Favorable Cardiovascular Health, Compression of Morbidity, and Healthcare Costs

Forty-Year Follow-Up of the CHA Study (Chicago Heart Association Detection Project in Industry)

Editorial, see p 1702

BACKGROUND: We examined the association of cardiovascular health at younger ages with the proportion of life lived free of morbidity, the cumulative burden of morbidity, and average healthcare costs at older ages.

METHODS: The CHA study (Chicago Heart Association Detection Project in Industry) is a longitudinal cohort of employed men and women 18 to 74 years of age at baseline examination in 1967 to 1973. Baseline measurements included blood pressure, cholesterol, diabetes mellitus, body mass index, and smoking. Individuals were classified into 1 of 4 strata of cardiovascular health: favorable levels of all factors, 0 factors high but ≥1 elevated risk factors, 1 high risk factor, and ≥2 high risk factors. Linked Medicare and National Death Index data from 1984 to 2010 were used to determine morbidity in older age. An individual's all-cause morbidity score and cardiovascular morbidity score were calculated from *International Classification of Disease, Ninth Revision* codes for each year of follow-up.

RESULTS: We included 25 804 participants who became ≥65 years of age by 2010, representing 65% of all original CHA participants (43% female; 90% white; mean age, 44 years at baseline); 6% had favorable levels of all factors, 19% had ≥1 risk factors at elevated levels, 40% had 1 high risk factor, and 35% had ≥2 high risk factors. Favorable cardiovascular health at younger ages extended survival by almost 4 years and postponed the onset of all-cause and cardiovascular morbidity by 4.5 and 7 years, respectively, resulting in compression of morbidity in both absolute and relative terms. This translated to lower cumulative and annual healthcare costs for those in favorable cardiovascular health ($P<0.001$) during Medicare eligibility.

CONCLUSIONS: Individuals in favorable cardiovascular health in early middle age live a longer, healthier life free of all types of morbidity. These findings provide strong support for prevention efforts earlier in life aimed at preserving cardiovascular health and reducing the burden of disease in older ages.

Norrina B. Allen, MPH, PhD
Lihui Zhao, PhD
Lei Liu, PhD
Martha Daviglus, MD, PHD
Kiang Liu, PhD
James Fries, MD
Ya-Chen Tina Shih, PhD
Daniel Garside, MS
Thanh-Huyen Vu, MD
Jeremiah Stamler, MD
Donald M. Lloyd-Jones, MD, ScM

Correspondence to: Norrina B. Allen, MPH, PhD, Department of Preventive Medicine, Northwestern University, 680 N Lake Shore Drive, Suite 1400, Chicago, IL 60611. E-mail norrina-allen@northwestern.edu

Sources of Funding, see page 1700

Key Words: cardiovascular diseases ■ morbidity ■ mortality ■ prevention and control ■ risk factors

Clinical Perspective

What Is New?

- This study presents the first information on the impact of cardiovascular health in middle age and the burden of morbidity, both all-cause and cardiovascular, in older age.
- Individuals in favorable cardiovascular health in middle age live a longer and healthier life than those with cardiovascular risk factors.
- Individuals in favorable cardiovascular health have a lower cumulative burden of morbidity and more years of healthy life.
- Important from a societal perspective, individuals in favorable cardiovascular health not only live longer but also have lower cumulative healthcare costs.

What Are the Clinical Implications?

- Our findings highlight the importance of prevention.
- At the individual level, living a longer and healthier life free of major morbidity can provide strong motivation to maintain and improve cardiovascular health across the life span.
- At the population and healthcare system levels, these findings directly support the need to improve prevention efforts and to target them earlier in life, before the development of adverse risk factor levels (ie, primordial prevention).
- Our data suggest that the resultant reductions in morbidity could translate to large savings in healthcare spending at the national level.

The burden of cardiovascular disease (CVD) is expected to increase dramatically over the next several decades, with estimates that 40.5% of the US population will be living with CVD by 2030.[1] Primordial prevention (ie, preventing the development of risk factors, not just preventing disease once risk develops) may represent the most effective means of reducing the burden of CVD[2] and was a key concept in guiding the development of national goals to improve the cardiovascular health of the United Sates, including the American Heart Association's 2020 Impact Goals[3] and the Healthy People 2010 Goals.[4] Favorable cardiovascular health in middle age has consistently been associated with decreased all-cause and cardiovascular mortality later in life, resulting in 5.8 to 9.5 additional years of life.[5] Beyond mortality, favorable cardiovascular health results in even more dramatic reductions in the risk for incident CVD events[6,7] and other major chronic diseases later in life.[8,9]

To date, little is known about how favorable cardiovascular health affects the overall burden and severity of morbidity in older age. The goal of this study was to determine whether favorable cardiovascular health is associated with longer, healthier lives or whether it simply extends life at the cost of increasing morbidity and cost.

METHODS

Sample

The CHA study (Chicago Heart Association Detection Project in Industry) is a longitudinal prospective investigation of 39 522 men and women (Asian, black, Hispanic, white, and other) 18 to 74 years of age at baseline in 1967 to 1973 and employed in the Chicago area.[10] Data were collected on demographic, medical history, and medical treatment by questionnaire; measurement of height, weight, heart rate, casual blood pressure and ECG; and collection of blood for measurement of serum total cholesterol and plasma glucose 1 hour after a 50-g oral glucose load. The study was approved by the institutional review board at Northwestern University, and all participants signed an informed consent.

The CHA cohort has been followed for >40 years since baseline through personal contact, National Death Index data, and linked Medicare files from 1984 through 2010. In this study, we included CHA participants who were ≥65 years of age during follow-up and enrolled in Medicare fee for service. We excluded individuals missing baseline risk factor levels or demographic information. The final study cohort for this analysis included 25 804 individuals who became ≥65 years of age by 2010, representing 65% of all original CHA participants (Figure I in the online-only Data Supplement).

Favorable Cardiovascular Health

Favorable cardiovascular health was defined as having favorable levels of all major cardiovascular risk factors, including blood pressure, cholesterol, diabetes mellitus, body mass index, and smoking (Table 1). Individuals without a favorable cardiovascular health profile were further classified into 3 mutually exclusive categories based on their risk factor levels: 0 high risk factors but ≥1 elevated above favorable levels, 1 high major risk factor, and ≥2 high major risk factors. Favorable, elevated, and high risk factor levels are defined in Table 1 according to appropriate clinical guidelines.

Morbidity Scores

All-cause morbidity was defined with the Gagne comorbidity score, a well-validated comorbidity score designed specifically for use with administrative (ie, Centers for Medicare & Medicaid Services [CMS]) data and based on *International Classification of Diseases, Ninth Revision* discharge diagnosis codes.[11] The score includes the following conditions (weights): metastatic cancer (5), congestive heart failure (2), dementia (2), renal failure (2), weight loss (2), hemiplegia, alcohol abuse, any tumor, cardiac arrhythmias, chronic pulmonary disease, coagulopathy, complicated diabetes mellitus, deficiency anemias, fluid and electrolyte disorders, liver disease, peripheral vascular disorder, psychosis, pulmonary circulation disorders, HIV/AIDS (−1), and hypertension (−1). A higher score represents a greater comorbidity burden.

Cardiovascular morbidity was quantified with a CVD comorbidity score, defined by the sum of the presence of 4 CVDs, including coronary heart disease (including myocardial

Circulation. 2017;135:1693–1701. DOI: 10.1161/CIRCULATIONAHA.116.026252

Table 1. Definitions of Favorable, Borderline, and High Levels of Cardiovascular Risk Factors

	Blood Pressure	Cholesterol	Diabetes Mellitus	Body mass index, kg/m^2	Smoking
Favorable	Untreated SBP ≤120 mm Hg and DBP ≤80 mm Hg	Untreated serum cholesterol <200 mg/dL (<5.17 mmol/L)	No	<25	Nonsmoker
Elevated but not high	Untreated SBP 121–139 mm Hg or DBP 81–89 mm Hg	Untreated serum cholesterol 200–239 mg/dL (5.17–6.18 mmol/L)		25.0–29.9	
High	SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medications	Serum cholesterol level ≥240 mg/dL (≥6.21 mmol/L) or taking cholesterol-lowering medication	Yes	≥30	Current smoker

DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

infarction), peripheral vascular disease, cerebrovascular disease, and chronic heart failure. The score ranged from 0 to 4, with increasing score reflecting a greater burden of CVD.

Scores were examined longitudinally over time for each CHA participant included in these analyses. Comorbid conditions were included in the score if they were present in any of the top 6 discharge diagnoses codes (*International Classification of Diseases, Ninth Revision* codes) for any of the participant's inpatient hospitalization or outpatient visit claims. The score was calculated for each participant at each year of age from 65 (or age in 1984, whichever is older) until death or the end of follow-up. If participants were not hospitalized or seen as an outpatient during any specific year, they were assigned a score of 0 for that year of age. Significant comorbidity was defined as a score of ≥1 consistent with having an intermediate to high risk of 1-year mortality.[11]

Healthcare Costs

We examined differences in average annual costs using Medicare claims for each of our 4 cardiovascular health strata. Average annual costs were calculated as the total cumulative cost divided by the years of follow-up. Cost data from CMS data reflect charges for medical services obtained as a result of an inpatient hospital stay; outpatient services obtained at a hospital, at a clinic, or in a physician's office; and fees for physician services. Because Medicare is considered the primary payer by other insurers, claims for individuals with additional coverage are still sent to CMS; thus, Medicare claims data provide a nearly complete documentation of hospital, home health agency, hospice, skilled nursing facility, and physician charges. Additional details are given in the online-only Data Supplement.

Statistical Analyses

In bivariate analyses, we examined demographic characteristics of included CHA participants stratified by their burden of cardiovascular risk factors. We used χ^2 tests and ANOVA to compare categorical and continuous characteristics of participants across the 4 risk factor strata, respectively. To examine the age at incidence of major morbidity, we restricted these models to the ≈70% (n=17 939 for all-cause morbidity and 18 714 for cardiovascular morbidity) of CHA participants for whom we had Medicare follow-up starting at age 65 and who had morbidity scores of 0 at age 65. We used a penalized spline model to obtain a nonparametric estimate of the mean comorbidity score over ages 65 to 90 for each stratum of cardiovascular health profile.[12] A random intercept was included in the model to take into account the within-individual correlation. We examined the times to 4 events: (1) time to morbidity score reaching 1 or death, (2) time to morbidity score reaching 2 or death, (3) time to morbidity score reaching 3 or death, and (4) time to death. Because censoring precludes estimation of these mean survival times, we used the Irwin restricted mean, which is the mean of the survival time restricted to a given time point and is mathematically equivalent to the area under the survival curve up to the selected restriction time point.[13] We then used the difference among the restricted mean survival times for these 4 events to examine the proportion of life lived with morbidity scores of 1, 2, and ≥3. Analyses were done overall and stratified by sex, morbidity status, and baseline age category (≤ 40, 41–50, >50 years).

Because medical costs are right skewed and heteroscedastic, we used quantile regression to model the median and third quartile (75%) medical costs instead of the mean to determine whether individuals with favorable cardiovascular health profile have lower cumulative and average annual healthcare costs across the range of medical costs. SAS Proc Quantreg was used to fit the model. All models were adjusted for age, sex, race, education, and whether the individual died during follow-up (in overall analyses). We also performed a subgroup analysis among participants who had died during follow-up.

RESULTS

Baseline Characteristics

This study included 25 804 CHA participants, of whom 5.6% had favorable levels of all major cardiovascular risk factors at baseline, 19.0% had ≥1 elevated but no high levels, 40.3% had 1 high level, and 35.1% had ≥2 high cardiovascular risk factor levels (Table 2). Individuals with favorable cardiovascular health at baseline were younger, were more likely to be female, and had a higher education level.

Cardiovascular Health at Younger Ages and Morbidity at Older Ages

With poorer cardiovascular health at baseline, both all-cause and cardiovascular morbidity scores were higher at age 65 and remained higher through age 90 (Figures II and III in the online-only Data Supplement).

Table 2. Demographic Characteristics and Baseline Risk Factors of the Chicago Heart Association Cohort, by Cardiovascular Risk Factor Level

	All Favorable (n=1440)	1 Elevated, 0 High (n=4902)	1 High (n=10 407)	≥2 High (n=9055)	*P* Value
Mean age at baseline, y	36.2	40.5	42.1	45.1	<0.001
Female, %	62.2	40.9	40.7	36.3	<0.001
Black, %	8.4	6.6	8.0	8.0	0.008
Education, %					<0.001
High school or less	42.3	47.7	56.2	65.6	
Some college	19.6	17.4	17.6	16.1	
College graduate	38.1	34.9	26.2	18.3	
Mean body mass index, kg/m^2	22.0	25.0	25.1	27.7	
Obese, %	0	0	4.7	32.3	<0.001
Mean systolic blood pressure, mm Hg	114.4	124.1	133.8	146.6	
Mean diastolic blood pressure, mm Hg	69.6	74.2	79.0	85.6	
Diabetes mellitus, %	0	0	0.9	4.8	<0.001
Hypertension, %	0	0	44.8	85.4	<0.001
Hypercholesterolemia, %	0	0	9.0	41.1	<0.001
Current smoker, %	0	0	40 .6	63.8	<0.001

When examining the cumulative burden of morbidity and the incidence of major morbidity, we restricted our analyses to the 17 939 participants with an all-cause morbidity score of 0 at age 65 and 18 714 participants with a cardiovascular morbidity score of 0 at age 65. Morbidity scores increased linearly with age (Figure 1 and Figures IV and V in the online-only Data Supplement), and individuals with a poorer cardiovascular health at younger ages experienced higher all-cause and cardiovascular morbidity scores from ages 65 through 90. The cumulative morbidity as defined by the area under the morbidity curve (which is equivalent to the sum of morbidity scores from ages 65 through 90) was lower for those with all favorable risk factor levels (P<0.05; Table I in the online-only Data Supplement).

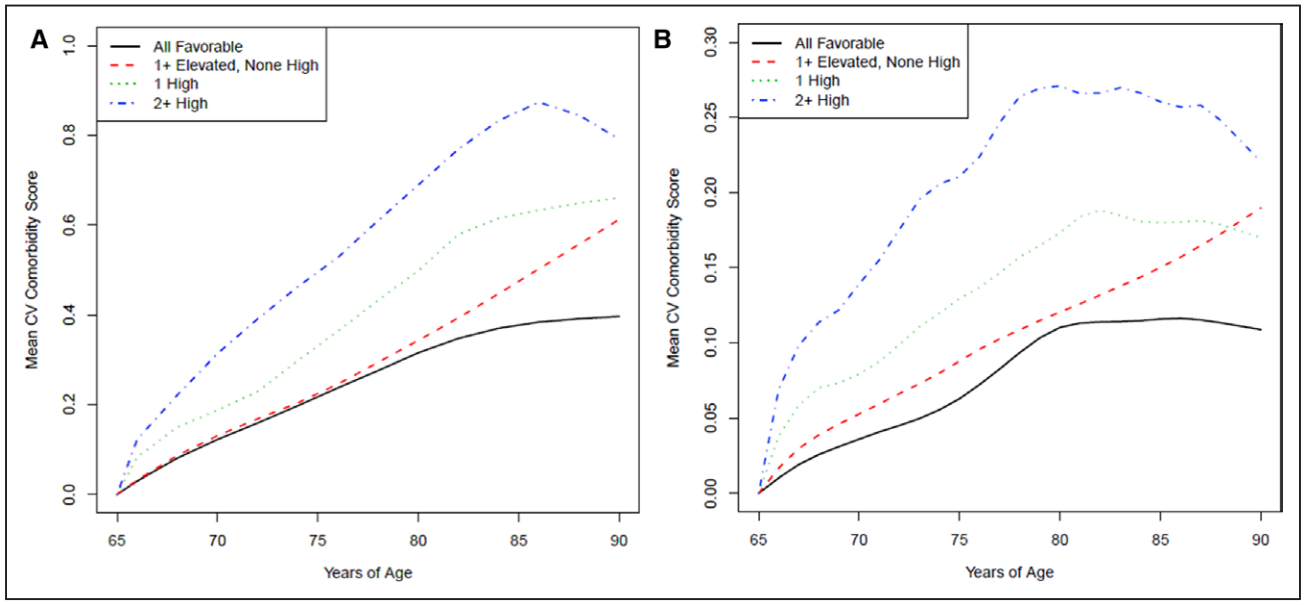


Figure 1. Mean follow-up morbidity score by cardiovascular (CV) risk factor level among those with morbidity score of 0 at age 65 years.
A, All-cause morbidity. **B**, Cardiovascular morbidity.

Morbidity-Free Survival and Compression of Morbidity

Being in favorable cardiovascular health significantly delayed the incidence of major all-cause and cardiovascular morbidity by an average of 4.5 and 6.9 years, respectively, compared with individuals with ≥2 high risk factors (Table I in the online-only Data Supplement and Figure 2). In addition to morbidity incidence, on average, individuals in favorable cardiovascular health lived 3.9 years longer than those with ≥2 high risk factor levels. Similar patterns were seen for women and men (Figures VI and VII in the online-only Data Supplement).

Baseline cardiovascular health was associated with a significant relative compression of both all-cause and cardiovascular morbidity. The proportion of later life (life after age 65 years) lived with any all-cause morbidity ranged from 39% for those with favorable cardiovascular health at younger ages to 50% for those with ≥2 high risk factors and from 23% to 43% for cardiovascular morbidity. We observed minimal absolute compression of all-cause morbidity. Regardless of risk factor strata, individuals lived on average 10 years with some all-cause morbidity (Table II in the online-only Data Supplement); however, the overall burden of major comorbidities that individuals experienced during these 10 years was lower for those people who were in favorable cardiovascular health at baseline, as evidenced by the shorter duration of extremely high levels of morbidity (score ≥3; $P<0.05$ compared with individuals in favorable cardiovascular health). Compression of the absolute number of years lived with morbidity was stronger among men, who lived almost 5 years longer without morbidity and 1 year less with morbidity (Figure VIA in the online-only Data Supplement).

In contrast to all-cause morbidity, cardiovascular health at younger ages was significantly associated with both absolute and relative compression of cardiovascular morbidity at older ages (Figure 2 and Tables II and III in the online-only Data Supplement). Similar to all-cause morbidity, men experienced a greater benefit in terms of the compression of morbidity than women (Table II in the online-only Data Supplement).

Medicare Costs

The differences in average and cumulative morbidity observed across cardiovascular health strata defined at younger ages translated to lower Medicare costs after age 65 among individuals in favorable cardiovascular health compared with those with ≥2 high risk factors (Table 3). Overall, there was a significant trend for increased average annual costs and cumulative costs with greater risk factor burden (P for trend <0.001). When the analysis was restricted to individuals who died during follow-up, patterns were consistent, although there was some attenuation of the P values as a result of reductions in sample size.

Sensitivity Analyses

Findings were consistent when limited to CHA participants who died during follow-up (Figure VIII and Table V in the online-only Data Supplement). After stratification by baseline age categories, similar patterns in the incidence of morbidity and compression of morbidity across all 3 baseline age groups were observed (Figure IX–XI in the online-only Data Supplement). The only difference was in the oldest age group (baseline age >50 in 1967–1973) in whom the cardiovascular health group with elevated but not high levels of cardiovascular risk factors had the longest life expectancy compared with those with favorable levels of all cardiovascular risk factors. This may be due to the existence of preexisting disease at baseline among this older group of participants. When risk factors were examined separately, the presence of each cardiovascular risk factor individually was associated with a higher cardiovascular morbidity score at each year of age from 65 throughout 90, resulting in a greater cumulative cardiovascular morbidity burden for the group with the risk factor compared with those without (Figure XII in the online-only Data Supplement).

DISCUSSION

We found that cardiovascular health status, defined by the presence and severity of cardiovascular risk factors, in young adulthood and middle age is associated with the burden of all-cause and cardiovascular morbidity up to 43 years later. Individuals with favorable cardiovascular health at baseline experienced greater longevity and lower all-cause and cardiovascular morbidity throughout older age, resulting in lower morbidity levels at every age from 65 to 90 and ultimately lower cumulative morbidity levels after age 65. These lower morbidity levels translated at the median into more than $5000 fewer dollars per year and almost $18000 fewer dollars cumulatively being spent by CMS on health care from age 65 on. In general, men experienced a greater benefit in terms of the compression of morbidity resulting from favorable cardiovascular health than women. Individuals in favorable cardiovascular health at younger ages not only live a longer life but live a healthier life and a greater proportion of life free of morbidity.

This study represents some of the first findings that favorable cardiovascular health in middle age is associated with older age at incidence of major morbidity and lower cumulative levels of disability, as well as with healthy, not just greater, longevity. Our findings on the benefits of being in favorable cardiovascular health at younger ages considerably extend the observations of

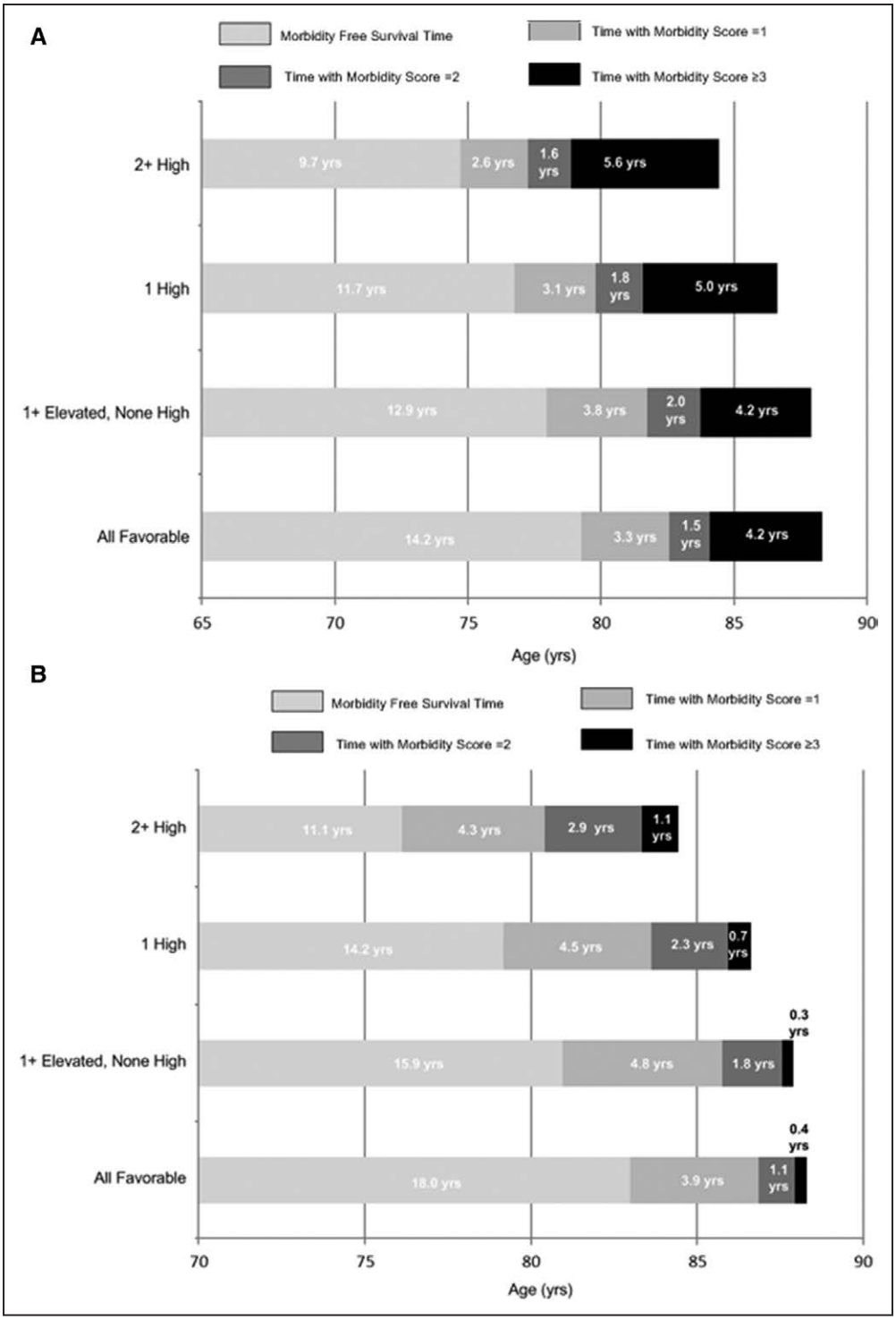


Figure 2. Morbidity-free survival and average time spent with morbidity after age 65 years.
A, All-cause morbidity. **B**, Cardiovascular morbidity.

prior research demonstrating a reduction in the incidence of specific CVDs, as well as cancer,[14] depression,[15] and higher cognitive functioning,[16] along with other favorable outcomes. We found that an increasing burden of cardiovascular risk factors was associated with a longer period of life lived with morbidity in a dose-dependent fashion, thus suggesting that any improvements in cardiovascular health will likely translate to reductions in morbidity in older age.

Favorable cardiovascular health in middle age has previously been shown to be associated with increased longevity.[17] The present study extends prior work to pro-

Table 3. Adjusted Differences in Cumulative and Average Costs, by Cardiovascular Risk Factor Level, Compared With Favorable Cardiovascular Health at the 50th and 75th Percentiles

	Estimate of Increased Cost at 50th Percentile, $	*P* Value	Estimate of Increased Cost at 75th Percentile, $	*P* Value
Cumulative costs				
Risk factor level				
All favorable	Referent		Referent	
≥1 Elevated, none high	841	0.755	1692	0.634
1 High	6547	0.005	13 413	0.0001
≥2 High	17 864	<0.0001	59 625	<0.0001
Average costs				
Risk factor level				
All favorable	Referent		Referent	
≥1 Elevated, none high	2294	<0.0001	4081	<0.0001
1 High	2818	<0.0001	6367	<0.0001
≥2 High	5458	<0.0001	11 488	<0.0001

All costs are adjusted for age, sex, race, education, length of follow-up, and death during follow-up. Because of convergence issues, we used 75.5% and 50.5% quantiles in some models.

vide an understanding of not only how much longer individuals in favorable cardiovascular health live but also what proportion of that increase is due to an extension of healthy life as opposed to a longer life with more disability.

Beyond disease incidence and mortality, healthcare costs represent an important outcome for public health and policy makers. Among a smaller subset of CHA participants followed up through 2004, favorable cardiovascular health has previously been found to be associated with reduced average annual costs and end-of-life costs.[18,19] Our findings extend this work to a broader portion of the CHA cohort and demonstrate that lower morbidity scores among those who were in favorable cardiovascular health at baseline translates to lower average annual and cumulative costs up to 40 years later. These findings support prior literature demonstrating lower healthcare costs for individuals in better cardiovascular health in middle age.[20]

Less is known about favorable cardiovascular health in middle age and its effects on morbidity and mortality. Since Fries[21] first described the theory of compression of morbidity in 1980, most work has focused on the role of health behaviors. Healthy lifestyle behaviors, that is, exercise, normal weight, and not smoking, have been shown to delay the onset of severe disability and to reduce cumulative disability.[22] Also called healthy aging, the compression of morbidity paradigm suggests that prevention strategies may delay the onset of ill health to a greater degree than they delay date of death, thus resulting in a decreased proportion of life with morbidity. Until now, whether favorable cardiovascular health results in a compression of morbidity was unclear. A previous study done among the Lifetime Risk Pooling Project found that at younger index ages individuals in favorable cardiovascular health lived up to 14 years longer free of total CVD, although differences in survival after CVD incidence were less dramatic.[23] Our findings provide some of the first information directly testing whether favorable cardiovascular health is associated not only with an extension life and life lived free of morbidity but with an absolute and relative compression of morbidity.

This study has several important strengths, including the use of a large cohort of >25 000 participants, all of whom were examined in person at baseline to measure cardiovascular risk factors objectively; >40 years of follow-up with nearly complete ascertainment of morbidity with CMS Medicare files; and the inclusion of a large proportion of participants who have been followed up to the end of their life, allowing us to estimate cumulative morbidity and end of life costs. Despite these strengths, there are some limitations to consider. We have only a single baseline measure of cardiovascular risk factor profile and are unable to account for changes in risk factor levels or treatments over time. However, the impact of a single measure of cardiovascular health early in middle age has proven to be predictive of long-term outcomes in previous publications from CHA and in other cohorts.[5,24–26] If anything, our findings are likely to be a conservative estimate because single estimates of risk factor burden are an underestimation of the strength of the associations as a result of regression dilution bias. We lacked informa-

tion on other measures of socioeconomic status beyond income; however, in theory, all participants had equal access to care given their enrollment in Medicare. We used CMS healthcare use files to identify morbidity, mortality, and cost outcomes and therefore we are able to examine only the 70% to 80% of the cohort enrolled in fee for service. We do not know the use for health maintenance organization users during years of health maintenance organization enrollment; however, risk factor level and morbidity status were not associated with health maintenance organization enrollment (data not shown), and thus, this bias should be nondifferential, leading us to underestimate the strength of our associations. We lack outcomes before age 65 and must use *International Classification of Diseases, Ninth Revision* codes to determine morbidity. Those codes have been shown to be reliable for the conditions included in the comorbidity scores in this study and have been used for a multitude of clinical investigations. General agreement between comorbidity scores derived from administrative data and chart review has been >85%.[27] Given the reliability of these scores and their well-documented association with mortality, physical functioning, and health-related quality of life, the Gagne comorbidity score serves as a valid and reliable measure of morbidity in older age.[11,28–30]

CONCLUSIONS

We found that individuals in favorable cardiovascular health in early middle age have lower levels of morbidity, both all-cause and cardiovascular, up to 40 years later in life and experience a lower cumulative morbidity burden translating to reduced average annual healthcare costs. Our findings have important implications for prevention. At the individual level, living a longer and healthier life free of major morbidity can provide strong motivation to maintain and improve cardiovascular health across the life span. At the population and healthcare system levels, these findings directly support the need to improve prevention efforts and to target them earlier in life, before the development of adverse risk factor levels (ie, primordial prevention). Our data suggest that the resultant reductions in morbidity could translate to large savings in healthcare spending at the national level.

SOURCES OF FUNDING

This work was supported by a grant from National Heart, Lung, and Blood Institute of the National Institutes of Health to Dr Allen (R01-60036640). Drs Liu and Shih are supported by Agency for Healthcare Research and Quality R01 HS 020263.

DISCLOSURES

None.

AFFILIATIONS

From Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL (N.B.A., L.Z., L.L., K.L., T.-H.V., J.S., D.M.L.-J.); Institute of Minority Health Research, University of Illinois College of Medicine, Chicago (M.D., D.G.); Department of Medicine, Stanford School of Medicine, CA (J.F.); and Department of Health Services Research, University of Texas MD Anderson Cancer Center, Houston (Y.-C.S.).

FOOTNOTES

Received April 11, 2016; accepted March 1, 2017.

The online-only Data Supplement, podcast, and transcript are available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.026252/-/DC1.

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ; American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123:933–944. doi: 10.1161/CIR.0b013e31820a55f5.
2. Weintraub WS, Daniels SR, Burke LE, Franklin BA, Goff DC Jr, Hayman LL, Lloyd-Jones D, Pandey DK, Sanchez EJ, Schram AP, Whitsel LP; American Heart Association Advocacy Coordinating Committee; Council on Cardiovascular Disease in the Young; Council on the Kidney in Cardiovascular Disease; Council on Epidemiology and Prevention; Council on Cardiovascular Nursing; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Clinical Cardiology, and Stroke Council. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation*. 2011;124:967–990. doi: 10.1161/CIR.0b013e3182285a81.
3. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703.
4. U.S. Department of Health and Human Services: Office of Disease Prevention and Health Promotion–Healthy People 2010. *Nasnewsletter*. 2000;15:3.
5. Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglus ML, Garside D, Dyer AR, Liu K, Greenland P. Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and

life expectancy: findings for 5 large cohorts of young adult and middle-aged men and women. *JAMA*. 1999;282:2012–2018.
6. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791–798. doi: 10.1161/CIRCULATIONAHA.105.548206.
7. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, Greenland P, Van Horn L, Tracy RP, Lloyd-Jones DM. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366:321–329. doi: 10.1056/NEJMoa1012848.
8. Lloyd-Jones DM. Cardiovascular health and protection against CVD: more than the sum of the parts? *Circulation*. 2014;130:1671–1673. doi: 10.1161/CIRCULATIONAHA.114.012869.
9. Daviglus ML, Liu K, Pirzada A, Yan LL, Garside DB, Feinglass J, Guralnik JM, Greenland P, Stamler J. Favorable cardiovascular risk profile in middle age and health-related quality of life in older age. *Arch Intern Med*. 2003;163:2460–2468. doi: 10.1001/archinte.163.20.2460.
10. Stamler J, Dyer AR, Shekelle RB, Neaton J, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. *Cardiology*. 1993;82:191–222.
11. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64:749–759. doi: 10.1016/j.jclinepi.2010.10.004.
12. Fitzmaurice G DM, Verbeke G, Molenberghs G. *Longitudinal Data Analysis*. Boca Raton, FL: Chapman and Hall; 2009.
13. Irwin J. The standard error of an estimate of expectational life. *J Hyg (Lond)*. 1949;47:188–189.
14. Rassmussen-Torvik LJ, Shay CM, Abramson J, Nettleton JA, Friedrich CA, Prizment AE, Folsom AF. The association of AHA ideal cardiovascular health with cancer incidence: the ARIC Study [abstract]. *Circulation*. 2011;124:A13601.
15. Kronish IM, Carson AP, Davidson KW, Muntner P, Safford MM. Depressive symptoms and cardiovascular health by the American Heart Association's definition in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. *PLoS One*. 2012;7:e52771. doi: 10.1371/journal.pone.0052771.
16. Yaffe K, Vittinghoff E, Pletcher MJ, Hoang TD, Launer LJ, Whitmer R, Coker LH, Sidney S. Early adult to midlife cardiovascular risk factors and cognitive function. *Circulation*. 2014;129:1560–1567. doi: 10.1161/CIRCULATIONAHA.113.004798.
17. Ford ES, Greenlund KJ, Hong Y. Ideal cardiovascular health and mortality from all causes and diseases of the circulatory system among adults in the United States. *Circulation*. 2012;125:987–995. doi: 10.1161/CIRCULATIONAHA.111.049122.
18. Daviglus ML, Liu K, Greenland P, Dyer AR, Garside DB, Manheim L, Lowe LP, Rodin M, Lubitz J, Stamler J. Benefit of a favorable cardiovascular risk-factor profile in middle age with respect to Medicare costs. *N Engl J Med*. 1998;339:1122–1129. doi: 10.1056/NEJM199810153391606.
19. Daviglus ML, Liu K, Pirzada A, Yan LL, Garside DB, Greenland P, Manheim LM, Dyer AR, Wang R, Lubitz J, Manning WG, Fries JF, Stamler J. Cardiovascular risk profile earlier in life and Medicare costs in the last year of life. *Arch Intern Med*. 2005;165:1028–1034. doi: 10.1001/archinte.165.9.1028.
20. Willis BL, DeFina LF, Bachmann JM, Franzini L, Shay CM, Gao A, Leonard D, Berry JD. Association of ideal cardiovascular health and long-term healthcare costs. *Am J Prev Med*. 2015;49:678–685. doi: 10.1016/j.amepre.2015.03.034.
21. Fries JF. Aging, natural death, and the compression of morbidity. *N Engl J Med*. 1980;303:130–135. doi: 10.1056/NEJM198007173030304.
22. Chakravarty EF, Hubert HB, Lingala VB, Fries JF. Reduced disability and mortality among aging runners: a 21-year longitudinal study. *Arch Intern Med*. 2008;168:1638–1646. doi: 10.1001/archinte.168.15.1638.
23. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA*. 2012;308:1795–1801. doi: 10.1001/jama.2012.14312.
24. Miura K, Daviglus ML, Dyer AR, Liu K, Garside DB, Stamler J, Greenland P. Relationship of blood pressure to 25-year mortality due to coronary heart disease, cardiovascular diseases, and all causes in young adult men: the Chicago Heart Association Detection Project in Industry. *Arch Intern Med*. 2001;161:1501–1508.
25. Cedres BL, Liu K, Stamler J, Dyer AR, Stamler R, Berkson DM, Paul O, Lepper M, Lindberg HA, Marquardt J, Stevens E, Schoenberger JA, Shekelle RB, Collette P, Garside D. Independent contribution of electrocardiographic abnormalities to risk of death from coronary heart disease, cardiovascular diseases and all causes: findings of three Chicago epidemiologic studies. *Circulation*. 1982;65:146–153.
26. Stokes J 3rd, Kannel WB, Wolf PA, Cupples LA, D'Agostino RB. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham study. *Circulation*. 1987;75(pt 2):V65–V73.
27. Quan H, Parsons GA, Ghali WA. Validity of information on comorbidity derived from ICD-9-CCM administrative data. *Med Care*. 2002;40:675–685. doi: 10.1097/01.MLR.0000020927.46398.5D.
28. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. *Health Qual Life Outcomes*. 2004;2:51. doi: 10.1186/1477-7525-2-51.
29. Fortin M, Bravo G, Hudon C, Lapointe L, Almirall J, Dubois MF, Vanasse A. Relationship between multimorbidity and health-related quality of life of patients in primary care. *Qual Life Res*. 2006;15:83–91. doi: 10.1007/s11136-005-8661-z.
30. Rigler SK, Studenski S, Wallace D, Reker DM, Duncan PW. Comorbidity adjustment for functional outcomes in community-dwelling older adults. *Clin Rehabil*. 2002;16:420–428. doi: 10.1191/0269215502cr515oa.

Favorable Cardiovascular Health, Compression of Morbidity, and Healthcare Costs: Forty-Year Follow-Up of the CHA Study (Chicago Heart Association Detection Project in Industry)

Norrina B. Allen, Lihui Zhao, Lei Liu, Martha Daviglus, Kiang Liu, James Fries, Ya-Chen Tina Shih, Daniel Garside, Thanh-Huyen Vu, Jeremiah Stamler and Donald M. Lloyd-Jones

Circulation. 2017;135:1693-1701
doi: 10.1161/CIRCULATIONAHA.116.026252
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Dr Carolyn Lam: Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to the journal and its editors. I'm Doctor Carolyn Lam, associate editor for the National Heart Center and Duke National University of Singapore. Our feature paper today presents the first information on the impact of cardiovascular health in middle age and the burden of mobility in older age. This exciting data is from the Chicago Heart Association study. First, let me give you your summary of this week's journal.

The first study tells us that patients with long QT syndrome type II are at increased risk of hypoglycemia. First author, Doctor Hilton Cavallius, co-corresponding authors Doctor Tarakov and Hanson from University of Copenhagen, Denmark, noticed that loss of function mutations in HERG, which encodes the voltage gate at potassium channel 11.1, causes long QT syndrome II, but that the specific voltage gate at potassium channels are also present in pancreatic alpha and beta cells and intestinal L and K cells, which secrete glucagon, insulin, and the incretins, glucagon-like peptide one or GLP1, and glucose-dependent insulinotropic polypeptide, or GIP.

All these hormones are crucial for glucose regulation. The authors therefore hypothesize that patients with long QT syndrome II may have increased incretin and beta cell, but decreased alpha cell function and thus, lower glucose levels. To test this hypothesis, they measured secretion of these hormones and cardiac repolarization in response to a six-hour, 75 gram oral glucose tolerance test in 11 patients with long QT syndrome II with functional mutations in HERG with 22 matched healthy participants.

They found that following glucose ingestion, patients with long QT syndrome II displayed exaggerated incretin and endocrine pancreatic function with more than 50% increased levelsq of circulating insulin, GLP1 , and GIP and defective glucagon secretion, causing low plasma glucose levels and thus, increased risk of symptomatic reactive hypoglycemia following the glucose load.

Furthermore, in rats, pharmacological blockade of these voltage gate at potassium channel 11.1 with [inaudible 00:02:43] had similar effects and inhibition of HERG in beta and L cells increased insulin and GLP1 secretion up to 50%. Finally, glucose ingestion aggravated cardiac repolarization disturbances in patients with long QT syndrome II with a 122% greater increase in QT interval in these patients compared to controls. The take home message is that clinicians should be more aware of the risk of hypoglycemia with glucose ingestion in patients with long QT II syndrome and also recognize that this reactive hypoglycemia can further increase the risk of malignant arrhythmia in these patients.

The next paper is the first study to describe the risk of myocardial infarction after discontinuation of thienopyridine therapy in the DAPT study, or dual antiplatelet therapy study. As a reminder, in this trial, after PCI and 12 months of clopidogrel or prasugrel plus aspirin, eligible patients remained on aspirin and

were randomized to continue thienopyridine versus placebo for 18 months. At 30 months, patients stopped the study drug and were observed for three months. In the current study by first author Doctor Schmidt, corresponding author Doctor Mauri, and colleagues from Brigham and Women's Hospital in Boston, Massachusetts. The authors looked at cumulative incidents of myocardial infarction assessed over three months after randomization and three months after study drug discontinuation. They found that discontinuing thienopyridine after either 12 or 30 months was associated with an early increase in myocardial infarction risk, mainly unrelated though to stent thrombosis. The magnitude of risk was highest in the early time frame and lower in patients not treated with the [inaudible 00:04:47] eluting stents.

The authors further compared pateints with DAPT scores above or below 2, and showed that both groups had lower rates of myocardial infarction with continued thienopyridine . Thus, while higher DAPT scores identify patients with a greater absolute ischemic benefit relative to bleeding with continued thienopyridine therapy, discontinuation at 12 months increases the myocardial infarction hazard regardless of DAPT score group.

The next paper describes the impact of depression treatment on one year mortality following acute myocardial infarction. Doctor [inaudible 00:05:28] and colleagues from the University of Missouri School of Medicine in Kansas City looked at the TRIUMPH study, which is an observational multicenter cohort study that enrolled more than 4000 patients with acute myocardial infarction between 2005 and 2008 from 24 US hospitals.

Patients were administered the patient health questionnaire 9 during the index myocardial infarction admission and depression was defined by a score of 10 or above. This was categorized as treated if there was a documentation of a discharged diagnosis, medication prescribed for depression, or referral for counseling, and is untreated if none of these three criteria were documented. Overall, 18.7% of patients met criteria for depression and 30.4% were treated. Compared without depression, patients with treated depression had one year mortality rates that were not different. However, patients with untreated depression had a higher one year mortality when compared to patients without depression. In summary, this study really shows that the association between depression following myocardial infarction and increased mortality differs by depression treatment status at the time of the index myocardial infarction. Patients with untreated depression have a 70 to 90% higher risk of dying at one year after the myocardial infarction than patients without depression or patients with treated depression. These findings should therefore encourage further research to examine the impact of depression recognition and treatment at the time of an acute myocardial infarction.

The final study provides insight into the paradox that folate deficiency is an independent risk factor for congenital heart disease, yet the maternal plasma folate level is paradoxically not a good diagnostic marker of this risk. In the

current study by first author Doctor Wang, co corresponding authors Doctors Chow and Wang, from Fudan University, Shanghai, China. The authors examined six folate related polymorphisms in three independent case control groups comprising 1489 patients with congenital heart disease and 1745 healthy individuals from the Han Chinese population. They found that a specific fidgetin intronic 4 variant was associated with decreased circulating folate levels and increased protection against congenital heart disease. They further showed that increased fidgetin expression inhibited proteasomal degradation of reduced folate carrier 1 and dihydrofolate reductase, thus facilitating [inaudible 00:08:29] uptake and metabolism of folate. Their results therefore demonstrated that folate utilization, rather than the circulating folate levels, determined the preventive effects of folate against congenital heart disease. These findings provide new insights into the relationship of circulating folate levels with congenital heart disease and potentially other folate associated diseases.

Well, that wraps it up for your summaries. Now, for our feature discussion.

Today's feature paper really represents the first data we have that tells us what our cardiovascular health in middle age is doing to us in older age, in terms of both morbidity and longevity. To discuss this paper today, I'm so happy to have the first and corresponding author, Doctor Norrina Allen from Northwestern University in Chicago and Doctor Jarett Berry, associate editor from UT Southwestern. Welcome, both.

Dr Norrina Allen: Thank you very much.

Dr Jarett Berry: Thanks, Carolyn.

Dr Carolyn Lam: Norrina, could I start with you? This represents the 40 year follow up of the Chicago Heart Association detection project and industry. Could you maybe start by telling us a little bit about the Chicago Heart Association study?

Dr Norrina Allen: The Chicago Heart Association study was a large study that recruited almost 40,000 individuals who were employed in Chicago. They did a baseline exam between 1967 and 1973. After that baseline exam, we followed those individuals for over 40 years using their Medicare records, so we've been able to monitor their healthcare utilization and the incidence of disease across their lifetime up through 2010.

Dr Carolyn Lam: Then you measured their cardiovascular health by specific measurements, right? Could you tell us how that was defined and then also how was morbidity burden defined?

Dr Norrina Allen: Of course. We really think the overall burden of cardiovascular health tells us something more than looking at individual risk factors, so we classified each of the CHA participants into one of four groups, and each of those groups was

defined by the level of main cardiovascular risk factors, including blood pressure, BMI, diabetes, smoking, and cholesterol level. We identified people who had favorable levels of all of those risk factors, individuals who had one elevated but not clinically of those high risk factors, individuals who had one high level, or individuals who had two or more high levels. That was based on their baseline exam. Overall we found that about 6% of the CHA participants had favorable levels of all of the risk factors at baseline, 19% had one or more that was elevated, 40% had one high, and 35% had two or more high risk factors, and again this was at the baseline exam when they were young to middle aged.

We then followed them, as I mentioned, using Medicare data and we identified the burden of whole morbidity based on the ICD9 codes in their Medicare record, and we identified the level of morbidity for each year of age, from entry into Medicare, [inaudible 00:11:54] all the way to their death.

Dr Carolyn Lam: And now, drum roll, your findings, they were pretty stunning.

Dr Norrina Allen: Yeah. As you mentioned when you introduced the study, this study is really the first to look at the whole of an individual's later life, meaning not just looking at the incidence of disease or longevity but taking those both into account. What we were particularly interested in was looking at the cumulative burden of morbidity in older age and the relative proportion of life that people live with cardiovascular or all cause morbidity. What we found was that individuals, who at baseline in young and middle age and favorable levels of all major cardiovascular risk factors, lived longer by almost four years but they also delayed the onset of all cause and cardiovascular morbidity by 4 and a half and almost 7 years respectively. What that means is that the proportion of their life that they live with morbidity was much shorter, they lived longer and healthier as compared to individuals who had one or two more high risk factors.

Dr Carolyn Lam: What an important public health message. Jarett, this concept of morbidity compression, tell us your thoughts.

Dr Jarett Berry: This is a really important paper. We've known for a long time, of course, that low risk individuals live longer, but the question of whether or not low risk individuals lived better throughout their life has been incompletely understood. The problem is that because low risk individuals live longer, the question that many have asked is that when we live longer is there a so-called expansion of misery, which some have talked about? That we live longer, but we have the same burden of disease or is that extended time horizon with the extended life span ... is the burden of morbidity compressed into a shorter period of time? In order to do that you need a couple things. You need a very large study that's followed for a very long time. Importantly, not just follow them for a long period of time, but follow enough individuals all the way until death so you know not just the first part of the story but we know the end of the story.

It really wasn't until [inaudible 00:15:18] paper, with not only the very large sample side but the very long term follow up until death, that we've been able to understand that actually low risk status in middle age does actually compress morbidity. This question of morbidity compression is not just an academic question but it actually has potential implications for cost savings and how we think about health care costs in our health care system. It'd be nice to hear [inaudible 00:15:18] thoughts about that as well, what else she found in regard to the Medicare costs.

Dr Norrina Allen: Right. As Jarett mentioned, not only from an individual perspective but at a societal level, what we're interested in is whether being in favorable cardiovascular health actually lowers healthcare costs at the same time as increasing an individual's health and longevity. What we found was that not only do the individuals in favorable health live longer and healthier, but they also have lower cumulative and annual healthcare costs, meaning that from a societal standpoint the compression of morbidity results in healthcare savings. We really think this is a strong method that provides support for earlier prevention efforts not only to improve an individual's quality of life but to reduce the healthcare costs associated with later life morbidity.

Dr Carolyn Lam: Indeed, what an important message to live longer and better and to save societal cost we need to get healthier cardiovascularly in middle age. Now, what really scares me though, is the statistic you told us a bit earlier. Only 6% of the individuals that you studied had a favorable level of all factors. What do you think this implies? What do you think needs to be done?

Dr Norrina Allen: Unfortunately, at this point, it's relatively rare in our population to reach middle age, 40 to 50 years of age, with favorable levels of all major cardiovascular risk factors. I think ... my research is really focused on trying to identify ways and times to intervene, to really help promote cardiovascular health early in life. I really think that we need to work hard to prevent the occurrence of these risk factors and the elevation of these risk factors much earlier in life. That means, even before the age of 40 and much earlier than that, we really need to be focusing on preserving cardiovascular health so that by the time individuals reach later life they can have a good quality of life and a longer, healthier life.

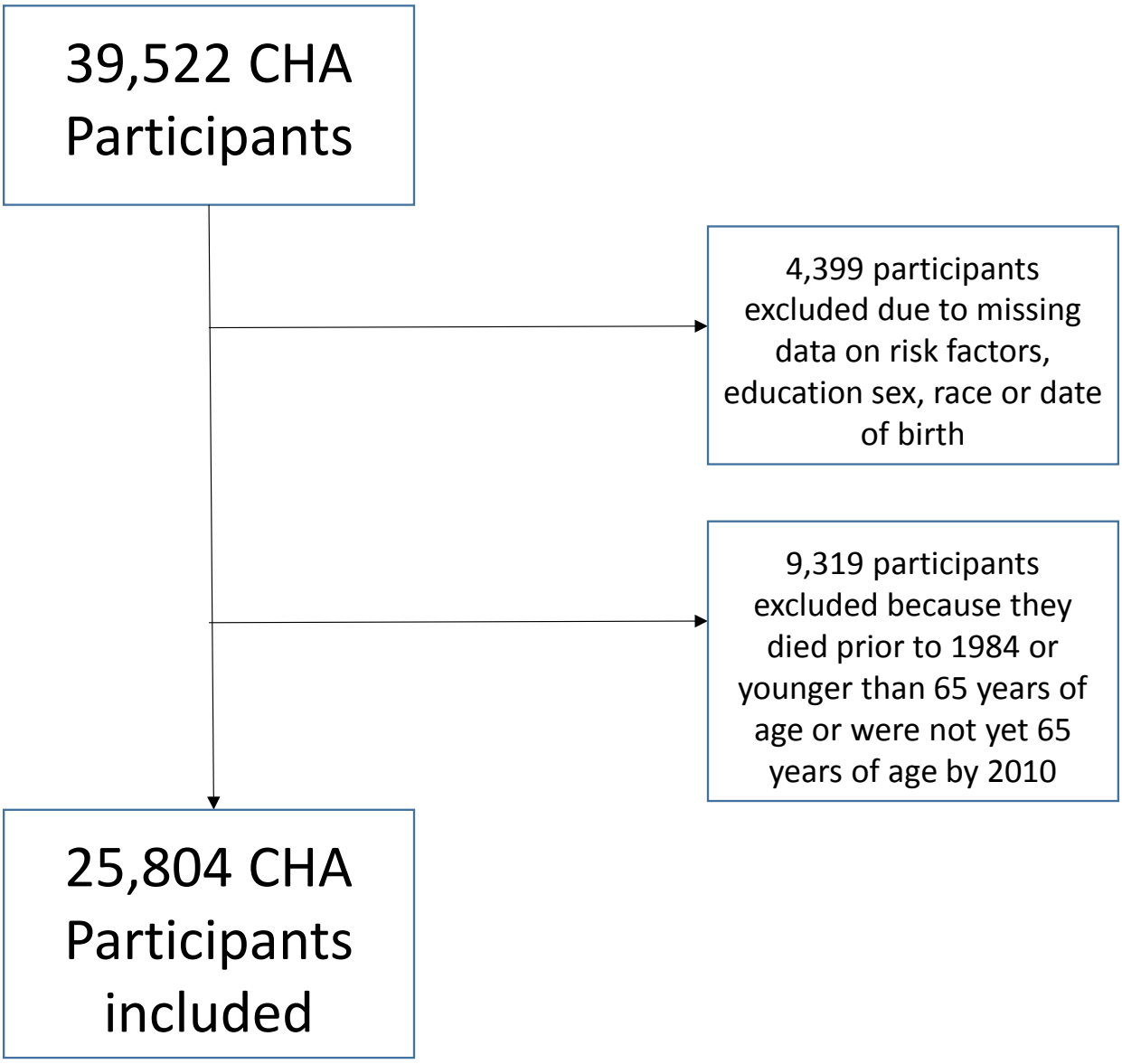
Dr Jarett Berry: I think the issue of the fact that low risk status is rare is that's a challenge that we continue to wrestle with as a society and as investagators interested in this are and how to improve that. When you look at your data, Norrina, I guess one silver lining here is we do see that ... when you look across the strata of risk groups ... it wasn't just the low risk individuals that seemed to benefit. It seemed that there was a little bit of a dose response. The goal obviously is to promote low risk status, but if we could limit the prevalence of those at the highest risk and shift them down a little bit, that could also have potential implications. I'd be interested to hear your thoughts about that.

Dr Norrina Allen: I think that's very accurate. There really is kind of a dose response level, so that every risk factor that's favorable adds a benefit and the more we can do to reduce the high risk factors over time, the better the long term outcomes are likely to be. I do really think prevention doesn't only have to exist before the development of the risk factors, but also there's a benefit to reducing risk factors that may have already developed or are elevated, and to try and reduce their level. I would say that I think that's an interesting next step that we really want to look at and try and think about how best to intervene even at middle age and help improve outcomes much later in life.

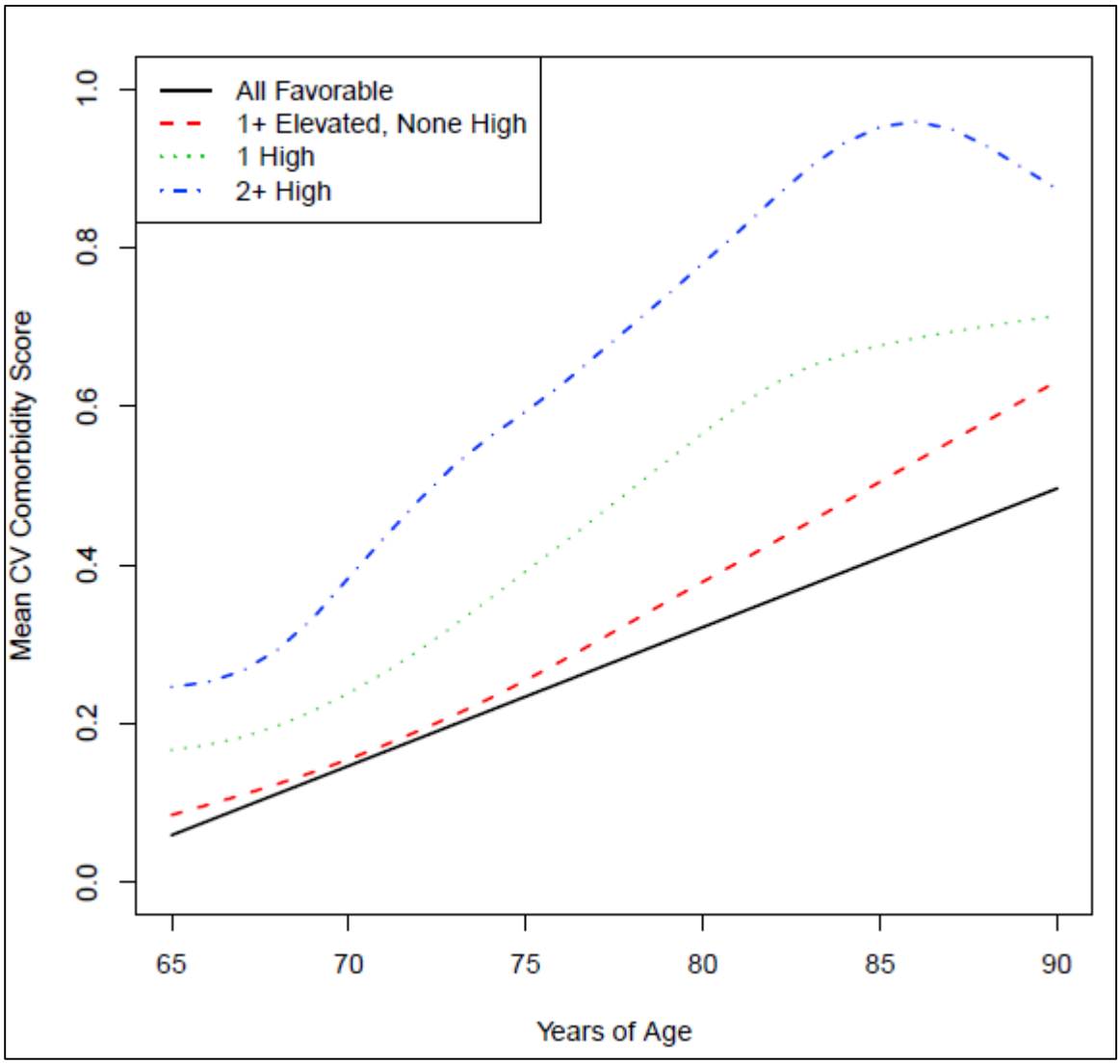
Dr Carolyn Lam: Thank you, listeners, for joining us today. I'm sure you agree, it's such an important message. Share it with your friends and tune in next week.

SUPPLEMENTAL MATERIAL

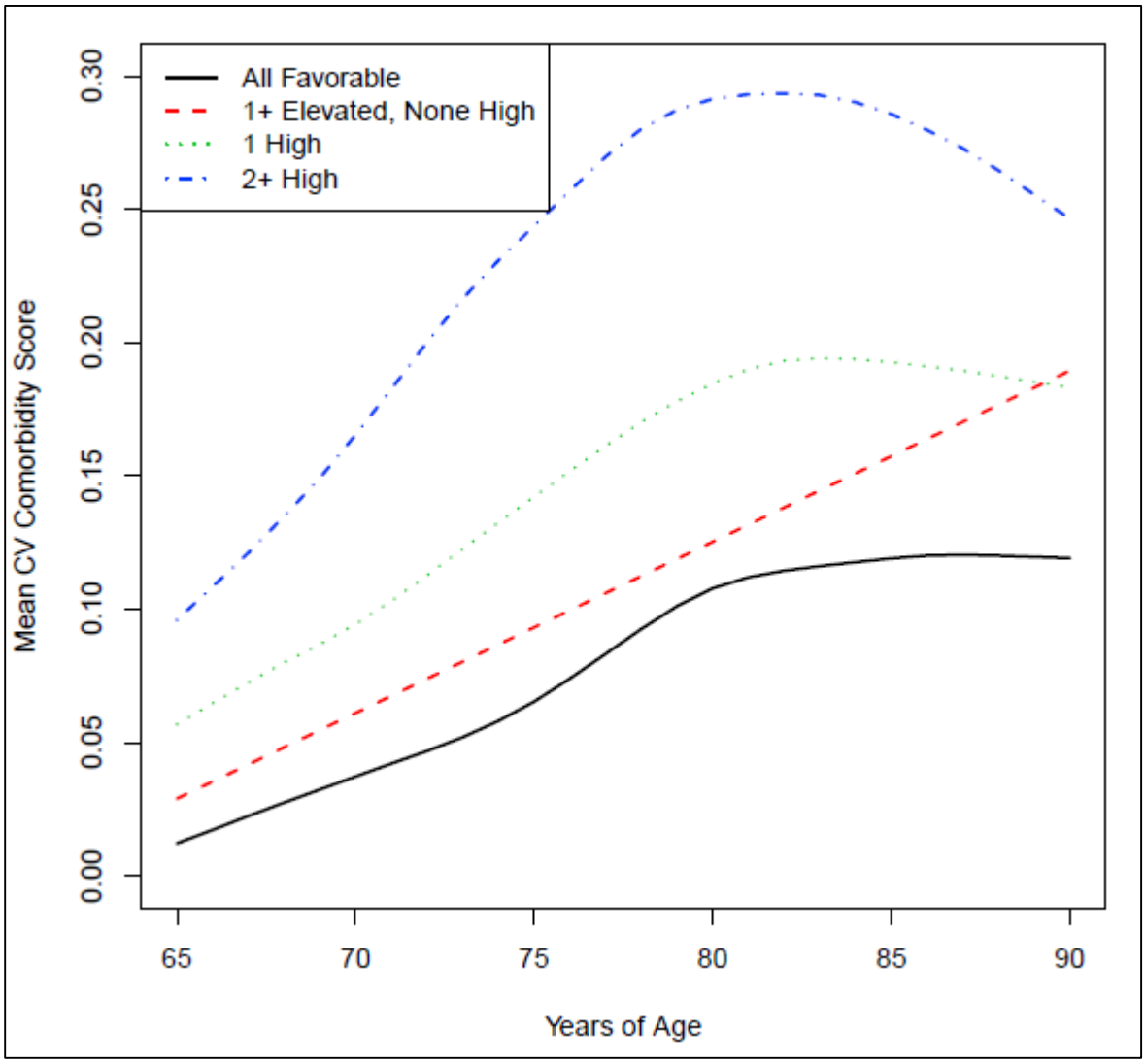
eFigure 1. Sample Exclusions



eFigure 2. Mean Follow Up All-Cause Morbidity Score by CV Risk Factor Level Starting at Age 65 Years

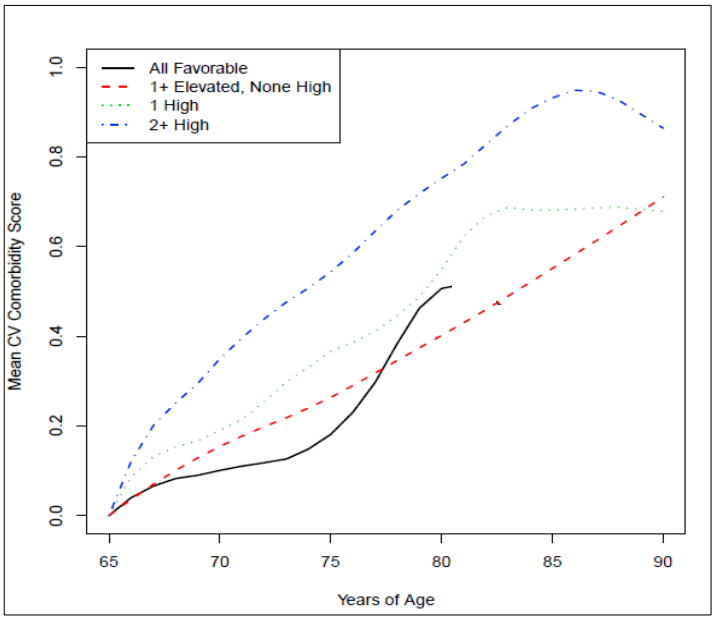


eFigure 3. Mean Follow Up CV Morbidity Score by CV Risk Factor Level Starting at Age 65 Years

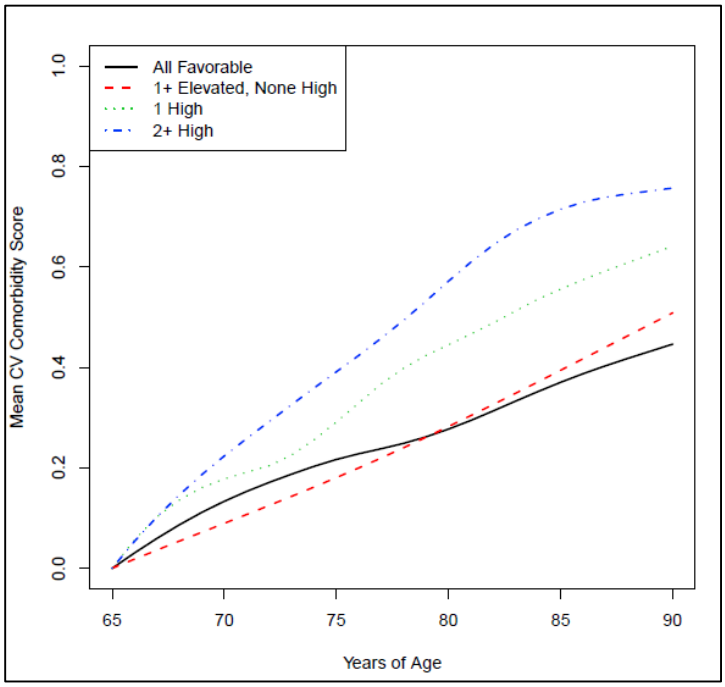


eFigures 4a and 4b. Mean Follow Up All-Cause Morbidity Score by CV Risk Factor Level at Age 65 Years Among those with Morbidity Score=0 at Age 65 Years for Men (A) and Women (B)

A. Men

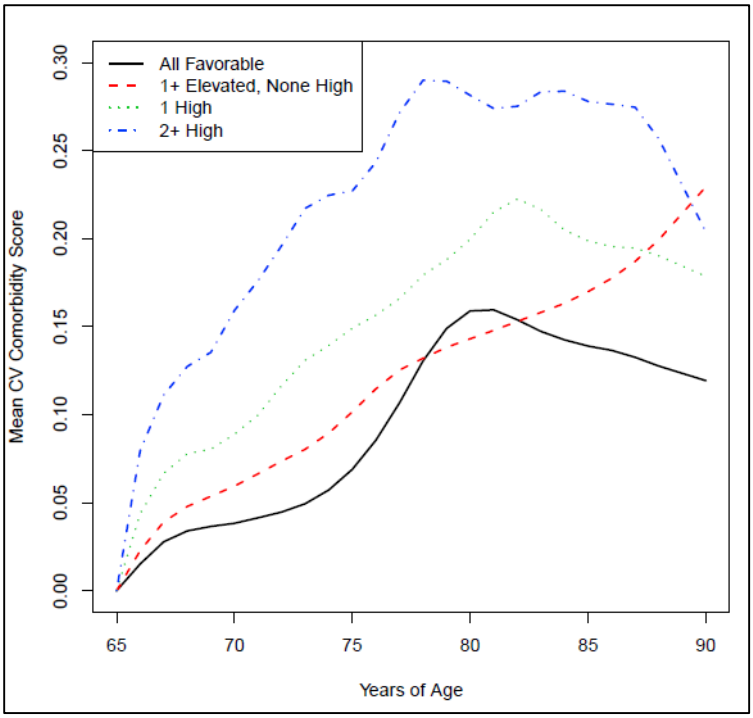


B. Women

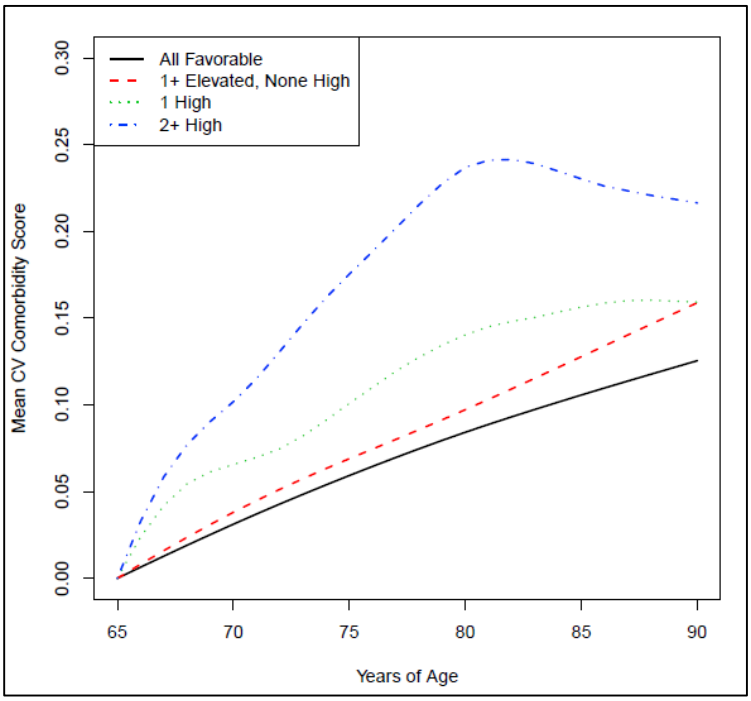


eFigures 5a and 5b. Mean Follow Up CV Morbidity Score by CV Risk Factor Level at Age 65 Years Among those with Morbidity Score=0 at Age 65 Years for Men (A) and Women (B)

A. Men



B. Women



eTable 1. Area Under the Curve (AUC) for All-Cause and CV Morbidity Overall and by Sex

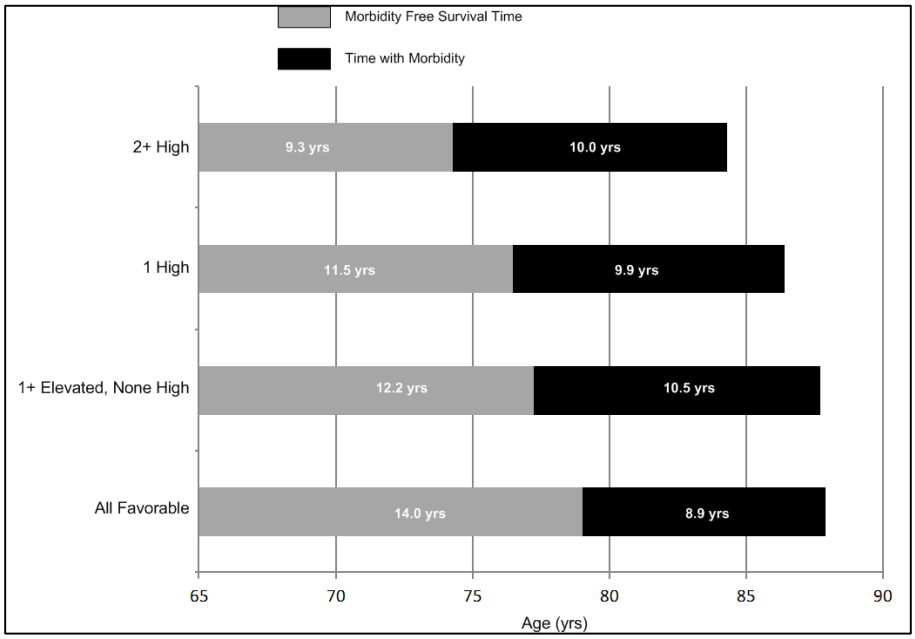
	All-Cause Morbidity		CV Morbidity	
	AUC* (95% CI)	p-value for comparison	AUC* (95% CI)	p-value for comparison
Overall				
All Favorable	5.9 (5.0-6.9)	Ref	1.9 (1.5-2.3)	Ref
1+ Elevated, None High	6.9 (6.5-7.4)	0.06	2.6 (2.3-2.8)	0.002
1 High	9.2 (8.8-9.7)	<0.0001	3.2 (3.1-3.4)	<0.001
2+ High	11.9 (11.2-12.6)	<0.0001	4.8 (4.5-5.0)	<0.001
Men				
All Favorable	6.3 (5.0-7.5)	Ref	2.5 (1.5-3.5)	Ref
1+ Elevated, None High	8.1 (7.3-9.0)	0.01	3.1 (2.7-3.8)	0.30
1 High	10.2 (9.5-10.8)	<0.0001	3.7 (3.5-4.0)	0.02
2+ High	13.4 (12.5-14.4)	<0.0001	5.3 (4.9-5.7)	<0.001
Women				

All Favorable	5.6 (4.6-6.6)	Ref	1.6 (1.2-2.0)	Ref
1+ Elevated, None High	5.9 (5.2-6.6)	0.65	2.1 (1.8-2.4)	0.04
1 High	8.0 (7.3-8.7)	<0.0001	2.6 (2.4-2.8)	<0.001
2+ High	9.9 (8.9-11.0)	<0.0001	4.0 (3.7-4.4)	<0.001

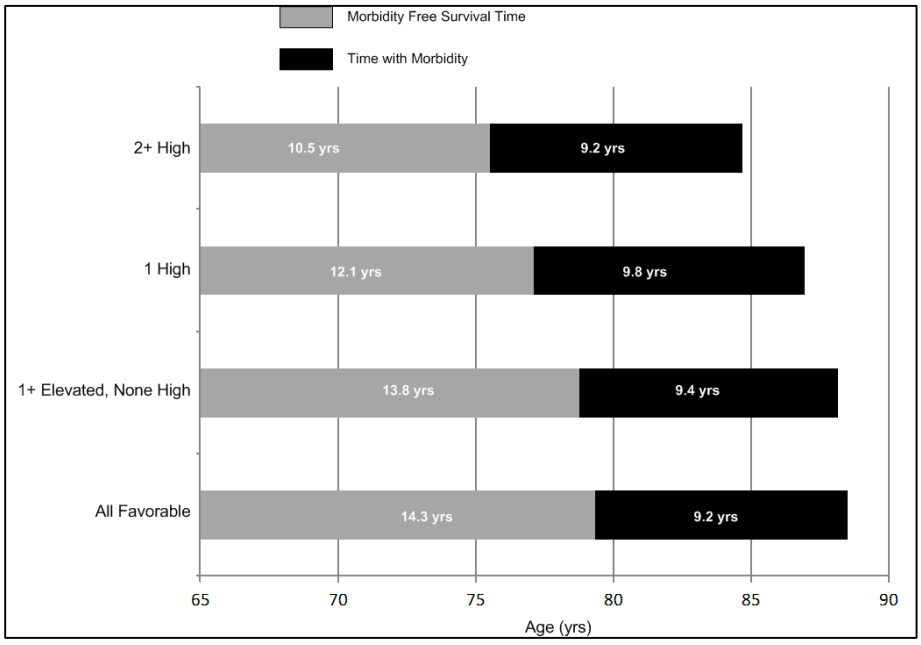
*units are in morbidity score-years; for all comparisons p-value for trend <0.001

eFigures 6a and 6b. Morbidity Free Survival and Time Spent with Morbidity by Sex

A. Men

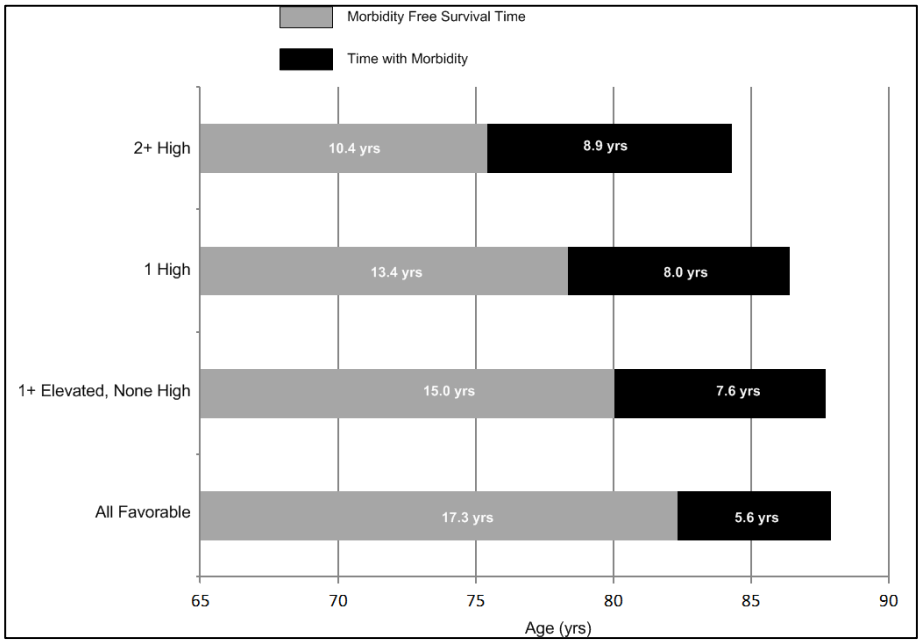


B. Women

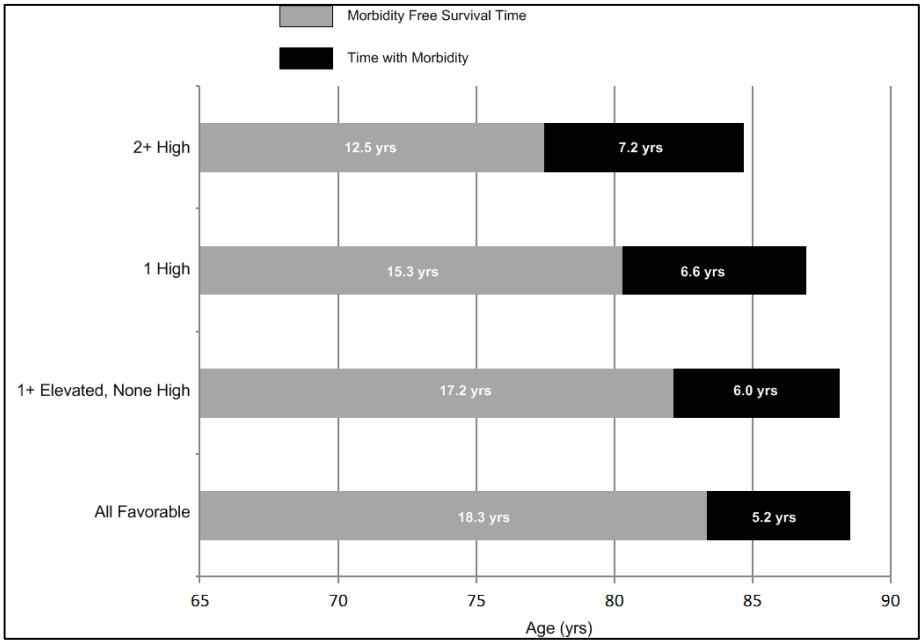


eFigures 7a and 7b. CV Morbidity Free Survival and Time Spent with CV Morbidity by Sex

A. Men



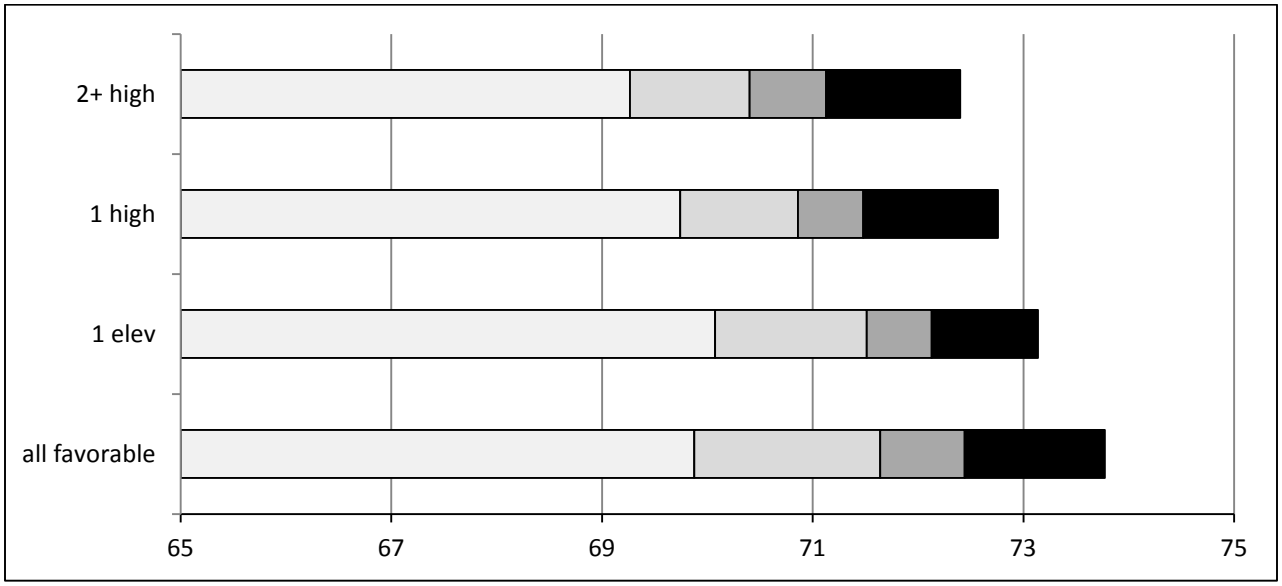
B. Women



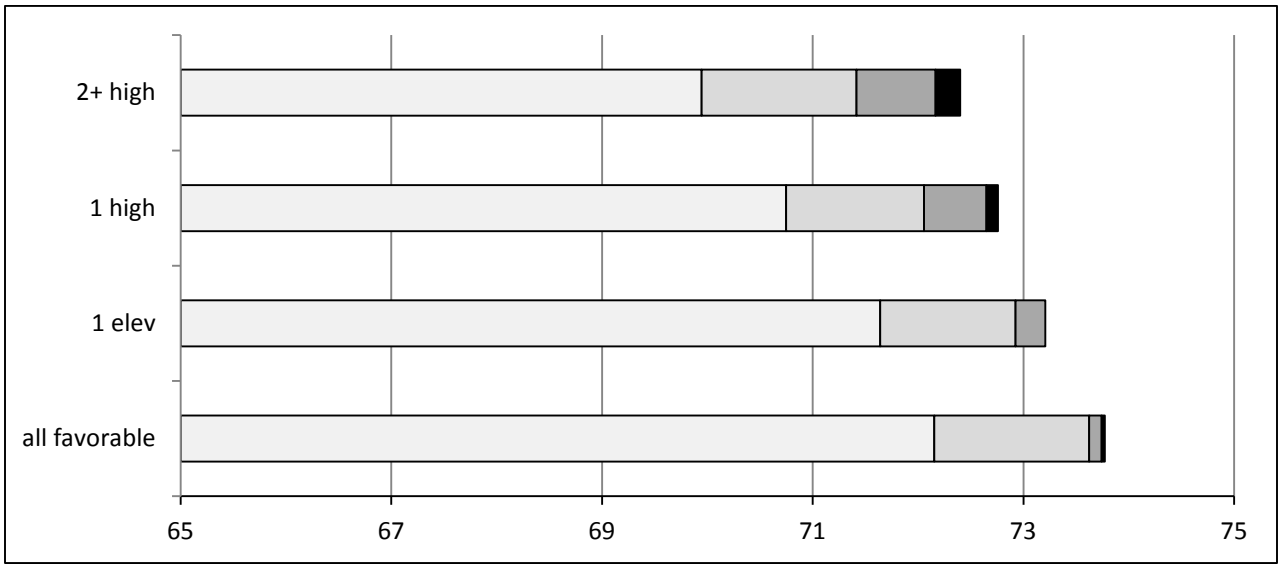
eFigures 8a and 8b. Morbidity Free Survival and Time Spent with Morbidity

Among CHA Participants Who Died During Follow-Up

A. All-Cause Morbidity

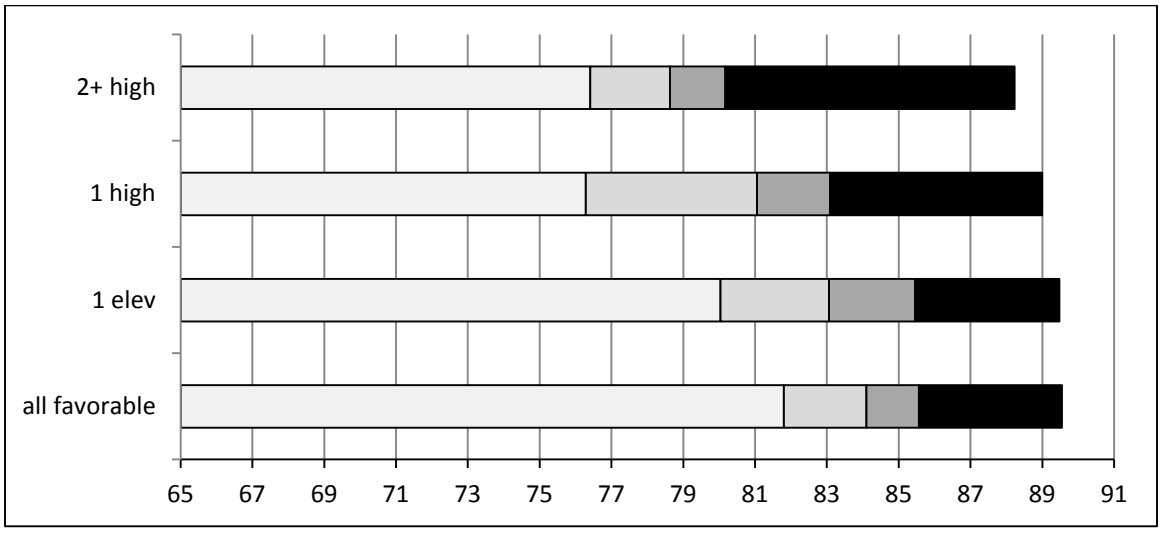


B. CV Morbidity

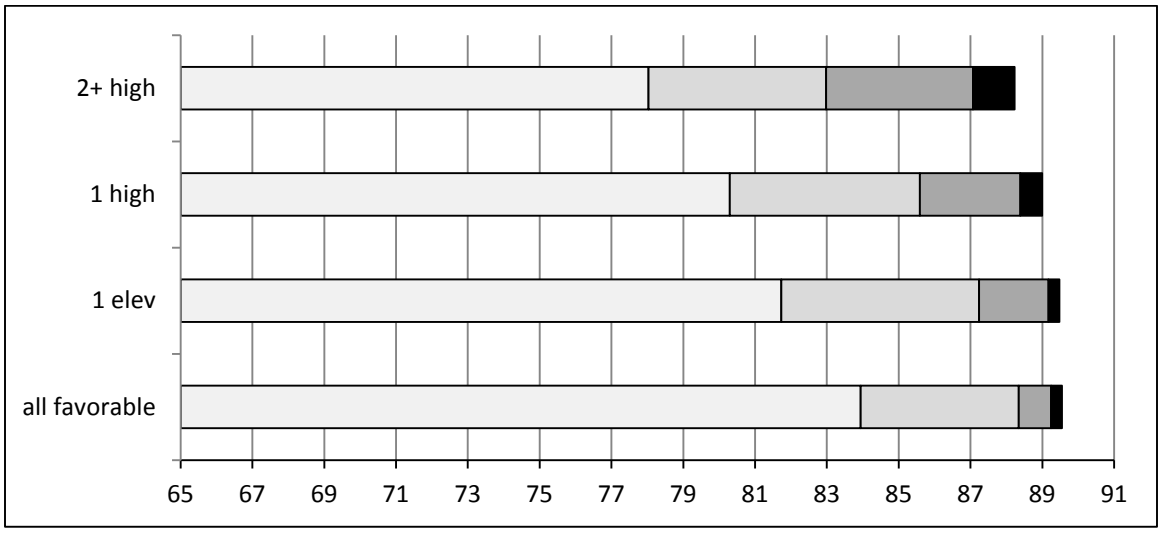


eFigures 9. Morbidity Free Survival and Time Spent with Morbidity Among CHA Participants Aged ≤ 40 years at Baseline

A. All-Cause Morbidity

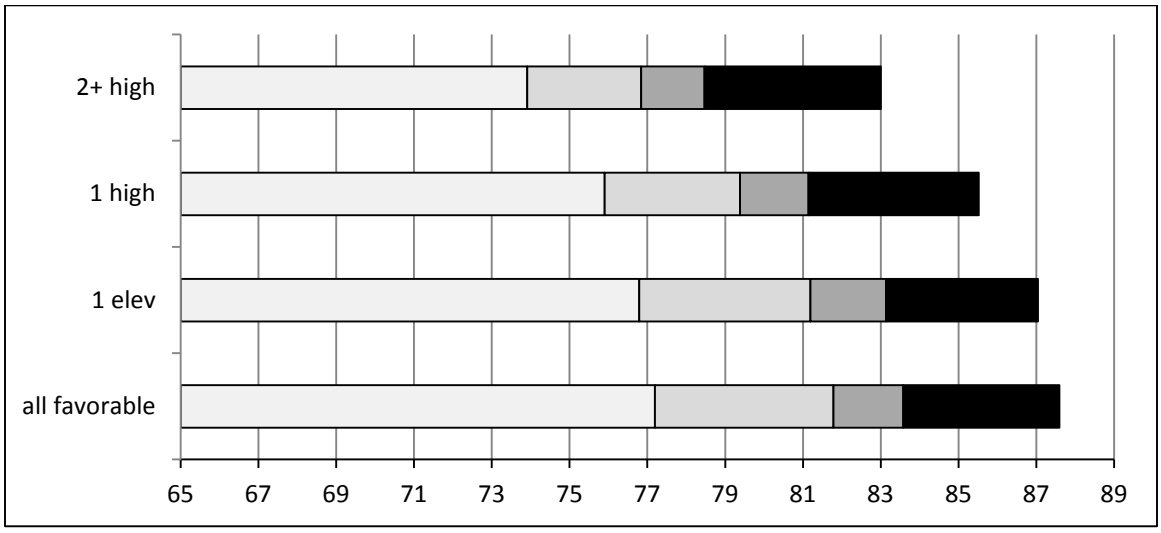


B. CV Morbidity

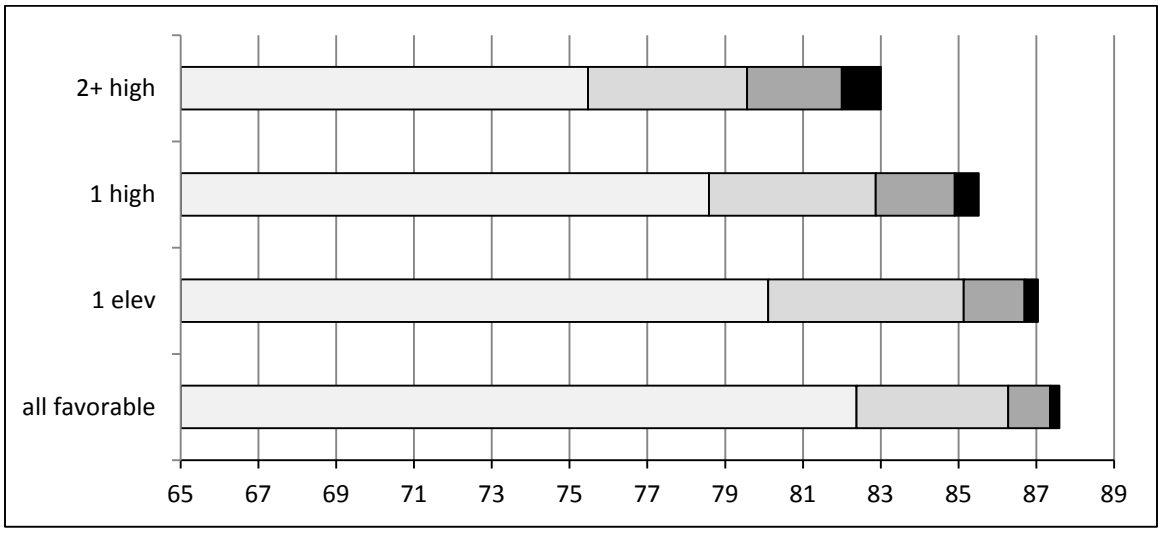


eFigures 10. Morbidity Free Survival and Time Spent with Morbidity Among CHA Participants Aged 41-50 years at Baseline

A. All-Cause Morbidity

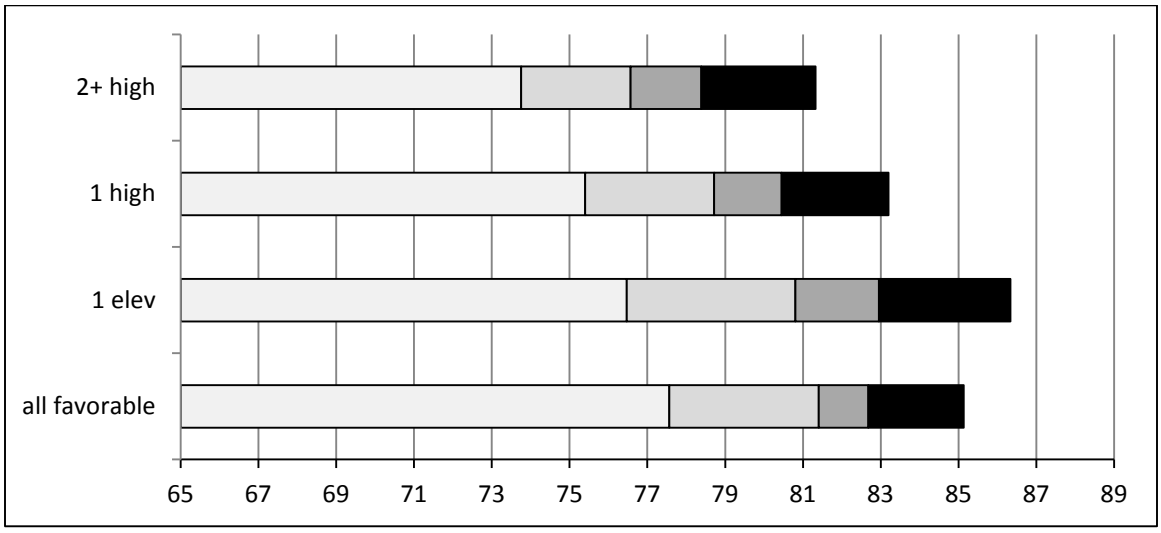


B. CV Morbidity

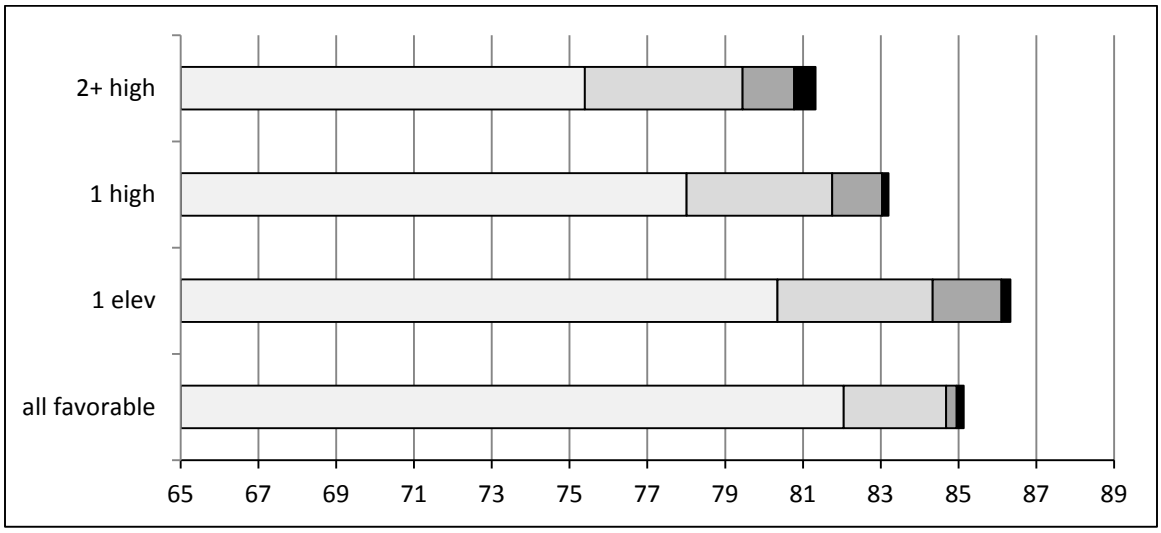


eFigures 11. Morbidity Free Survival and Time Spent with Morbidity Among CHA Participants Aged > 50 years at Baseline

A. All-Cause Morbidity

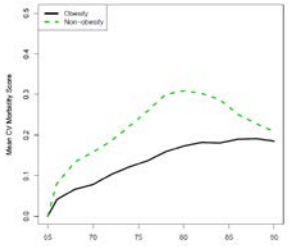


B. CV Morbidity

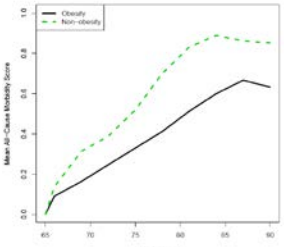


eFigures 12. Mean Follow Up Morbidity Score by Individual CV Risk Factor Starting at Age 65 Years

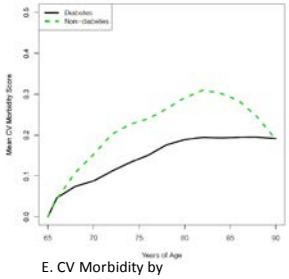
A. CV Morbidity by Obesity



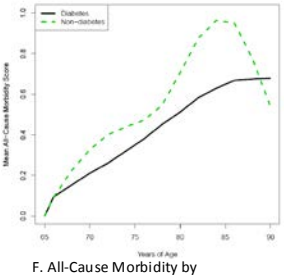
B. All-Cause Morbidity by Obesity



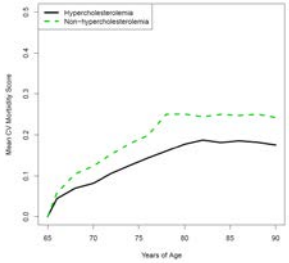
C. CV Morbidity by Diabetes



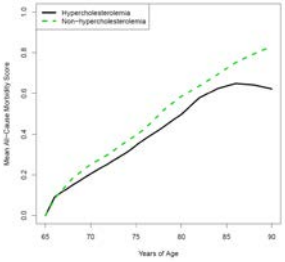
D. All-Cause Morbidity by Diabetes



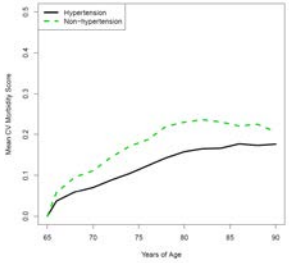
E. CV Morbidity by Hypercholesterolemia



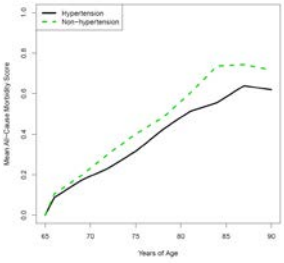
F. All-Cause Morbidity by Hypercholesterolemia



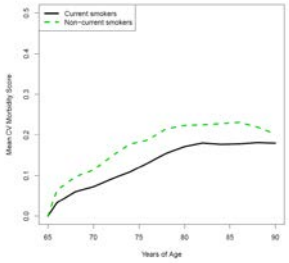
G. CV Morbidity by Hypertension



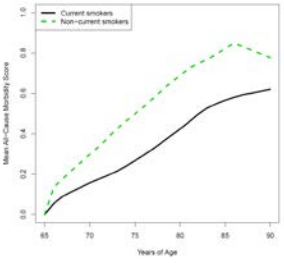
H. All-Cause Morbidity by Hypertension



I. CV Morbidity by Smoking



J. All-Cause Morbidity by Smoking



eTable 2. Average Age of Morbidity Incidence, Death and the Proportion of Life Years lived with Morbidity

	Age at Major Morbidity Incidence (95% CI)	Age at CV Morbidity Incidence (95% CI)	Age at Death (95% CI)	Proportion of Life Past 65 Lived with Morbidity	Number of Years Lived with Major Morbidity	Proportion of Life Past 65 Lived with CV Morbidity	Number of Years Lived with CV Morbidity
Overall							
All Favorable	79.2 (78.6-80.0)	83.0 (82.3-83.6)	88.3 (87.9-88.7)	39%	9.1	23%	5.3
1+ Elevated, None High	77.9 (77.6-78.3)*	80.9 (80.6-81.3)*	87.9 (87.7-88.1)	43%	10.0	30%*	7.0*
1 High	76.7 (76.5-76.9)*	79.2 (78.9-79.4)*	86.6 (86.4-86.8)*	46%*	9.9*	35%*	7.5*
2+ High	74.7 (74.5-74.9)*	76.1 (75.9-76.4)*	84.4 (84.2-84.6)*	50%*	9.7*	43%*	8.3*
Men							
All Favorable	79.0 (77.8-80.2)	82.3 (81.2-83.4)	87.9 (87.2-88.6)	39%	8.9	24%	5.6

1+ Elevated, None High	77.2 (76.8-77.6)*	80.0 (79.6-80.5)*	87.7 (87.4-88.0)	46%	10.5	34%*	7.6*
1 High	76.5 (76.2-76.8)*	78.4 (78.0-78.7)*	86.4 (86.1-86.7)*	46%	9.9	38%*	8.0*
2+ High	74.3 (74.0-74.6)*	75.4 (75.1-75.7)*	84.3 (84.0-84.6)*	52%*	10.0*	46%*	8.9*
Women							
All Favorable	79.3 (78.5-80.2)	83.3 (82.5-84.1)	88.5 (88.0-89.0)	39%	9.2	22%	5.2
1+ Elevated, None High	78.8 (78.3-79.3)	82.2 (81.7-82.6)	88.2 (87.9-88.4)	41%	9.4	26%	6.0
1 High	77.1 (76.7-77.5)*	80.3 (79.9-80.7)*	86.9 (86.6-87.2)*	45%*	9.8*	30%*	6.6*
2+ High	75.5 (75.1-76.0)*	77.5 (77.0-77.9)*	84.7 (84.3-85.1)*	46%*	9.2*	37%*	7.2*

**=p-value<0.05 when compared to the All Favorable group*

eTable 3. Number Life Years (95% CI) lived with Morbidity Levels 0,1,2 and 3

	Years with Morbidity Score 1+ (95% CI)	Years with Morbidity Score 2+ (95% CI)	Years with Morbidity Score 3+ (95% CI)
All-Cause Morbidity			
All Favorable	9.06 (8.35-9.77)	5.76 (5.21-6.31)	4.22 (3.75-4.69)
1+ Elevated, None High	9.95 (9.60-10.30)	6.18 (5.87-6.49)	4.17 (3.90-4.44)
1 High	9.89 (9.65-10.13)	6.83 (6.61-7.05)*	5.04 (4.84-5.24)*
2+ High	9.72 (9.45-9.99)	7.15 (6.91-7.39)*	5.55 (5.33-5.76)*
Cardiovascular Morbidity			
All Favorable	5.31 (4.72-5.90)	1.46 (1.11-1.81)	0.36 (0.20-0.52)
1+ Elevated, None High	6.95 (6.63-7.26)*	2.14 (1.92-2.36)*	0.34 (0.24-0.44)
1 High	7.46 (7.24-7.68)*	3.01 (2.85-3.17)*	0.69 (0.59-0.79)*
2+ High	8.3 (8.05-8.55)*	3.99 (3.79-4.19)*	1.09 (0.97-1.21)*

** indicates P<0.05 when compared to the All Favorable group.*

eTable 4. Adjusted Differences in Cumulative and Average Costs by CV Risk Factor Level as Compared to Favorable CV Health at 50th and 75th Percentiles Among Participants Who Died

	Estimate of Increased Cost at 50th Percentile	p-value	Estimate of Increased Cost at 75th Percentile	p-value
Cumulative Costs, $				
Risk Factor Level				
All Favorable	Ref		Ref	
1+ Elevated, None High	$17,901	0.246	$16,657	0.559
1 High	$31,385	0.016	$38,637	0.168
2+ High	$40,606	0.002	$60,498	0.033
Average Costs, $				
Risk Factor Level				
All Favorable	Ref		Ref	
1+ Elevated, None High	$947	0.562	$4,180	0.227
1 High	$2,886	0.068	$6,303	0.049

2+ High	$4,207	0.007	$10,770	0.001

All costs are adjusted forage, gender, race, education, length of follow-up and death during follow-up. Due to convergence issues, we used 75.5% and 50.5% quantiles for cumulative cost in the model for all participants