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Growth hormone concentration and risk of all-cause and cardiovascular mortality: The REasons for Geographic And Racial Disparities in Stroke (REGARDS) study

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Abstract

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Background and aims: Identifying individuals at elevated risk for mortality, especially from cardiovascular disease, may help guide testing and treatment. Risk factors for mortality differ by sex and race. We investigated the association of growth hormone (GH) with all-cause and cardiovascular mortality in a racially diverse cohort in the United States.

Methods: Among an age, sex and race stratified subgroup of 1046 Black and White participants from the REasons for Geographic And Racial Disparities in Stroke (REGARDS) study, 881 had GH available; values were log_2 transformed. Associations with all-cause and cardiovascular mortality were assessed in the whole subgroup, and by sex and race, using multivariable Cox-proportional hazard models and C-index.

Results: The mean age was 67.4 years, 51.1% were women, and 50.2% were Black participants. The median GH was 280 (interquartile range 79–838) ng/L. There were 237 deaths and 74 cardiovascular deaths over a mean of 8.0 years. In multivariable Cox analysis, GH was associated with higher risk of all-cause mortality per doubling (hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.09–1.25) and cardiovascular mortality (HR 1.21, 95% CI 1.06–1.37). The association did not differ by sex or race (interaction $p > 0.05$). The addition of GH to a model of clinical variables significantly improved the C-index compared to clinical model alone for all-cause and cardiovascular death.

Conclusions: Higher fasting GH was associated with higher risk of all-cause and cardiovascular mortality and improved risk prediction, regardless of sex or race.

1. Introduction

Appropriately risk stratifying individuals is pertinent to guide testing and treatment. This is especially relevant for cardiovascular disease where there are significant sex and race differences in causes of death [1]. Notably, the prevalence of coronary artery disease (CAD), the largest contributor to cardiovascular mortality, is higher in men until the age of 75 and the overall rate of cardiovascular mortality is significantly higher in men compared to women while age-adjusted death rates from cardiovascular disease are 33% higher in Black individuals compared to the general US population [1,2]. These differences, as well as other studies, have highlighted the need to better understand and research potential sex- and racial-specific differences risk and cardiometabolic diseases [3,4].

Growth hormone (GH) is produced in the anterior pituitary by somatotroph cells in a pulsatile fashion stimulating circulating insulin-like growth factor 1 (IGF-1), which mediates the physiologic effects [5]. The GH/IGF-1 axis is important for somatic growth, metabolism and cardiovascular physiology [5,6]. Both pathological deficiency and excess of GH are associated with higher mortality and cardiovascular disease through alterations in body composition, carbohydrate metabolism, lipid composition, blood pressure and cardiovascular function [7–9]. Yet even in relatively healthy populations, GH may be associated with mortality and cardiovascular risk. An analysis from the Paris Prospective Study of 864 policemen without cardiovascular disease found higher fasting GH was associated with

higher all-cause and cardiovascular mortality during 18 years of follow up [10]. More recently, fasting GH was measured in 4323 healthy Swedish participants in the Malmo Diet and Cancer Study (MDC) using a highly sensitive assay [11]. Higher fasting GH was associated with a higher risk of incident CAD, heart failure (HF), stroke, cardiovascular mortality and all-cause mortality over the median follow up of 16.2 years [11]. Notably, a significant interaction was found between GH and sex, with GH only associated with a higher risk of CAD, cardiovascular mortality and all-cause mortality in men suggesting GH may be a sex-specific biomarker [11]. Other studies have shown higher GH is associated with higher adverse cardiovascular outcomes for individuals with prevalent HF and CAD [12,13]. The pathophysiologic link between higher GH and outcomes is unknown. Elevated GH may result from GH receptor resistance or a deficiency in IGF-1 production leading to increased GH production from lack of a negative feedback. Conversely, elevated GH may be inappropriate production leading to over-production of IGF-1.

While these studies suggest GH may improve risk stratification, especially in men, further evaluation in racially diverse populations is needed to confirm and expand these findings. Thus, we investigated the association of fasting GH with all-cause and cardiovascular mortality in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study – a large prospective cohort of White and Black individuals enrolled throughout the continental United States (US) [14, 15]. We hypothesized that higher GH would be associated with all-cause and cardiovascular mortality, especially in men, and this association would not differ by race.

2. Patients and methods

2.1. Study design

Results herein are from an ancillary study of the REGARDS study. The details and design of the REGARDS study have been previously described [14,15]. Briefly, REGARDS is a large prospective cohort study evaluating risk factors for racial and geographic disparities in stroke mortality in the US. From 2003 to 2007, 30,239 Black and White community-dwelling adults   45 years of age were enrolled by mail and telephone from all 48 contiguous US states with oversampling of Black participants and the southeastern US because of higher stroke mortality. A telephone interview was conducted to collect baseline demographics, medical history, and health status. An in-home examination subsequently collected direct measurements including blood pressure, electrocardiogram, height, weight, and blood and urine samples. Participants or their surrogates were contacted by phone every 6 months for potential clinical events, with medical records associated with suspected events retrieved and centrally adjudicated. Written consent was obtained during the in-person evaluation and the study was approved by human subjects research review committees at all participating institutions. The cohort consisted of 58% women, 42% Black participants, and 56% from the Southeastern US. From this population, a random cohort of 1046 individuals stratified by sex, age, and race was selected. Stratification was designed to achieve a target distribution of 50% men and 50% women, 50% White participants and 50% Black participants, and 20% ages 45–54 years, 20% ages 55–64 years, 25% ages 65–74 years, 25% ages 75–84 years, 10% ages 85 years and older.

2.2. Growth hormone measurement

GH was measured with a high sensitivity two-site chemiluminescence sandwich immunoassay as previously described [13,16]. The analytical assay sensitivity was 2 ng/L with an inter-assay coefficient of variance of 20% at 10 ng/L.

2.3. Outcomes

The outcomes were all-cause mortality and cardiovascular mortality. Study participants or proxies were contacted by telephone every 6 months to obtain information about clinical events including death. If a death occurred, next of kin or proxies were interviewed to ascertain circumstances surrounding death. Medical records for hospitalizations or emergency department visits in the months preceding death, along with death certificates, autopsy reports and data from the National Death Index, were collected for central adjudication [17]. Cardiovascular mortality was defined as death due to myocardial infarction, stroke, heart failure, sudden cardiac death, and other cardiovascular causes such as ruptured aortic aneurysm. Adjudication of cardiovascular mortality was completed through 12/31/2018 and all-cause mortality was completed through 3/31/2021. Both outcomes had follow-up truncated at 10 years from enrollment.

2.4. Statistical analysis

Values were expressed as means and standard deviations (SD), medians and interquartile ranges (IQR), or counts and percentages as appropriate. Group comparisons of continuous variables were performed using the Student's t-test, analysis of variance (ANOVA), Mann-Whitney U, or Kruskal-Wallis test as appropriate, and categorical data were compared using the chi-square test. Normality was visually assessed. GH was right skewed and thus $\log_2$ transformed such that higher GH could be interpreted as "per 2-fold higher level" of GH.

Kaplan Meier curves for all-cause and cardiovascular mortality were constructed by quartiles of GH. For the less than 5% of data missing for certain variables, we performed multiple imputations by chained equations with a total of 5 imputations using all the variables from the fully adjusted model below. Estimates were combined using Rubin's rule to account for variability in the imputation procedure [18]. Univariable and multivariable Cox proportional-hazards regression were used to examine the association of GH with all-cause and cardiovascular mortality. Confounding variables in the model included age, sex, systolic blood pressure (SBP), body mass index (BMI), antihypertensive therapy use, diabetes, current cigarette smoking, low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C), as these were previously tested in the analysis of GH from the MDC cohort study [11]. We also included features unique and relevant to REGARDS: race, region of residence, annual household income, and education. Blood pressure was obtained from two measurements after 5 min of seated rest with both feet on the floor, with the average reading used in analyses. Smoking was based on current use regardless of frequency. Antihypertensive medications were self-reported or by medication review. Diabetes was classified by fasting glucose >126 mg/dl (or a non-fasting glucose >200 mg/dl for those failing to fast) or self-report with use of diabetes medications [19]. Region was categorized into stroke buckle, stroke belt, or other region of the continental US. Annual household income was dichotomized at more than or less than or equal to

$20,000, with participants who refused to state income categorized as more than $20,000. Education was dichotomized at less than a high school education or high school education or higher. When models were examined by sex or race, these variables were removed from the multivariable model.

Predictive utility of GH was evaluated by constructing receiver operating curves (ROCs) and determining the concordance index (C-index). For multivariable models, a bootstrap corrected version of the C-index was given. To test for added predictive value of GH, we used the multivariate Wald test for imputed nested models.

All statistical tests were assessed with a two-sided *p*-value <0.05 indicating significance. Analyses were performed using R (http://www.r-project.org, library design, Hmisc) and Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Participant characteristics

The subgroup initially consisted of 1046 individuals; after excluding 165 individuals without fasting GH, the final subgroup was composed of 881 participants. The average age was 67.4 ± 12.2 years, 51.1% were women, 50.2% were Black individuals, 51.8% were receiving antihypertensive therapy, and 19.1% had diabetes (Table 1A). The median GH was 280 (IQR 79–838) ng/L.

When evaluated by sex, men had higher SBP, higher diastolic blood pressure, lower BMI, lower HDL-C, more often smoked, and less often had an annual income $20,000 (Table 1). Men had lower GH (median 128 [IQR 49–483] ng/L) compared to women (median 460 [IQR 167–1120] ng/L). When evaluated by race, Black individuals had higher SBP, higher diastolic blood pressure, BMI, LDL-C, and HDL-C, more often were diabetic, currently smoking, using antihypertensive therapy, had an annual income $20,000, had less than a high school education, and less often lived in the stroke buckle. GH was not different between Black (median 249 [IQR 76–743] ng/L) and White individuals (median 315 [IQR 81–902] ng/L). When examined by GH quartiles, age and HDL-C increased, while SBP, diastolic blood pressure, BMI, and prevalence of women decreased with higher GH quartiles (Supplemental Table 1). The prevalence of diabetes was similar in the first three GH quartiles but was significantly lower in the highest quartile.

3.2. All-cause mortality

There were 237 deaths with a restricted mean survival time (rmst) of 8.8 years: 132 for men (rmst 8.6 years), 105 for women (rmst 9.0 years), 124 for Black individuals (rmst 8.6 years) and 113 for White individuals (rmst 9.0 years). Fig. 1 shows Kaplan Meier survival curves for all-cause mortality by quartiles of GH for the entire cohort and by sex and race. Mortality was higher with higher quartiles of GH for the whole cohort, in Black and White individuals, and in men, but not in women. Variables associated with all-cause mortality in univariable analysis included age, sex, SBP, BMI, antihypertensive use, LDL-C, annual income, education level, and GH (Supplemental Table 2A).

The unadjusted HR per doubling of GH was 1.17 (95% CI 1.10 to 1.25, Table 2). GH was associated with all-cause mortality in both sexes with a higher HR in men. GH was associated with all-cause mortality in Black and White individuals with similar HRs. In multivariable analysis, GH remained associated with all-cause mortality with a HR of 1.17 (95% CI 1.09 to 1.25). GH was associated with all-cause mortality in men with a HR of 1.21 (95% CI 1.11 to 1.33) but not in women (HR 1.12, 95% CI 0.99 to 1.27) with no significant interaction by sex (p-interaction = 0.23 for GH*sex). GH was associated with all-cause mortality in Black (HR 1.15, 95% CI 1.04 to 1.28) and White (HR 1.19, 95% CI 1.07 to 1.32) individuals with no significant interaction by race (p-interaction = 0.69 for GH*race).

GH alone had fair predictive ability for all-cause mortality with a C-index of 0.605 (95% CI 0.570–0.639; Table 3). When GH was added to a model of clinical variables, it significantly improved the C-index of the clinical model from 0.767 (95% CI 0.736–0.795) to 0.774 (95% CI 0.743–0.802). In men, White individuals and Black individuals, the addition of GH to the clinical model significantly improved the C-index compared to the clinical model alone, but it did not improve the C-index for women.

3.3. Cardiovascular mortality

There were 74 cardiovascular deaths with a rmst of 9.5 years: 46 for men (rmst 9.4 years), 28 for women (rmst 9.7 years), 43 for Black individuals (rmst 9.4 years) and 31 for White individuals (rmst 9.7 years). Fig. 2 shows Kaplan Meier survival curves for cardiovascular mortality by quartiles of GH. Cardiovascular mortality was higher with higher quartiles of GH for the whole cohort, White individuals, and men, but not Black individuals or women. Variables associated with cardiovascular mortality in univariable analysis included age, sex, SBP, antihypertensive use, and GH (Supplemental Table 2B).

The unadjusted HR per doubling of GH was 1.18 (95% CI 1.06 to 1.31, Table 2). GH remained associated with cardiovascular mortality in men, but not women. GH was significantly associated with cardiovascular mortality in both Black and White individuals with similar HRs. In multivariable analysis, GH was associated with cardiovascular mortality (HR 1.21, 95% CI 1.06 to 1.37). GH was associated with cardiovascular mortality in men (HR 1.21, 95% CI 1.04 to 1.42) but not women with no significant interaction by sex (p-interaction = 0.92 for GH*sex). GH was associated with cardiovascular mortality in Black individuals (HR 1.20, 95% CI 1.00 to 1.44) but not White individuals (HR 1.20, 95% CI 0.97 to 1.48) with no significant interaction by race (p-interaction = 0.63 for GH*race).

The C-index for GH alone for cardiovascular mortality was similar to all-cause mortality (Table 3). When GH was added to the model of clinical variables, it significantly improved the C-index with a good predictive performance of 0.813 (95% CI 0.765 to 0.854). While the C-index for the clinical model with GH was numerically higher than the clinical model for all subgroups, this increase was not statistically significant in any group.

4. Discussion

In this subgroup of 881 Black and White individuals from REGARDS, higher GH was associated with higher risk of all-cause and cardiovascular mortality, and the addition of GH to a clinical model improved risk prediction. These findings did not significantly differ by sex or race. These findings add further evidence that fasting GH may be useful for risk stratification and advance prior literature by showing no difference between Black and White individuals.

Prior studies in European cohorts showed GH hormone was associated with all-cause mortality, cardiovascular mortality, CAD, HF, and stroke primarily in men [10,11]. Our findings validate GH's prognostic and predictive utility, but we did not find a sex specific association in our US based cohort. This could be from a lack of power as our cohort consisted of 881 participants while MDC had more than 4200 participants, but we cannot exclude population differences in biomarker performance [11]. And while the interaction for GH and sex was not significant, given the significant difference in median and range of GH values in each sex, it may still be helpful to interpret GH by sex. Further, we have expanded prior findings by demonstrating similar performance characteristics for GH in a racially diverse US population of Black and White individuals. This latter finding is notable as race has been shown to influence performance of other biomarkers and studies have highlighted a need for more research of sex- or race-specific differences in cardiometabolic disease [3,4,20]. Overall, we found the risk associated with elevated GH could be substantial. In our cohort, an individual with GH near the third quartile would have almost double the risk of all-cause and cardiovascular mortality than a man with GH near the first quartile. Thus, our findings support using fasting GH for risk stratification and advance prior research by confirming results in a diverse population.

It is unknown why higher GH is associated with all-cause and cardiovascular mortality. As mentioned, this could be from either a relative GH resistance or an inadequate production of IGF-1 or possibly inappropriate excessive production of GH. Either could lead to abnormalities in carbohydrate metabolism, lipids, cardiovascular function and body composition. In HF patients, GH has been found elevated while IGF-1 is low and this is associated with a higher risk of mortality and HF hospitalization supporting the concept of GH resistance or inadequate IGF-1 production [12,21,22]. However, the GH/IGF-1 is complex and not fully understood and other studies in HF patients have conflicting findings [23]. While these studies were in HF, it is unknown if similar pathophysiology occurs in healthier individuals like our cohort or the MDC study.

Beyond determining why GH is associated with higher mortality and cardiovascular disease, other questions remain for its clinical use. It is unknown if serial measurement of GH improves risk stratification by identifying individuals with rising GH and subsequent higher risk. Also, what treatments, if any, alter GH and whether these changes in GH in response to treatment are associated with a change in risk warrants further research. In a study of 953 patients presenting with acute myocardial infarction, patients in the lowest tertile of GH had no difference in major adverse cardiac events (MACE) regardless of receipt of beta-blocker or angiotensin inhibiting therapies, while patients in higher tertiles had significantly lower

rates of MACE when prescribed beta-blockers and angiotensin inhibiting therapies [13]. In this setting, GH may help guide which patients derive the greatest benefit from medical therapies. Whether this translates to other cardiovascular populations or healthy subjects with elevated GH requires further research.

Our study has multiple strengths including the use of an established longitudinal cohort. This cohort provides a sex balanced and racially diverse population, and long follow-up time with adjudicated outcomes. Our study also has limitations. The sample size was modest at 881 participants and may have been underpowered to demonstrate sex-specific findings with GH. The limited number of cardiovascular deaths reduces the power for analysis of cardiovascular death, especially when considering subgroups by sex and race as reflected by wide confidence intervals. Thus. we cannot exclude a possibly clinically important association. Our findings are observational and cross-sectional in design, so temporal directions of associations between GH and outcomes cannot be proven. There is also the potential for residual confounding.

In conclusion, fasting GH levels were associated with higher risk of all-cause and cardiovascular mortality regardless of sex or race. The addition of GH to clinical models improved risk prediction for all-cause and cardiovascular mortality. Fasting GH may be a useful biomarker for risk prediction and prognosis of all-cause and cardiovascular mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.
Kaplan Meier curve for all-cause mortality at 10 years by growth hormone quartiles.
Kaplan Meier curves for all-cause mortality by quartiles of growth hormone in whole cohort
(A), men (B), women (C), Black participants (D), and White participants (E). Mortality is
generally higher with higher quartiles of growth hormone.
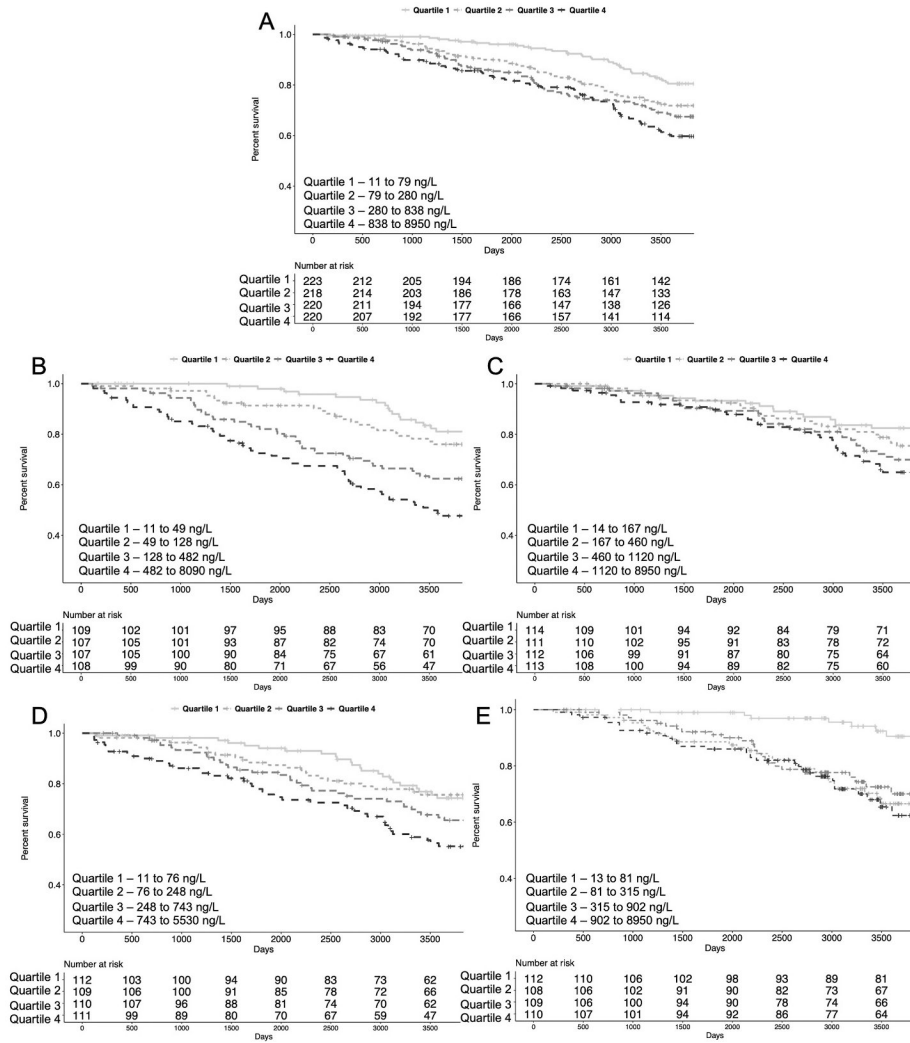
Fig. 2.
Kaplan Meier curve for cardiovascular mortality at 10 years by growth hormone quartiles.
Kaplan Meier curves for cardiovascular mortality by quartiles of growth hormone in whole cohort (A), men (B), women (C), Black participants (D), and White participants (E).
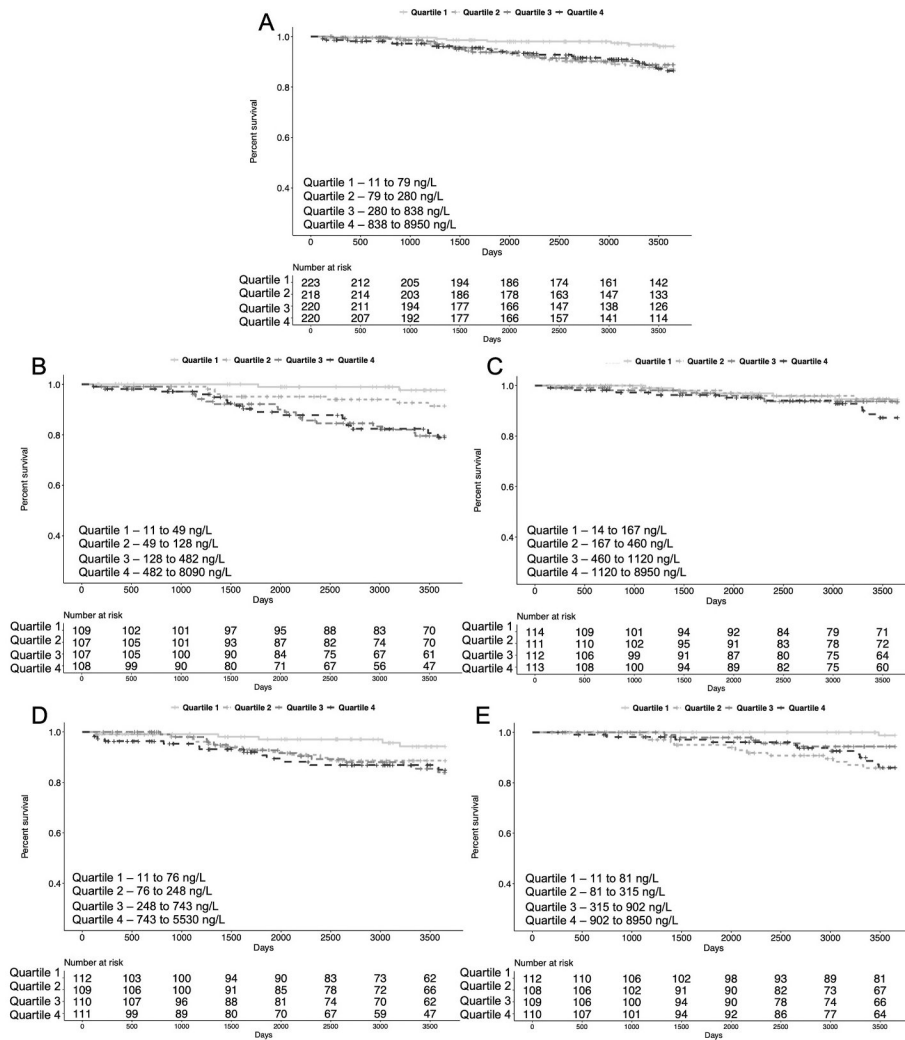Mortality is generally higher with higher quartiles of growth hormone.

Table 1

Baseline characteristics of total cohort and separated by sex and race.

	All	Men	Women	Black	White
Number (%)	881	431 (48.9)	450 (51.1)	442 (50.2)	439 (49.8)
Age in years, mean (SD)	67.4 (12.2)	67.4 (12.3)	67.3 (12.1)	67.2 (12.2)	67.5 (12.2)
Sex, men (%)	431 (48.9)	–	–	215 (48.6)	216 (49.2)
Race black, No. (%)	442 (50.2)	215 (49.9)	227 (50.4)	–	–
Antihypertensive use, No. (%)	456 (51.8)	211 (49.0)	245 (54.4)	271 (61.3)	185 (42.1)
DM, No. (%)	168 (19.1)	83 (19.3)	85 (18.9)	104 (23.5)	64 (14.6)
Current smoker, No. (%)	124 (14.1)	72 (16.7)	52 (11.6)	83 (18.8)	41 (9.3)
Region: Stroke belt, No. (%)	304 (34.5)	151 (35.0)	153 (34.0)	149 (33.7)	155 (35.3)
Region: Stroke buckle, No. (%)	162 (18.4)	72 (16.7)	90 (20.0)	68 (15.4)	94 (21.4)
Region: Other, No. (%)	415 (47.1)	208 (48.3)	207 (46.0)	225 (50.9)	190 (43.4)
Income <$20,000, No. (%)	159 (18.0)	62 (14.4)	97 (21.6)	109 (24.7)	50 (11.4)
Education < high school, No. (%)	132 (15.0)	68 (15.8)	64 (14.2)	101 (22.9)	31 (7.0)
BMI (kg/m^2), mean (SD)	28.7 (5.8)	28.2 (5.0)	29.1 (6.4)	29.6 (6.1)	27.7 (5.3)
SBP (mmHg), mean (SD)	128 (17)	130 (17)	127 (17)	132 (18)	125 (15)
DBP (mmHg), mean (SD)	77 (10)	77 (11)	76 (10)	79 (11)	75 (9)
LDL-C (mmol/L), mean (SD)	2.92 (0.88)	2.92 (0.91)	2.92 (0.85)	3.00 (0.91)	2.82 (0.83)
HDL-C (mmol/L), mean (SD)	1.34 (0.41)	1.19 (0.36)	1.50 (0.41)	1.40 (0.41)	1.29 (0.41)
GH (ng/L), median [IQR]	280 [79–838]	128 [49–483]	460 [167–1120]	249 [76–743]	315 [81–902]
log$_2$GH (ng/L), mean (SD)	8.0 (2.2)	7.3 (2.2)	8.7 (2.0)	7.9 (2.1)	8.2 (2.3)
All-cause mortality, No. (%)	237 (26.9)	132 (30.6)	105 (23.3)	124 (28.1)	113 (25.7)
CV mortality, No. (%)	74 (8.4)	46 (10.7)	28 (6.2)	43 (9.7)	31 (7.1)

BMI – body mass index; CV – cardiovascular; DBP – diastolic blood pressure; DM – diabetes mellitus; HDL-C – high density lipoprotein cholesterol; GH –growth hormone; IQR – interquartile range; LDL-C – low density lipoprotein cholesterol; No. – number; SD – standard deviation; SBP – systolic blood pressure.

Table 2

Growth hormone's association with all-cause mortality and cardiovascular mortality in univariable and multivariable Cox analysis in REGARDS.

		Events	Univariable		Multivariable[a]	
			HR	95% CI	HR	95% CI
All-cause mortality	All	236	1.17	1.10–1.25	1.17	1.09–1.25
	Men	132	1.27	1.17–1.37	1.21	1.11–1.33
	Women	105	1.16	1.05–1.29	1.12	0.99–1.27
	Black	124	1.19	1.09–1.31	1.15	1.04–1.28
	White	113	1.17	1.08–1.27	1.19	1.07–1.32
Cardiovascular mortality	All	74	1.18	1.06–1.31	1.21	1.06–1.37
	Men	46	1.28	1.12–1.47	1.21	1.04–1.42
	Women	28	1.21	0.98–1.50	1.20	0.91–1.58
	Black	43	1.19	1.02–1.39	1.20	1.00–1.44
	White	31	1.20	1.01–1.42	1.20	0.97–1.48

CI – confidence interval; GH – growth hormone; HR –hazard ratio.

[a] Covariates for multivariable analysis include age, sex, systolic blood pressure, body mass index, antihypertensive therapy, diabetes mellitus, current tobacco use, low density lipoprotein cholesterol, high density lipoprotein cholesterol, race, region, education, and annual income.

Table 3

C-index of GH alone, a multivariable model based of clinical variables without GH, and the multivariable model with the addition of GH for all-cause mortality and cardiovascular mortality in REGARDS.

Outcome	Sex	GH (95% CI)	Clinical Model* (95% CI)	Clinical Model + GH* (95% CI)	*p*-value (Clinical Model vs. Clinical Model + GH)
All-cause mortality	All	0.605 (0.570–0.639)	0.767 (0.736–0.795)	0.774 (0.743–0.802)	0.01
	Men	0.657 (0.611–0.700)	0.749 (0.705–0.789)	0.763 (0.719–0.801)	0.01
	Women	0.577 (0.522–0.630)	0.795 (0.753–0.831)	0.797 (0.757–0.833)	0.14
	Black	0.610 (0.560–0.658)	0.744 (0.700–0.785)	0.754 (0.709–0.794)	0.05
	White	0.603 (0.553–0.651)	0.794 (0.752–0.830)	0.800 (0.758–0.836)	0.03
Cardiovascular mortality	All	0.599 (0.541–0.655)	0.803 (0.753–0.845)	0.813 (0.765–0.854)	0.04
	Men	0.670 (0.600–0.732)	0.794 (0.727–0.848)	0.809 (0.743–0.861)	0.07
	Women	0.594 (0.486–0.693)	0.812 (0.732–0.873)	0.829 (0.756–0.883)	0.22
	Black	0.605 (0.523–0.683)	0.777 (0.701–0.839)	0.788 (0.713–0.848)	0.11
	White	0.607 (0.524–0.684)	0.878 (0.817–0.920)	0.888 (0.832–0.927)	0.14

Variables in clinical multivariate model were age, sex, systolic blood pressure, body mass index, antihypertensive therapy, diabetes mellitus, current tobacco use, low density lipoprotein cholesterol, high density lipoprotein cholesterol, race, region, education level and income with sex or race excluded from models that evaluated specific genders or races.

The *p*-value refers to the added chi square of growth hormone on top of the clinical model.

CI – confidence interval; GH – growth hormone.