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Authors

Bielinski, Suzette J
Berardi, Cecilia
Decker, Paul A
et al.

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Hepatocyte Growth Factor Demonstrates Racial Heterogeneity as a Biomarker for Atherosclerotic Coronary Heart Disease: The Multi-Ethnic Study of Atherosclerosis

Short title: Bielinski HGF Associated with heart disease

Suzette J. Bielinski, PhD, Cecilia Berardi, MD, MS, Paul A. Decker, MS, Nicholas B. Larson, PhD, Elizabeth J. Bell, PhD, MPH, James S. Pankow, PhD, MPH, Michele M. Sale, PhD,

Weihong Tang, MD, PhD, Naomi Q. Hanson, MS, Christina L. Wassel, PhD, Mariza de Andrade, PhD, Matthew Budoff, MD, Joseph F. Polak, MD, Hugues Sicotte, PhD, Michael Y. Tsai, MD, PhD

From the Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN (S.J.B., C.B., E.J.B.); Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN (P.A.D., N.B.L., M.d.A., H.S.); Department of Internal Medicine, Albert Einstein College of Medicine, and Montefiore Medical Center, Bronx, NY (C.B).; Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN (J.S.P., W.T.); Center for Public Health Genomics, University of Virginia, Charlottesville, VA (M.M.S.); Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN (N.Q.H., M.Y.T.); University of Vermont College of Medicine, Colchester, VT (C.L.W.) Los Angeles Biomedical Research Institute (M.B.); Tufts University School of Medicine, Boston, (J.F.P.).

Correspondence to Suzette J. Bielinski, PhD, MEd; Mayo Clinic, Department of Health Sciences Research, Division of Epidemiology, Harwick Building 6-56, 200 First Street Southwest; Rochester, MN 55909; Phone: (507) 538-4914; Fax: (507) 284-1516; E-mail: bielinski.suzette@mayo.edu

Abstract

Background—Hepatocyte growth factor (HGF) is a promising biomarker of coronary heart disease (CHD) given its release into circulation in response to endothelial damage; however the relationship of HGF with CHD and associated risk factors is largely unknown.

Methods and Results—HGF was measured in 6738 participants of the Multi-Ethnic Study of Atherosclerosis (MESA). Highest mean HGF values (ng/mL) were observed in Hispanic (1036±269), followed by African (934±249), non-Hispanic white (916±255), then Chinese (839±216) Americans. In all races/ethnicities, HGF levels were associated with older age, higher systolic blood pressure and BMI, lower HDL, diabetes, and current smoking. In fully adjusted models, each standard deviation (SD) higher HGF was associated with an average increase in coronary artery calcium of 55 Agatston units for non-Hispanic white (P<0.001) and 51 for African (P=0.007) Americans, but was not associated with coronary artery calcium in Chinese nor Hispanic Americans (race interaction P=0.02). HGF was positively associated with internal carotid intima medial thickness in non-Hispanic whites only (P<0.001, race interaction P<0.001). Furthermore, we observed an increase in the odds of the presence of plaque regardless of race/ethnicity (odds ratio [OR], 1.10, P=0.002). There were 529 incident CHD events and CHD risk was 41% higher in African (P<0.001), 17% in non-Hispanic white (P=0.026) and Chinese (P=0.36), and 6% in Hispanic (P=0.56) Americans per SD increase in HGF.

Conclusion—In a large and diverse cohort, HGF demonstrates racial/ethnic heterogeneity as an independent predictor of subclinical and CHD.

Key Words: atherosclerosis, coronary disease, epidemiology, risk factors

Hepatocyte growth factor (HGF) was originally identified and studied due to its mitogenic role in liver regeneration.[1] However, evidence is mounting that indicates HGF activities have cardioprotective effects in tissues through activation of anti-apoptotic, anti-inflammatory, anti-oxidant, anti-fibrotic, and angiogenesis pathways.[2-6] Subsequent research has shown that circulating HGF is elevated as a compensatory response to endothelial damage and accumulates in injured organs via its receptor c-Met.[7] Therefore, circulating HGF has been proposed as a potential clinical biomarker for assessing disease burden and predicting cardiovascular disease (CVD) and mortality.

Studies of circulating HGF in humans are predominantly limited to clinical populations with CVD. Collectively, these studies found higher circulating levels of HGF were associated with intima medial thickness (IMT), aorto-iliac artery atherosclerosis, and presence of coronary atherosclerosis.[8-13] Similarly, higher concentrations were associated with myocardial infarction (MI), unstable angina, and heart failure.[14-17] Likewise, HGF has been shown to be higher in those with cardiovascular risk factors such as hypertension, diabetes, and obesity.[18-20]

Despite the evidence linking HGF and atherosclerotic disease, little information is known about the relationship of HGF with disease and related risk factors in the general population. Prior studies were limited in scope, sample size, and racial/ethnic diversity. Importantly, previous research has demonstrated race/ethnicity-specific genetic regulation of HGF levels, justifying the exploration of potential heterogeneity in phenotype associations.[21] Therefore, using the diverse cohort comprising the prospective Multi-Ethnic Study of Atherosclerosis (MESA), the objective of this study is to describe the shared and race/ethnicity-specific relationships of circulating HGF with cardiovascular risk factors and determine if levels of HGF are associated with subclinical atherosclerosis and incident coronary heart disease (CHD).

Methods

Study Participants

MESA enrolled 6814 participants from 2000-2002 without known clinical CVD who were aged 45-84 years of which 38% were non-Hispanic white, 28% African, 22% Hispanic, and 12% Chinese Americans. MESA participants were examined at 6 field

centers located in Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; Northern Manhattan, NY; and Saint Paul, MN. The MESA study has been described in detail elsewhere.[22] As part of the MESA ancillary study titled Multi-Scale Biology of Atherosclerosis in the Cellular Adhesion Pathway (HL98077 – MESA Adhesion Study), 6738 participants had serum HGF measured at the first MESA exam (2000-2002). The study was approved by the Institutional Review Boards at each research center and informed consent was obtained from all participants.

Measurements

Self-administered and interview-administered questionnaires were used to collect data such as environmental exposures (e.g., smoking history), and health status (e.g., menopause). In addition, participants were asked to bring in all their medications to each exam to be recorded. Height was measured while participants were standing without shoes, heels together against a vertical mounted ruler. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Resting seated blood pressure was measured 3 times using an automated oscillometric method (Dinamap), and the average of the second and third readings was used in analyses. Hypertension was defined as systolic blood pressure (SBP) of ≥140 mm Hg, diastolic blood pressure (DBP) of ≥90 mm Hg, or taking antihypertensive medication.

Serum glucose was assayed by a glucose oxidase method on the Vitros analyzer (Johnson and Johnson Clinical Diagnostics, Rochester, NY). Diabetes was defined as any participant who self-reported a physician diagnosis, used diabetes medication, or had a fasting glucose ≥126 mg/dL. Total cholesterol was measured in ethylenediaminetetraacetic (EDTA) plasma using a cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN) on a Roche COBAS FARA centrifugal analyzer. After precipitation of non-HDL-cholesterol with magnesium/dextran, HDL-cholesterol was also measured in EDTA plasma using the cholesterol oxidase cholesterol method (Roche Diagnostics). Triglyceride was measured in EDTA plasma using Triglyceride Glycerol Blanked reagent (Roche Diagnostics) on a Roche COBAS FARA centrifugal analyzer. Serum creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). Glomerular filtration rate (GFR) was estimated using the simplified MDRD (Modification of Diet in Renal Disease study) equation.[23]

Circulating levels of HGF protein were measured at MESA Exam 1 in serum by a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) using the Human soluble HGF/CD62P Immunoassay kit (R&D Systems, Minneapolis, MN), with a lower limit of detection of 40 pg/mL. The interassay laboratory coefficients of variation for the HGF method were 12.0%, 8.0%, and 7.4% at respective mean concentrations of 686.6, 2039.1, and 4079.5 pg/mL for lyophilized manufacturer's controls; and 10.4% at a mean concentration of 687.7 pg/mL for an in-house pooled serum control.

Computed tomography (CT) of the coronary arteries was performed at exam 1 and methods have been previously described.[24] In brief, at 3 of 6 clinical centers, electron beam scanners (Imatron C-150; Imatron, Inc., San Francisco, CA) were used with cardiac-gating at 80% of the R-R interval. At the other 3 centers, a prospective electrocardiogram-triggered multi-detector scan was acquired at 50% of the R-R interval. All scanners were comparable in their ability to measure calcium.[24] Scans were read centrally at Harbor-University of California Medical Center (Los Angeles, CA), and Agatston coronary artery calcium (CAC) scores were quantified by blinded CT image analysts. Using high-resolution B-mode ultrasonography, images of the near and far walls of the bilateral common carotid and internal carotid arteries were obtained using a Logiq 700 ultrasound machine (GE Medical Systems, Waukesha, Wisconsin). Central reading of intima-media thickness (IMT) was done at the Tufts Medical Center (Boston, Massachusetts).[25] A semi-quantitative scale was used to report the presence of atherosclerotic plaque; those with 0% were considered to be absent a plaque, and those with >0% were positive for the presence of a plaque.[26]

Cardiovascular Events

Complete details of event ascertainment have been summarized previously,[27] and the MESA exam and follow-up forms for ascertaining events are available on the MESA website (http://www.mesa-nhlbi.org). In brief, the cohort was followed for 12.3 years via telephone interviews with participants at 9-12 month intervals, and with next of kin for out-of-hospital deaths. Hospital records were obtained on an estimated 99% of hospitalized cardiovascular events and some information on 97% of outpatient diagnostic encounters. Trained personnel abstracted any hospital records suggesting possible cardiovascular events that included MI, angina, resuscitated cardiac arrest, stroke (not transient ischemic attack), CHD, or other

CVD death. MI was defined by integrating cardiac pain, biomarker level, and ECG changes using the Minnesota code.[28]

Statistical Analyses

Exam 1 characteristics were compared across racial/ethnic strata using regression models. In race/ethnicity-stratified analyses, regression models were used to assess the association of HGF levels and traditional CVD risk factors (ie, age, sex, BMI, SBP, hypertension treatment, total and HDL cholesterol, and smoking and diabetes status). To investigate the association of HGF protein levels and subclinical atherosclerosis at Exam 1 (CAC, IMT, and presence of plaque), regression models were fit with HGF as the independent variable with adjustment for traditional risk factors. Assumptions of linearity for HGF were evaluated using generalized additive models with cubic B-splines. There were no indications of major departures from linearity. Because the distribution of CAC has a large percentage of zero measurements, standard normalization transformations are not adequate; therefore, the Tobit model was used to investigate the relationship between CAC and protein concentration levels. The association of HGF with time to CHD was assessed using Cox proportional hazards regression, adjusting for CHD risk factors. Race/ethnicity-stratified Kaplan Meier curves, adjusted for traditional risk factors, were created to illustrate cumulative incidence of CHD by tertile of HGF. We used a Bonferroni correction to account for multiple comparisons (0.05/4 strata x 5 outcomes = 0.0025). All testing for interactions between HGF and strata was conducted by pooling subjects across strata and testing the significance of HGF-by-strata interaction terms.

Results

Baseline characteristics of the MESA cohort stratified by race/ethnicity are provided in Table 1. Significant differences in HGF (ng/mL) by race/ethnicity were observed, with highest mean values in Hispanic (1036±269), followed by African (934±249), non-Hispanic white (916±255), then Chinese (839 ± 216) Americans (race/ethnicity interaction $P<0.001$). Furthermore, levels of HGF were positively associated with age (Figure 1). Exploring the relationship of HGF and traditional CVD risk factors, HGF levels were associated with higher BMI and SBP and lower HDL in all race/ethnicities after adjustment for age and sex (Table 2). Likewise, hypertensives,

current smokers, and diabetics had higher HGF levels. In females, lower levels of HGF were associated with use of hormone replacement therapy, albeit the association was strongest in non-Hispanic white and African American women. Exclusively in non-Hispanic whites, HGF levels were higher in females compared to males independent of age and inversely associated with current alcohol consumption.

Table 3 summarizes the association of HGF with subclinical and clinical atherosclerotic disease after adjustment for cardiovascular disease risk factors. In fully adjusted models, one standard deviation (SD) increase in HGF was associated with an average increase in CAC of 55 Agatston units for non-Hispanic white Americans ($P<0.001$), 51 for African ($P=0.007$) Americans, with no significant association in either Chinese or Hispanic Americans. A formal test of the race/ethnicity interaction term was significant ($P=0.02$).

Likewise, there was race/ethnicity differences in the relation between HGF and internal carotid IMT with a 1 SD increase in HGF associated with 0.07 mm higher internal carotid IMT in non-Hispanic whites ($P<0.001$). In contrast, levels of HGF were not associated with common carotid IMT in any of the four race/ethnicities. Furthermore, we observed an increase in the odds of the presence of plaque (OR = 1.10 per SD of HGF; $P=0.002$); results were similar in race/ethnicity stratified analyses.

There were 529 incident CHD events during the follow-up period. We observed racial/ethnic differences in crude CHD rates, with non-Hispanic whites having the highest rates at 8.3 per 1000 person years, followed by Hispanic and African (6.9), and Chinese (5.5) Americans. In models adjusted for traditional risk factors, CHD risk was 41% higher per SD increase in HGF in African ($P<0.001$), 17% in non-Hispanic whites ($P=0.026$) and Chinese ($P=0.36$), and 6% in Hispanic ($P=0.56$) Americans. Similarly, adjusted Kaplan Meier curves of the cumulative incidence of CHD by tertile of HGF displayed racial/ethnic differences (Figure 2). However, the formal test of interaction between the races was not significant ($P=0.18$). In race/ethnicity pooled analyses, each 1 SD increase in HGF was associated with a 20% higher risk of CHD ($p<0.001$).

To assess the impact of healthy participant bias in MESA, we conducted sensitively analyses stratifying by age. Stratifying the MESA cohort into two age groups (ie, 45-64 and 65-84), we observed similar associations with subclinical

disease. In contrast, a significant difference by age group was observed for incident CHD with a 1 SD increase in HGF associated with a 32% increased risk of CHD in the younger group ($P<0.001$), while a 12% increased risk was observed in the older group ($P=0.04$, age by HGF interaction $P=0.03$).

Discussion

HGF was positively associated with subclinical and clinical CHD in this large and diverse population. Increased circulating levels of HGF were associated with greater CAC and incident CHD in African and non-Hispanic white Americans independent of other cardiovascular risk factors. In contrast, levels of HGF were not associated with subclinical disease in Chinese or Hispanic Americans nor were levels of HGF significantly associated with increased risk of CHD in these groups. These findings provide initial evidence that HGF may be to be a valuable clinical marker and further demonstrate the utility of HGF may be limited to specific populations.

HGF is thought to be primarily produced by mesenchymal cells and acts on cells expressing MET.[31] HGF and MET expression are simulated in response to tissue injury resulting in the activation of anti-apoptotic pathways, increased angiogenesis, and upregulation of IL-10, a cytokine that limits inflammation.[32] Additionally, activation of HGF/Met enhances critical protective pathways that act against hypoxia-induced autophagy.[2] A substantial body of evidence exists regarding the cardioprotective effects of these tissue activities in atherosclerotic heart disease, which have been summarized previously.[33] Consequently, HGF has been hypothesized as a potential biomarker for disease prediction as well as a biomarker of disease burden. Herein, we demonstrate racial/ethnic heterogeneity in the association of HGF with atherosclerotic heart disease.

The mechanisms underlying the racial/ethnic heterogeneity in the association of HGF with CAC and internal carotid IMT remain unclear. However, these results support the notion that subclinical measures of atherosclerosis may not reflect the extent of disease similarly across race/ethnicity groups. Numerous studies, including MESA, have found that non-Hispanic whites have higher prevalence and density of CAC compared other race/ethnicities and that African Americans have the lowest prevalence.[34-37] Our novel finding that higher HGF is associated with CAC in both non-Hispanic whites and African Americans suggest that despite the distributional

differences in CAC between the two groups, HGF is a potential biomarker of underlying disease.

Prior investigations of HGF and IMT have focused predominantly in small Japanese clinical populations. The largest study investigated 317 residents of Japan and reported that those in the upper 50th percentile of HGF had increased common carotid IMT compared to those with lower levels.[9] Of note, a previous MESA study demonstrated that common carotid IMT predicted CHD, albeit not as strongly as CAC.[39] In contrast and despite the large sample size in MESA, HGF was associated specifically with internal carotid IMT in non-Hispanic whites. These seemingly mixed results need to be viewed in the context of MESA IMT measurements. The common carotid artery IMT measurements were made below the bulb but did not consider presence or absence of early plaque and thus there was no exclusion of plaque. Therefore, this IMT measure is less of a surrogate for atherosclerosis and more likely related to hypertrophy of the medial layer. In contrast, the internal carotid artery IMT focused on capturing any plaque present in either the bulb or proximal internal carotid artery and thus there are site-specific differences in the association of risk factors and these two IMT measurements.[40-42]

Similar to the results for CAC, the increased risk of CHD in those with higher levels of HGF was most compelling for African and non-Hispanic white Americans. However, in contrast to the results for subclinical disease, low CHD event numbers in Chinese and Hispanic Americans may be impacting our ability to detect meaningful associations. The increased risk of CHD observed with higher levels of HGF in MESA, extends our knowledge of this relationship beyond highly selected clinical populations that have dominated the literature to date. For example, higher HGF has been associated with increased risk of death in heart failure patients,[43] and in patients undergoing percutaneous coronary revascularization.[44] Likewise, higher levels of HGF are associated with acute MI. Herein we show that levels of HGF predict the development of clinical disease.

HGF is released in response to tissue injury and thus we expect circulating levels to be associated with adverse risk factors. In relatively small clinical populations, circulating HGF has been associated with advanced age, current smoking and diabetes, and systolic blood pressure. Likewise, obesity is associated with higher levels of HGF with concomitant decreases following weight loss.[50] In MESA, we more fully elucidated the shared and race/ethnicity specific relationships

with traditional cardiovascular risk factors. Collectively, these results support the hypothesis that HGF levels are associated with a more adverse risk profile suggestive of systemic inflammation and endothelial injury. We further demonstrate that HGF levels add additional information as to underlying disease risk.

The major limitation of the study is the relatively small number of CHD events in Chinese and Hispanic Americans that may have hindered our ability to detect an association with HGF. Furthermore, MESA participants were required to be free of known CVD at baseline resulting in a healthy participant bias that is likely stronger in the older ages. To attempt to understand how this bias could affect the association of HGF and incident CHD, we stratified the cohort by age and observed a stronger association in the 45-64 year olds then in the older group. These results suggest that our pooled point estimate could be biased toward the null, and the increased risk of CHD per SD of HGF could be higher in a general population sample. Strengths of the study include the large sample sizes in four race/ethnicity groups as prior investigations were limited in both size and diversity. Given the high prevalence of CAC in all four racial/ethnic groups (>40%), there was adequate power to detect an association in race/ethnicity stratified analyses.

Conclusion

In a large and diverse population-based cohort, we report that HGF is associated with subclinical and incident CHD. We demonstrate evidence of racial/ethnic heterogeneity within these associations, as the results are most compelling in African and non-Hispanic white Americans. We provide novel evidence that HGF is a biomarker of atherosclerotic disease that is independent of traditional risk factors and thus could have utility as a prognostic marker of CHD risk.

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Disclosures

None

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LEGENDS

Figure 1. Hepatocyte growth factor by race/ethnicity and age strata.

Figure 2. Kaplan-Meier curves for incident coronary heart disease by tertile of hepatocyte growth factor by Race/Ethnicity.

Table 1. Baseline Characteristics by Race/Ethnicity for Those With Hepatocyte Growth Factor Measured at Exam 1 (Mean ± Standard Deviation or Percentage)

Characteristics	African American	Chinese American	Hispanic American	Non-Hispanic white American	*P* Value
n	1861	799	1477	2604	
HGF, ng/mL	934.4 (249.8)	839.4 (216.1)	1035.9 (268.7)	915.8 (255.1)	<0.001
Age, years	62.1 (10.0)	62.4 (10.3)	61.2 (10.3)	62.6 (10.2)	<0.001
Sex, % female	56	51	52	52	0.058
Body mass index, kg/m2	30.2 (5.8)	24.0 (3.3)	29.4 (5.1)	27.7 (5.1)	<0.001
Systolic blood pressure, mmHg	131.7 (21.6)	124.6 (21.6)	126.5 (21.8)	123.5 (20.4)	<0.001
Diastolic blood pressure, mmHg	74.5 (10.2)	72.0 (10.4)	71.5 (10.1)	70.2 (10.0)	<0.001
Hypertension, % yes	59	38	41	38	<0.001
Blood pressure status					<0.001
Normotensive < 120 mmHg, % yes	41	63	59	62	
Hypertensive (controlled), % yes	48	26	30	28	
Hypertensive (uncontrolled), % yes	12	12	12	11	
Diabetes mellitus, % yes	17.5	12.9	17.3	6	<0.001
Laboratory Values					
Total cholesterol, mg/dL	189.6 (36.1)	192.7 (31.8)	198.3 (37.5)	195.8 (35.1)	<0.001
HDL cholesterol, mg/dL	52.4 (15.2)	49.5 (12.7)	47.7 (13.1)	52.3 (15.7)	<0.001
LDL cholesterol, mg/dL	116.5 (32.9)	115.2 (29.0)	119.8 (32.9)	117.1 (30.1)	0.003
Triglycerides, mg/dL	104.8 (68.8)	142.9 (84.9)	157.5 (101.5)	132.9 (90.4)	<0.001
Creatinine, mg/dL	1.0 (0.3)	0.9 (0.2)	0.9 (0.3)	1.0 (0.2)	<0.001
Glomerular filtration rate (GFR)	86.4 (19.2)	82.3 (16.6)	83.4 (18.2)	75.9 (17.0)	<0.001

Lifestyle factors					
Smoking status					<0.001
Never, % yes	45	75	54	44	
Former, % yes	37	19	32	44	
Current, % yes	18	6	14	11	
Current use of alcohol, % yes	50	31	47	72	<0.001
Current medication use					
Antilipidemic therapy, % yes	16	14	13	18	<0.001
Statin use, % yes	15	13	12	17	<0.001
Hypertension medication use, % yes	50	29	32	33	<0.001
Calcium channel blockers, % yes	21	10	11	8	<0.001
Inhibitors of ADP-induced platelet aggregation, % yes	0.2	0.1	0.3	0.3	0.6
Angiotensin type 2 antagonists	4	5	3	3	0.003
Aspirin use, % yes	31	18	26	40	<0.001
Diabetes medication use, % yes (diabetics only)	79	74	80	70	0.073
Diuretic use, % yes	22	4	8	13	<0.001
Hormone replacement therapy % yes (females only)	46	34	40	64	<0.001
Subclinical and Clinical Disease					
CAC > 0, % yes	43	50	45	57	<0.001
CAC categories					<0.001
< 50, %	76	71	74	63	
50-149, %	10	14	11	11	
150-399, %	7	9	7	12	
> 400, %	8	6	8	13	

Common carotid IMT, mm	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)	0.9 (0.2)	<0.001
Internal carotid IMT, mm	1.1 (0.6)	0.9 (0.5)	1.0 (0.6)	1.1 (0.6)	<0.001
Presence of plaque, % Yes	44	26	39	47	<0.001

P Value from regression model comparing variables across ethnic groups.

Table 2. Race-Ethnicity Specific Association of Tertiles of Hepatocyte Growth Factor and Cardiovascular Disease Risk Factors

	African American				Chinese American				Hispanic American				Non-Hispanic white American			
Characteristics	Tertile 1	Tertile 2	Tertile 3	*P* Value	Tertile 1	Tertile 2	Tertile 3	*P* Value	Tertile 1	Tertile 2	Tertile 3	*P* Value	Tertile 1	Tertile 2	Tertile 3	*P* Value
HGF Range	342.6-813.9	814.3-999.6	1000.0-2151.8		292.4-738.3	738.3-892.1	892.4-2135.9		317.7-903.2	903.7-1112.9	1113.4-2094.1		313.6-783.5	783.6-993.1	993.2-2117.0	
Age, years	59.1 (9.3)	62.3 (9.9)	65.0 (10.0)	<0.001	57.9 (9.5)	62.6 (9.3)	66.6 (10.3)	<0.001	58.0 (9.4)	61.3 (9.9)	64.3 (10.7)	<0.001	59.3 (9.5)	62.6 (10.1)	65.9 (10.1)	<0.001
Sex, % female	50	61	55	0.39	52	48	54	0.64	49	52	55	0.08	47	52	57	<0.001
Body Mass Index, kg/m2	29.3 (5.3)	30.4 (5.9)	30.7 (6.2)	<0.001	23.2 (2.9)	24.2 (3.3)	24.5 (3.6)	<0.001	28.2 (4.5)	29.2 (4.6)	30.9 (5.7)	<0.001	26.4 (4.3)	27.6 (4.9)	29.2 (5.5)	<0.001
Systolic Blood Pressure, mmHg	128.4 (20.0)	131.6 (22.2)	135.2 (22.1)	0.01	118.6 (18.8)	125.6 (21.7)	129.8 (22.7)	0.02	121.0 (19.4)	126.9 (21.2)	131.8 (23.2)	<0.001	119.3 (18.7)	122.7 (19.9)	128.4 (21.7)	<0.001
Hypertension, % Yes	49	59	70	<0.001	25	38	49	0.001	30	41	53	<0.001	29	36	50	<0.001
Diabetes Mellitus, % Yes	11	17	24	<0.001	6	13	20	<0.001	8	19	25	<0.001	2	5	11	<0.001
Total Cholesterol, mg/dL	190.0 (35.6)	192.8 (36.8)	186.0 (35.6)	<0.001	194.0 (32.8)	190.1 (32.0)	194.1 (30.5)	0.47	202.4 (38.0)	200.9 (37.9)	191.6 (35.5)	<0.001	195.3 (33.3)	197.3 (36.1)	194.9 (35.8)	0.31
HDL Cholesterol, mg/dL	54.1 (15.4)	52.3 (15.4)	50.8 (14.7)	<0.001	51.3 (13.7)	49.1 (11.8)	48.1 (12.3)	<0.001	49.2 (13.9)	47.4 (12.9)	46.4 (12.2)	<0.001	54.2 (16.7)	52.2 (15.4)	50.4 (14.7)	<0.001
Triglycerides, mg/dL	97.2 (75.2)	107.3 (70.3)	109.9 (59.5)	<0.001	133.0 (83.7)	135.3 (72.2)	160.5 (94.9)	<0.001	155.6 (111.6)	162.4 (109.2)	154.5 (80.9)	0.82	117.8 (69.4)	133.6 (105.1)	147.3 (90.6)	<0.001
Creatinine, mg/dL	1.0 (0.2)	1.0 (0.2)	1.0 (0.3)	<0.001	0.9 (0.2)	0.9 (0.2)	0.9 (0.3)	0.03	0.9 (0.2)	0.9 (0.2)	0.9 (0.4)	0.68	0.9 (0.2)	1.0 (0.2)	1.0 (0.2)	<0.001
Glomerular Filtration Rate (GFR)	88.4 (17.0)	85.9 (18.5)	84.8 (21.7)	0.43	85.2 (14.1)	83.0 (16.4)	78.7 (18.5)	0.3	83.6 (15.8)	83.9 (17.4)	82.7 (21.0)	0.005	78.3 (20.4)	75.6 (13.8)	73.8 (15.9)	0.15
Current Smoker, % Yes	13	17	23	<0.001	3	6	8	<0.001	9	14	18	<0.001	8	11	15	<0.001
Current Use of Alcohol, % Yes	52	51	46	0.58	34	32	28	0.45	51	49	43	0.56	76	73	66	<0.001
Antilipidemic Therapy, % Yes	15	16	19	0.91	9	14	20	0.02	12	13	14	0.22	15	18	22	0.008
Statin Use, % Yes	14	15	18	0.89	9	12	17	0.4	11	12	13	0.25	14	16	20	0.05
Hypertension Medication Use, % Yes	40	49	62	<0.001	18	28	40	<0.001	24	31	42	<0.001	24	33	42	<0.001
Calcium Channel Blockers, % Yes	18	17	28	0.005	5	10	14	0.03	9	9	14	0.03	6	6	11	0.01
Angiotensin Type 2 Antagonists	4	3	5	0.36	3	4	9	0.07	1	3	4	0.02	2	2	4	0.1
Aspirin Use, % Yes	29	30	33	0.51	10	21	24	0.03	23	26	30	0.61	35	41	42	0.55
Diabetes Medication Use, % Yes	80	74	83	0.31	67	79	72	0.85	66	84	82	0.12	47	70	75	0.26
Diuretic Use, % Yes	18	21	26	0.17	2	5	6	0.004	5	8	12	0.004	7	12	21	<0.001
Females Only																
Hormone Replacement Therapy, % Yes	55	45	40	0.004	44	31	28	0.09	45	41	34	0.76	68	69	57	<0.001
Post-menopause, % Yes	82	85	87	0.65	78	85	94	0.55	82	90	90	0.95	79	85	90	0.33

P Values from a linear regression model adjusted for age and sex.

Table 3. Association of Hepatocyte Growth Factor and Subclinical and Clinical Atherosclerotic Disease

	Pooled Sample		Race/Ethnicity Interaction	African American		Chinese American		Hispanic American		Non-Hispanic white American	
	*Beta (S.E.)	*P* Value	*P* Value	Beta (S.E.)	*P* Value	Beta (S.E.)	*P* Value	Beta (S.E.)	*P* Value	Beta (S.E.)	*P* Value
CAC, Agatston Score											
Model 1	65 (8)	<0.001	0.031	71 (18)	<0.001	31 (19)	0.097	38 (19)	0.044	86 (13)	<0.001
Model 2	37 (8.9)	<0.001	0.022	51 (19)	0.007	-2.5 (19)	0.90	17 (20)	0.39	55 (14)	<0.001
Common Carotid IMT, mm											
Model 1	0.009 (0.002)	<0.001	0.53	0.007 (0.004)	0.13	0.015 (0.007)	0.042	0.008 (0.004)	0.069	0.01 (0.004)	0.005
Model 2	-0.001 (0.002)	0.81	0.74	0.002 (0.005)	0.62	0.001 (0.007)	0.88	-0.009 (0.005)	0.84	-0.004 (0.004)	0.28
Internal Carotid IMT, mm											
Model 1	0.06 (0.007)	<0.001	<0.001	0.036 (0.015)	0.015	0.05 (0.02)	0.014	0.03 (0.014)	0.035	0.098 (0.012)	<0.001
Model 2	0.036 (0.008)	<0.001	<0.001	0.014 (0.015)	0.35	0.029 (0.021)	0.18	0.008 (0.015)	0.60	0.071 (0.013)	<0.001
	OR (95% CI)	***P* Value**		**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Presence of Plaque											
Model 1	1.19 (1.13-1.26)	<0.001	0.35	1.11 (1.0 - 1.24)	0.045	1.21 (0.99-1.48)	0.070	1.18 (1.06-1.32)	0.004	1.26 (1.15-1.38)	<0.001
Model 2	1.10 (1.04-1.17)	0.002	0.37	1.04 (0.93-1.16)	0.52	1.10 (0.89-1.37)	0.38	1.12 (0.99-1.27)	0.064	1.14 (1.04-1.26)	0.007
Number of CHD Events	529			134		48		109		238	
Total Person-Years	72833			19552		8805		15709		28767	
Crude CHD Rate, per 1,000 person-years	7.3			6.9		5.5		6.9		8.3	
	HR (95% CI)	***P* Value**		**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**

Time to Coronary Heart Disease											
Model 1	1.30 (1.20-1.41)	<0.001	0.24	1.47 (1.27-1.71)	<0.001	1.32 (0.98-1.77)	0.067	1.13 (0.95-1.35)	0.17	1.30 (1.15-1.47)	<0.001
Model 2	1.20 (1.10-1.31)	<0.001	0.18	1.41 (1.20-1.66)	<0.001	1.17 (0.84-1.62)	0.36	1.06 (0.87-1.28)	0.56	1.17 (1.02-1.33)	0.026

Results are reported per standard deviation increase in hepatocyte growth factor (SD=259).

Model 1 = age and sex (+ race/ethnicity in pooled analyses).

Model 2 = age, sex, BMI, systolic blood pressure, hypertension treatment, total cholesterol, HDL cholesterol, smoking and diabetes status (+ race/ethnicity in pooled analyses).

Table 4 Association of Hepatocyte Growth Factor and Subclinical and Clinical Atherosclerotic Disease by Baseline Age Grouping

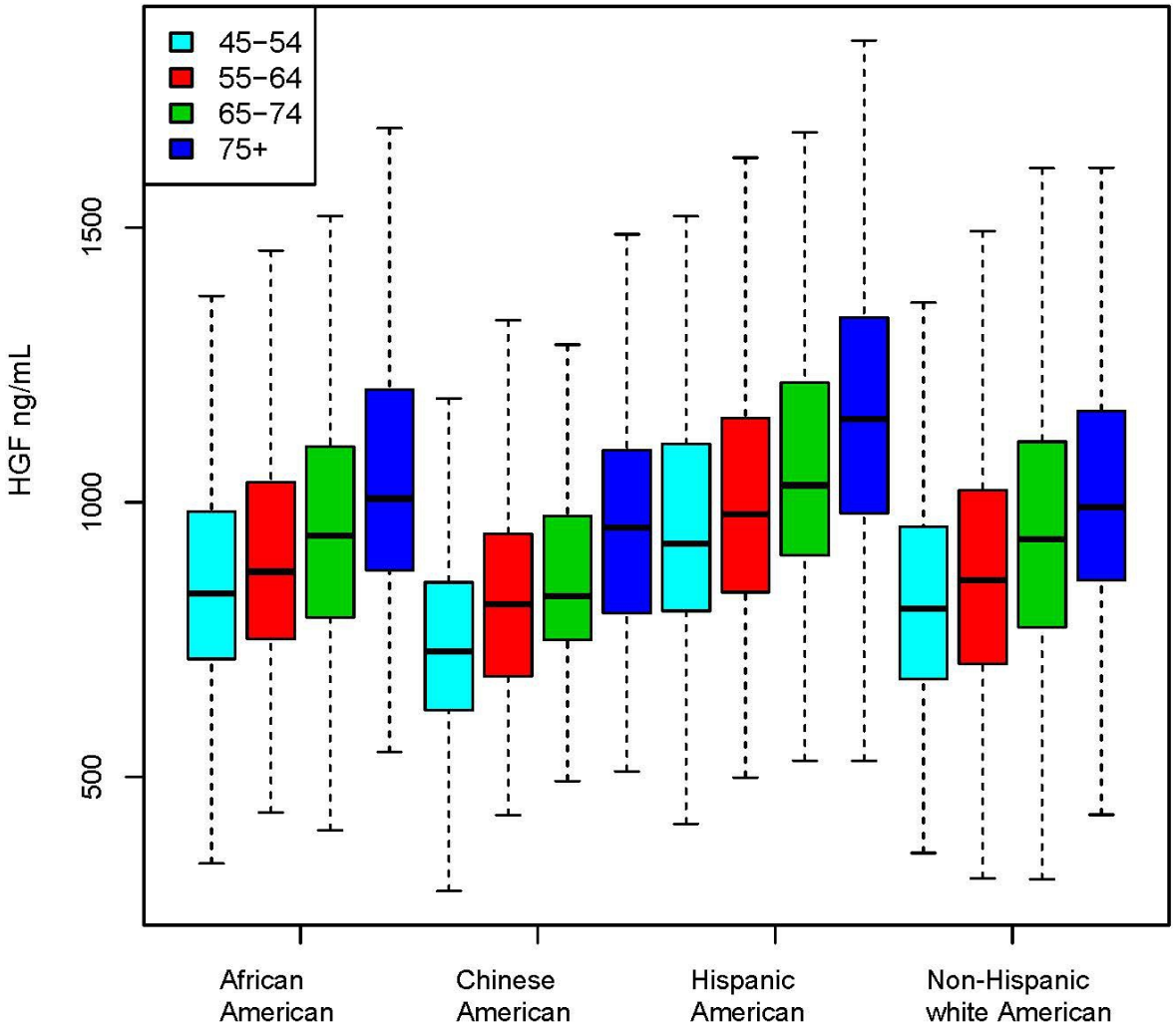
	Exam 1 Age 45-64 (n=3790)		Exam 1 Age 65-84 (n=2951)	
	Beta (S.E.)	*P* Value	Beta (S.E.)	*P* Value
CAC, Agatston Score				
Model 1	56 (8.3)	<0.001	61 (13)	<0.001
Model 2	27 (8.8)	0.002	37 (14)	0.008
Common Carotid IMT, mm				
Model 1	0.015 (0.003)	<0.001	0.001 (0.004)	0.75
Model 2	0.003 (0.003)	0.27	-0.005 (0.004)	0.17
Internal Carotid IMT, mm				
Model 1	0.054 (0.008)	<0.001	0.065 (0.014)	<0.001
Model 2	0.025 (0.008)	0.002	0.044 (0.014)	0.002
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Presence of Plaque				
Model 1	1.23 (1.14-1.33)	<0.001	1.16 (1.07-1.26)	<0.001
Model 2	1.10 (1.01-1.19)	0.028	1.11 (1.02-1.21)	0.02
Number of CHD Events	193		336	
Total Person-Years	43,379		29,454	
Crude CHD Rate, per 1,000 person-years	4.4		11.4	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Time to Coronary Heart Disease				

Model 1	1.52 (1.35-1.72)	<0.001	1.18 (1.06-1.31)	0.002
Model 2	1.32 (1.15-1.51)	<0.001	1.12 (1.01-1.26)	0.04

Model 1 = age, sex and race/ethnicity.

Model 2 = age, sex, BMI, systolic blood pressure, hypertension treatment, total cholesterol, HDL cholesterol, smoking and diabetes status and race/ethnicity.

Figure 1 Hepatocyte Growth Factor by Race/Ethnicity and Age Strata



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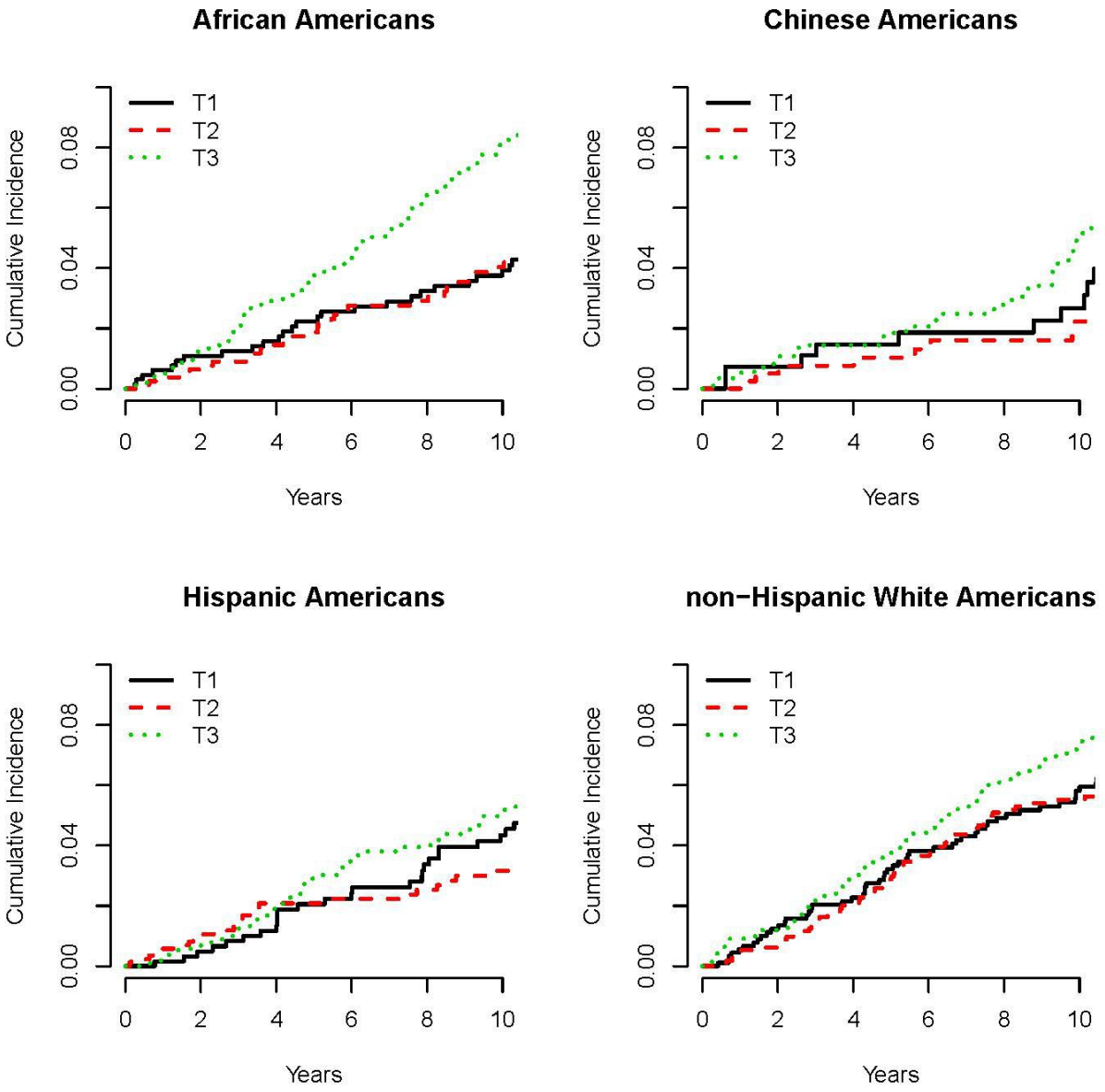
African Americans
Chinese Americans
Hispanic Americans
non−Hispanic White Americans
T1
T2
T3
Cumulative Incidence
0.00
0.04
0.08
0
2
4
6
8
10
Years

520

46
47