure 2). The most common cause was accidents, injuries, etc. (ICD-9 "E" codes) which accounted for 18.2% of deaths. Neoplasms of the digestive system (150-159, 13.8%) and of the respiratory system (160-165, 8.1%) were the second and fifth leading causes. The third leading cause was cerebrovascular disease (430-438, 10.8%) and ischemic heart disease (410, 9.3%) was the fourth leading cause.

The causes were divided into seven groups based on the shape of their association with BMI_L and their relation to smoking. Two causes do not exhibit an association with BMI_L: other neoplasms (140-239) and diseases of the nervous system and mental disorders (290-359). These causes were combined for the analysis into Group A. They were responsible for 13.2% of deaths. Group B includes five causes (17.8% of deaths) that show a linear association with BMI_L (Figure 2): Neoplasms of the lymphatic system (200-208), acute myocardial infarction (410), other CHD (410-414), and other diseases of the circulatory system, and other causes not otherwise stated (240-289,680-759, 780-799). The other groups show a quadratic association with BMI_L (Figures 2 and 3).

Figure 3 shows the risks for Groups C and D, both of which are associated with smoking. Both show a "reverse J-shape" relationship with BMI_L. Group C is neoplasms of the respiratory system (160-165, 8.1%) which decline with BMI_L up to about 25 after which the risk rises again. Group D combines bronchitis, emphysema, asthma, etc. (490-496) and all other diseases of the respiratory system (the rest of 490-519) which are responsible for 7.8% of deaths. For these causes, the risk declines sharply with increasing BMI_L then level off after a BMI_L of about 25. The high relative risks at low BMI is not affected by reverse causation caused by weight loss preceding death. Using all years of risk, the risk of death at a BMI_L of 20 relative to a BMI_L of 25 is 2.41 (95% C.I.: 1.87-2.96). Dropping the first five years of risk leads to an estimate of 2.29 which is well within the confidence interval of the previous estimate.

Group E is cerebrovascular diseases (430-438, 10.4%) which shows a strong J-shape with the risks rising very rapidly above a BMI_L of about 24 (Figure 4). The final two groups show very similar U-shaped curves with minima near a BMI_L of about 25. Group F includes neoplasms of the digestive system (150-159, 13.8%) and other diseases of the digestive system (520-579, 2.3%). Group G is dominated by accidents, injuries, poisonings, etc. (E codes, 18.2%), but includes the other categories of deaths not included in the other groups (5.5%).

Table 3 presents the regression estimates for linear and quadratic effects for BMI_L and the relative risks associated with smoking status for each group of cases. Lung cancer is the only cause for which those who quit smoking before age 45 have elevated risk. The risk among early quitters is 3.0 times that of those who never smoked. The relative risk for current

smokers is 24.7 and for late smokers it is 5.4. When the risk among late quitters is fixed at the square root of that for smokers (Table 3), these risks become 24.4 and 4.9.

Table 4 presents the coefficient estimates for models that add BMI_E. The causes in group A (other neoplasms and neurologic conditions) were not associated with BMI_L. Those causes also show no associated with BMI_E. Groups D (Bronchitis and other respiratory conditions) and group E (cerebrovascular) which have a quadratic association with BMI_L show no association with BMI_E.

Group B, which is dominated by IHD and other CHD, is associated linearly with BMI_E – higher levels are associated with increased risk. However, it is clear whether these are independent effects. Adding BMI_E reduces the coefficient on BMI_L substantially: from 0.106 to 0.068. Although the coefficient on BMI_E (0.100) is much larger than the coefficient on BMI_L, the two are not significantly different. This is consistent with a model in which the important determinant of risk is years of exposure to higher BMI.

Groups F (cancers of the digestive tract and other digestive conditions) and G (accidents and miscellaneous causes) both show a quadratic association with BMI_L but a positive association with BMI_E. Higher BMI_E is always associated with increased risk. In both cases, the coefficients on the linear and quadratic terms on BMI_L are virtually unchanged by the addition of BMI_E.

The other groups showed a quadratic association with BMI_L. In the case of the group of miscellaneous causes and the group that includes bronchitis and other respiratory disease, the effect of BMI_E is significant, substantial and independent of the effect of BMI_L. When BMI_E is added to the model for these causes, the coefficients on BMI_L and BMI_L^2 remain virtually unchanged. For both groups of causes, the effect of BMI_E leads to a relative risk of 2.25 for a BMI_E of 30 compared to BMI_E of 20.

The most complex pattern appears for group C, respiratory and intrathoracic malignancies. For these causes, the effects of BMI_L and BMI_E are both quadratic. For any given value of BMI_E, the effect of BMI_L still has an essentially inverse-J shape with the highest risks for BMI_L under 20. However, the effects indicated for BMI_E show the lowest risks at the lowest observed values; the relative risks decline from the lowest ages up to a BMI_E of about 23 often level off in the range 23-27. Although the quadratic suggests the risks drop off at higher levels of BMI_E, only 1.4% of the sample has a BMI_E over 28. Therefore, at younger ages the BMI values below 23 are associated with the lowest risk, however, staying at these low levels until later ages is associated with increased risk.

This complex association between respiratory neoplasm and BMI is due to an interaction between smoking and BMI_L. This association is only found for smokers. In a regression including BMI_L, BMI_E and an interaction between smoking and BMI_L, the interaction is significant ($p=0.011$) and negative implying higher BMI_L lowers risk. However, the coefficient on BMIL is positive, but not significant ($p=0.327$) which suggests no association with BMI_L among no-smokers and early quitters. No other cause of death exhibited a significant interaction between BMI and smoking status.

We next tested whether gaining or losing weight between age 25 and later ages contributes to the models. Gains and loses were expressed as a percentage of BMI_E. Only one group of causes exhibited an associated with weight change: group B which is dominated by CHD and other heart diseases. The effects of gains and losses were consistent and of very

similar magnitude: gaining weight increased risk and losing weight reduced risk. When these were included in the model, the effect of BMI_L was no longer significant. Therefore, the final model for group B states that each point of BMI_E increases the risk of death to this group of causes by 17.9%. Each one percent increase raises risk by a factor of 1.5%. In this population, the average increase in BMI was 9.6% which is associated with an increased risk of causes in group B by 16.3%.

Figure 5 shows the relative risks death from all causes at age 50, 75, and 85 by BMI_L after controlling for BMI_E. These rates come from the life table that aggregates together all causes of death and all smoking groups. The figure gives the values for individuals with a BMI_E of 21 (the mean). These curves are J-shaped with the curve flattening out a bit at the older ages. The minimum mortality occurs for a BMI_L of 23.4.

Summary and Conclusions:

The data from the Honolulu Heart Program provide important insights into the association among older Japanese-American men between BMI and mortality. Because BMI over 30 was rare in this population, this sample provides a detailed picture of the effects of BMI in the normal and overweight range.

High BMI at age 25 was always associated with increased risk of death after age 50. This was true for all causes of death except for groups A (neurological conditions and miscellaneous neoplasms which show no association with BMI) and F (digestive neoplasms and other digestive diseases). For the fit to all-cause mortality, each 1 point increase in BMI at age 25 increased the risk of death by about 20%.

The association between mortality and BMI at later ages is more complex. Most causes show a non-linear association with BMI. For most causes, the risks increase above a BMI of 25. This is especially true of cerebrovascular diseases. The two striking exceptions are respiratory neoplasms, and bronchitis and other respiratory diseases. The risk of these causes decline sharply as BMI increases then levels off after a value of about 25. For respiratory neoplasms, this appears to be due to a simple linear relationship between BMI and mortality that is only found among smokers. Among current smokers, the risk of death from respiratory neoplasms declines by about 11% per one point increase in BMI.

The analysis of all-cause mortality looks very complex when we add in the percentage change in BMI between younger and older ages. Higher BMI at younger ages is associated with high mortality, but BMI at later ages appears to be negatively associated with mortality. However, change in BMI with age is associated with a large increase in mortality. This confusing picture becomes clearer when we examine the individual causes. The only group of causes associated with the change in BMI is group B which is dominated by heart diseases. Each one percentage point increase in BMI between early and later adult ages is associated with an increase in risk by a factor of 1.5%.

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Table 1: Covariates Used for Life Tables Summarizing the Effects of BMI by Cause of Death

		Never Smokers	Early Quitters	Late Quitters	Current Smokers	
					Less than High School	High School or Greater
Distribution		30%	10%	15%	28%	17%
Education						
	High School	35%	35%	35%	None	80%
	Some College of More	10%	10%	10%	None	20%
Exercise		328	328	328	328	328

Table 2: Characteristics of the Sample of Japanese-American Men living in Hawaii in 1965, Born 1900-1920.

Variable	N	Mean (%)	Range
Age:	8006	54.4	46-68
45-49	1859	23.2%	
50-54	2775	34.7%	
55-59	1593	19.9%	
60-64	1336	16.7%	
65-68	443	5.5%	
Height	8003	64.1 inches	58-70
Weights: Baseline	8001	139.1 pounds	93-202
Selective Service Exam	7777	129.6	99-196*
Self-Report for Age 25	7645	129.8	99-196*
BMI	8001	23.84	16.5-33.1
Education: High School	2773	34.6	
College	831	10.4%	
Smoking: Current Smoker	8004	43.8%	
Former Smoker		26.1%	
Exercise	7939	328	241-655

Notes: * These weights were limited to 45-89 kilograms.

Table 3: Regression Parameter Estimates of the Association between for Seven Groups of Causes of Death Mortality and BMI at Ages 45-68, Age and Smoking Status Japanese-American Men Living in Hawaii Born 1900-1920.

		Age (Cohort)	BMI	BMI-squared	Smokers Current*	Smokers Quit before 45
Flat		0.006	---	---	0.213	---
COD Nos. 5 and 7	p-value	0.478	N.S.	N.S.	0.036	N.S.
Linear		0.030	0.106	---	0.650	---
Nos. 4, 9, 10, 14, 19	p-value	<0.001	<0.001	N.S.	<0.001	N.S.
Respiratory Neoplasms		-0.028	-0.618	0.012	3.491	1.188
No. 3	p-value	0.12	0.047	0.061	<0.001	0.003
Bronchitis & Other Respiratory Diseases		0.014	-0.815	0.014	1.100	---
Nos. 15 & 16	p-value	0.210	<0.001	0.002	<0.001	N.S.
Cerebrovascular		0.029	-0.402	0.010	0.553	---
No. 13	p-value	0.006	0.034	0.014	<0.001	N.S.
Digestive Diseases		0.016	-0.665	0.014	0.711	---
Nos. 2 & 17	p-value	0.099	0.003	0.002	<0.001	N.S.
Accidents, etc. & Misc.		0.042	-0.418	0.009	0.460	---
Nos. 1 8, 11, 12, 18, 20	p-value	<0.001	<0.001	<0.001	<0.001	N.S.

Gopertz regression with gamma frailty with controls for education and exercise.

* The coefficient for smokers who quit after age 45 is set equal to half of the coefficient for current smokers.

Table 4: Regression Parameter Estimates of the Association between for Seven Groups of Causes of Death and BMI at Age 25 and BMI at Ages 45-68
Japanese-American Men Living in Hawaii Born 1900-1920.

		BMI at 25		BMI at 45-68	
		BMI	BMI^2	BMI	BMI^2
A: Flat		---	---	---	---
	p-value	N.S.	N.S.	N.S.	N.S.
B: Linear		0.091	---	0.068	---
	p-value	<0.001	N.S.	<0.001	N.S.
C. Respiratory Neoplasms		0.864	-0.017	-0.654	0.012
	p-value	0.035	0.055	0.032	0.054
D. Bronchitis, etc		0.060	---	-0.806	0.014
	p-value	0.045	N.S.	<0.001	0.003
E. Cerebrovascular		---	---	-0.384	0.009
	p-value	N.S.	N.S.	0.043	0.019
F. Digestive Diseases		---	---	-0.639	0.013
	p-value	N.S.	N.S.	0.003	0.003
G. Accidents, etc. & Misc.		0.069	---	-0.392	0.008
	p-value	<0.001	N.S.	<0.001	0.002

Gopertz regression with gamma frailty with controls for age, smoking, education and exercise.

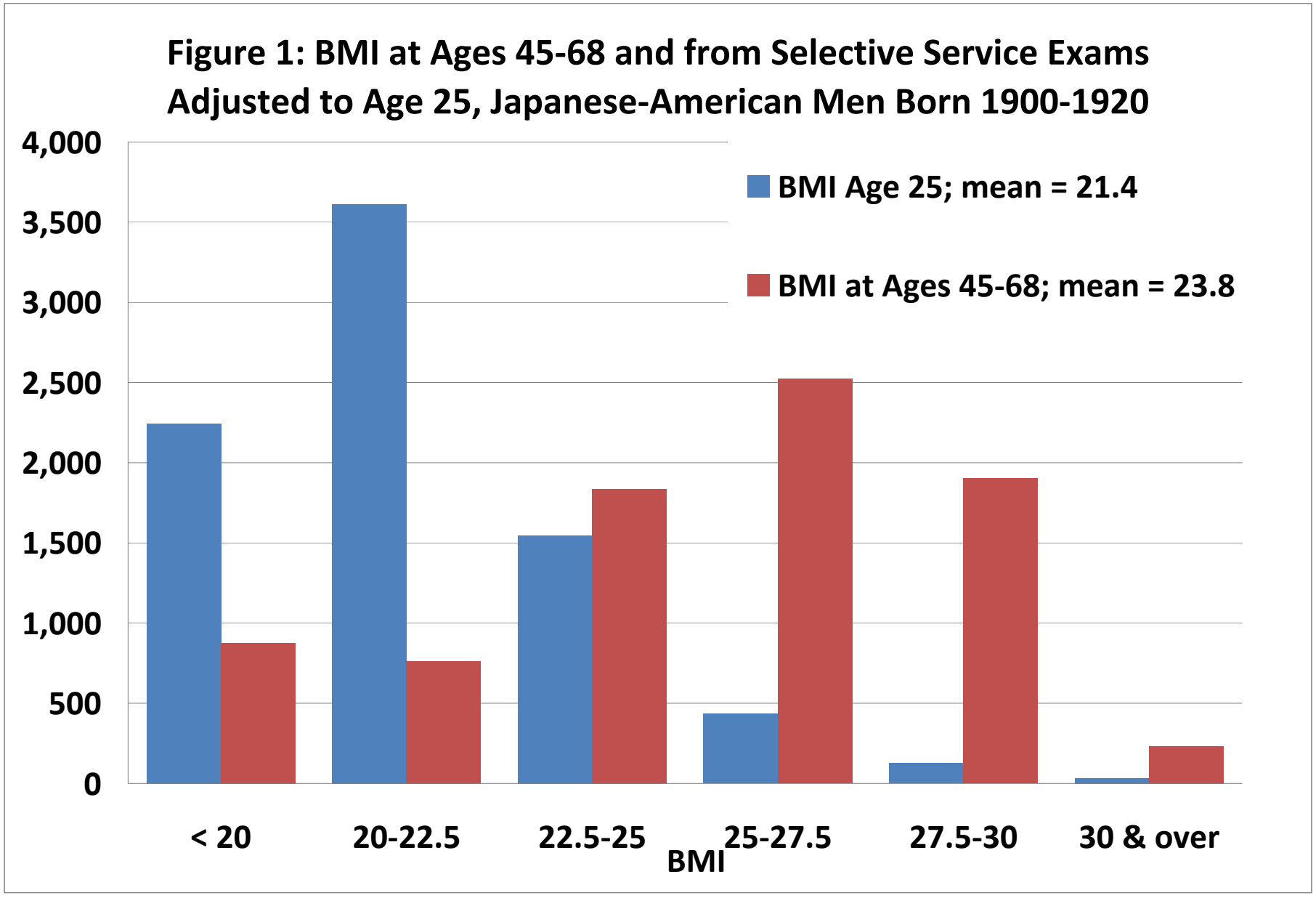
Figure 1: BMI at Ages 45-68 and from Selective Service Exams
Adjusted to Age 25, Japanese-American Men Born 1900-1920
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
BMI Age 25; mean = 21.4
BMI at Ages 45-68; mean = 23.8
< 20
20-22.5
22.5-25
25-27.5
27.5-30
30 & over
BMI

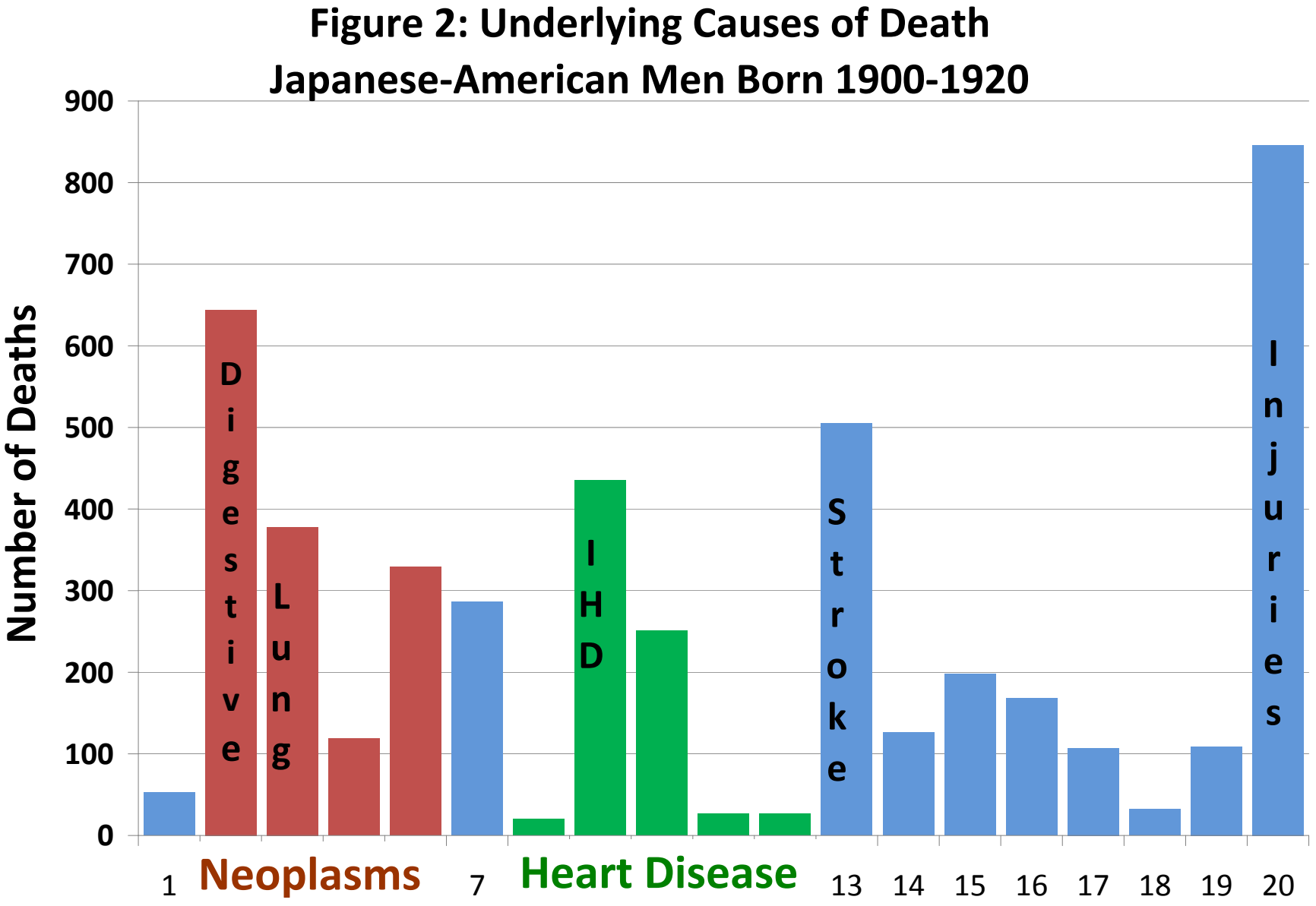
Figure 2: Underlying Causes of Death
Japanese-American Men Born 1900-1920
Number of Deaths
900
800
700
600
500
400
300
200
100
0
Digestive
Lung
IHD
Stroke
Injuries
1
Neoplasms
7
Heart Disease
13
14
15
16
17
18
19
20

Figure 3: Relative Risk of Death from Lung Cancer and Respiratory Infections

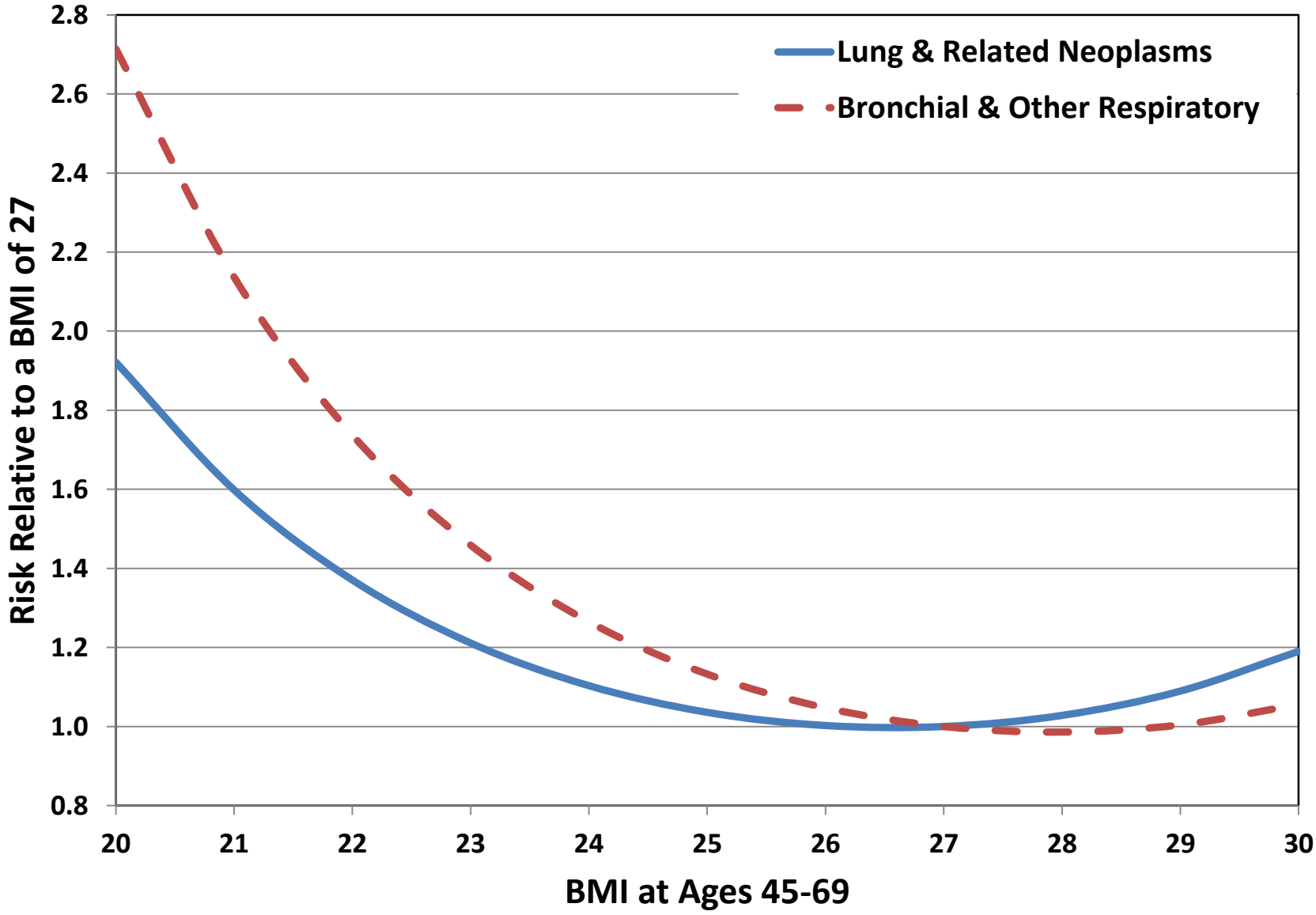

Figure 4: Relative Risk of Death from Four Groups of Causes

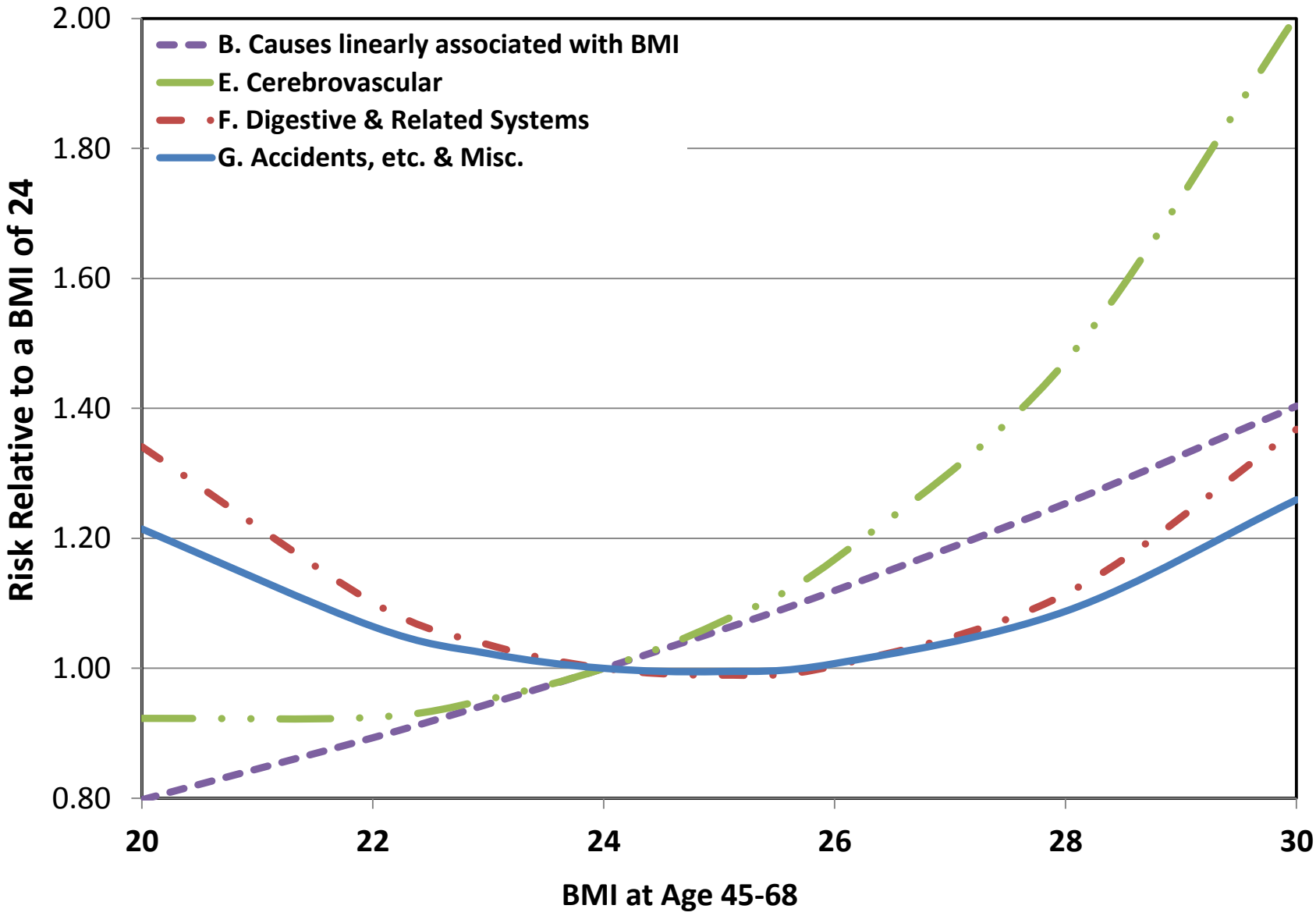

Figure 5: Mortality Rates at Ages 50, 75, and 85 by BMI at Middle Age Relative to a BMI of 23.5 with BMI at Age 25 of 21.0