HHS Public Access

Author manuscript

Heart. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Heart. 2017 August ; 103(15): 1185–1193. doi:10.1136/heartjnl-2016-310450.

Hepatocyte growth factor demonstrates racial heterogeneity as a biomarker for coronary heart disease

Suzette J. Bielinski, PhD[1], **Cecilia Berardi, MD, MS**[1,2], **Paul A. Decker, MS**[3], **Nicholas B. Larson, PhD**[3], **Elizabeth J. Bell, PhD, MPH**[1], **James S. Pankow, PhD, MPH**[4], **Michele M. Sale, PhD**[5], **Weihong Tang, MD, PhD**[4], **Naomi Q. Hanson, MS**[6], **Christina L. Wassel, PhD**[7], **Mariza de Andrade, PhD**[3], **Matthew J. Budoff, MD**[8], **Joseph F. Polak, MD**[9], **Hugues Sicotte, PhD**[3], and **Michael Y. Tsai, MD, PhD**[6]

[1]Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

[2]Department of Internal Medicine, Albert Einstein College of Medicine, and Montefiore Medical Center, Bronx, NY, USA

[3]Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

[4]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA

[5]Center for Public Health Genomics, University of Virginia, Charlottesville, VA, USA

[6]Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA

[7]Department of Pathology and Laboratory Medicine, University of Vermont College of Medicine, Colchester, VT, USA

[8]Los Angeles Biomedical Research Institute, Harbor-UCLA, Torrance, CA, USA

[9]Tufts University School of Medicine, Boston, MA, USA

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; bielinski.suzette@mayo.edu.

Contributors

Study design: SJB, CB, PAD, NBL, EJB, CLW
Data collection: SJB, NQH, MYT
Data analysis: PAD, NBL, MA
Outcome adjudication: MB, JFP
Manuscript draft: All authors contributed, read and approved the final manuscript.

Completing interests None declared.

Ethics approval MESA and its ancillary studies were approved by the Institutional Review Board at participating centers and all participants gave written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement MESA Coordinating Center distributes only deidentified Datasets (with **HIP**AA defined identifiers removed) to Recipient Investigators with approved manuscripts proposals in compliance with MESA and NHLBI/NIH data privacy and sharing standard practices and policy. Additionally, access to MESA datasets require completion of a Data Distribution Agreement (MESA Data and Materials Distribution Agreement if the Investigator is not at a MESA affiliated Institution) and review and approval of a detailed proposal by MESA Publications and Steering Committees for soundness in science, methodology, and adherence to MESA policy. Manuscript pen drafts (and presentation abstracts) are also reviewed by these same committees.

Abstract

Objective—To determine if hepatocyte growth factor (HGF), a promising biomarker of coronary heart disease (CHD) given its release into circulation in response to endothelial damage, is associated with subclinical and clinical CHD in a racial/ethnic diverse population.

Methods—HGF was measured in 6738 participants of the Multi-Ethnic Study of Atherosclerosis. Highest mean HGF values (pg/mL) were observed in Hispanic, followed by African, non-Hispanic white, then Chinese Americans.

Results—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 in the other race/ethnic groups (interaction $p=0.02$). 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 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 evidence that HGF is a biomarker of atherosclerotic disease that is independent of traditional risk factors.

Keywords

atherosclerosis; coronary disease; epidemiology; risk factors

INTRODUCTION

Hepatocyte growth factor (HGF) was originally identified and studied due to its mitogenic role in liver regeneration.[1] Evidence is mounting that indicates HGF activities have cardioprotective effects in tissues through activation of anti-apoptotic, anti-inflammatory, anti-oxidant, and anti-fibrotic, pathways.[2] However, it is unknown if HGF contributes to the progression of atherosclerosis given that it is also a strong promotor of angiogenesis,[3, 4] an essential component of atherosclerotic plaque neovascularization. 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.[5] Therefore, circulating HGF has been proposed as a potential clinical biomarker for assessing disease burden and predicting cardiovascular disease (CVD).

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.[6–8] Similarly, higher concentrations were associated with myocardial infarction (MI), unstable angina, and heart failure.[9, 10] Likewise, HGF has

been shown to be higher in those with cardiovascular risk factors such as hypertension, diabetes, and obesity.[11, 12]

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.[13] 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.[14] As part of the MESA ancillary study titled Multi-Scale Biology of Atherosclerosis in the Cellular Adhesion Pathway (HL98077), 6738 participants had serum HGF measured at the first 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

Questionnaires were used to collect data such as environmental exposures (e.g., smoking history), and health status (e.g., menopause). 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-high density lipoprotein (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.

Circulating levels of HGF protein were measured at 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.[15] In brief, at 3 of 6 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.[15] 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 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). 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.

Coronary heart disease events

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 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. CHD events included all MI, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), and CHD death.

Statistical analyses

Exam 1 characteristics were compared across racial/ethnic strata using linear regression models for continuous variables and the chi-square test for categorical variables. In race/ethnicity-stratified analyses, regression models were used to assess the association of HGF levels and CVD risk factors (i.e., age, sex, BMI, SBP, hypertension treatment, total and HDL cholesterol, and smoking and diabetes status). To investigate the association of HGF levels and CAC, IMT, and presence of plaque at Exam 1, regression models were fit with HGF as the independent variable with adjustment for 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. Linear regression was used for IMT and logistic regression was used for plaque. Because the distribution of CAC has a large percentage of zero measurements, standard normalization transformations are not adequate; therefore, the Tobit model (type II) was used to investigate the relationship between CAC and protein concentration levels.[16] An additional two-stage modeling analysis was performed to assess the association of HGF with CAC. Stage 1 assessed the relationship of HGF with CAC limited to subjects with CAC>0 using linear regression models as described previously; Stage 2 assessed the relationship of HGF with any CAC using logistic regression. The association of HGF with time to CHD was assessed using Cox proportional hazards regression, adjusting for CHD risk factors. Associations are reported per race-pooled standard deviation increase in HGF (259 pg/mL). Proportional hazards were verified by examination of the Schoenfeld residuals. 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 × 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 stratified by race/ethnicity are provided in Table 1. Significant differences in HGF (pg/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.

Education and income level did not impact the effect, therefore, Table 3 summarizes the association of HGF with atherosclerotic disease after adjustment for traditional 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) and 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). Similar results were observed for models limited to CAC>0 and when modeling any CAC. For those participants with measurable CAC, a one SD increase in HGF associated with an average increase in CAC of 33 Agatston units for non-Hispanic white Americans (p=0.025) and 53 for African (p=0.01) Americans. However, when modeling any CAC, we only see a significant increase in odds in Non-Hispanic whites (OR=1.23, 95% CI 1.10–1.36).

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); similar effect sizes were observed for Chinese (OR=1.10; p=0.38), Hispanic (OR=1.12; p=0.064) and non-Hispanic White Americans (OR=1.14; p<0.001).

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) and 17% in non-Hispanic whites (p=0.026). Although not statistically significant, we observed a 17% increase in CHD risk in 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 sensitivity analyses stratifying by age. Stratifying the MESA cohort into two age groups (i.e., 45–64 and 65–84), we observed similar associations with subclinical disease (Table 4). 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.[2] HGF and MET expression are stimulated 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.[17] Additionally, activation of HGF/Met enhances critical protective pathways that act against hypoxia-induced autophagy.[18] A substantial body of evidence exists regarding the cardioprotective effects of these tissue activities in atherosclerotic heart disease, which have been summarized previously.[2] In contrast, the angiogenic properties of HGF and associations of circulating HGF and cardiovascular risk factors and disease implicate HGF in atherosclerotic disease. Despite the uncertainty regarding the role of HGF in atherosclerosis, 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.[19, 20] 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.[7, 21] The largest study investigated 317 Japanese residents and reported that those in the upper 50^{th} percentile of HGF had increased common carotid IMT compared to those with lower levels.[6] Of note, a previous MESA study demonstrated that common carotid IMT predicted CHD, albeit not as strongly as CAC.[22] 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.[23]

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,[24] and in patients undergoing percutaneous coronary revascularization.[25] Likewise, higher levels of HGF are associated with acute MI. [9] 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,[10, 25–27] and systolic blood pressure.[7, 28, 29] Likewise, obesity is associated with higher levels of HGF[12, 30] with concomitant decreases following weight loss.[31] 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. Likewise, our ability to formally evaluate the prognostic value of HGF is limited by the number of events to date and thus will be the focus of future research as the cohort ages. Furthermore, MESA participants were required to be free of known CVD at baseline and thus are likely more representative of a primary prevention population as opposed to the general population. Healthy participant bias may be a factor and one that is likely stronger in the older ages. To attempt to understand if 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 evidence that HGF is a biomarker of atherosclerotic disease that is independent of traditional risk factors. However, further research is needed to assess HGF as a clinically useful risk marker of atherosclerotic disease.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-

nhlbi.org. MESA is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with MESA investigators.

Funding This research was supported by the NIH contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute (NHLBI) at NIH and by grants UL1-TR-000040 and UL1-TR-001079 from National Center for Research Resources at NIH. Funding for adhesion protein levels was provided by the NHLBI by grant R01 HL98077. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

REFERENCES

1. Nakamura T, Nawa K, Ichihara A. Partial purification and characterization of hepatocyte growth factor from serum of hepatectomized rats. Biochem Biophys Res Commun. 1984; 122:1450–1459. [PubMed: 6477569]
2. Gallo S, Sala V, Gatti S, et al. Cellular and molecular mechanisms of HGF/Met in the cardiovascular system. Clin Sci. 2015; 129:1173–1193. [PubMed: 26561593]
3. Bussolino F, Di Renzo MF, Ziche M, et al. Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell motility and growth. J Cell Biol. 1992; 119:629–641. [PubMed: 1383237]
4. Grant DS, Kleinman HK, Goldberg ID, et al. Scatter factor induces blood vessel formation in vivo. Proc Natl Acad Sci U S A. 1993; 90:1937–1941. [PubMed: 7680481]
5. Tajima H, Higuchi O, Mizuno K, et al. Tissue distribution of hepatocyte growth factor receptor and its exclusive down-regulation in a regenerating organ after injury. J Biochem (Tokyo). 1992; 111:401–406. [PubMed: 1316892]
6. Yamamoto Y, Kohara K, Tabara Y, et al. Plasma hepatocyte growth factor and the relationship between risk factors and carotid atherosclerosis. Hypertens Res. 2002; 25:661–667. [PubMed: 12452316]
7. Kawamoto R, Oka Y, Yoshida O, et al. Significance of serum circulating hepatocyte growth factor in the development of carotid atherosclerosis. J Atheroscler Thromb. 2003; 10:154–159. [PubMed: 14564084]
8. Tateishi J, Waku S, Masutani M, et al. Hepatocyte growth factor as a potential predictor of the presence of atherosclerotic aorto-iliac artery disease. Am Heart J. 2002; 143:272–276. [PubMed: 11835030]
9. Sato T, Yoshinouchi T, Sakamoto T, et al. Hepatocyte growth factor(HGF): a new biochemical marker for acute myocardial infarction. Heart Vessels. 1997; 12:241–246. [PubMed: 9846810]
10. Lamblin N, Susen S, Dagorn J, et al. Prognostic significance of circulating levels of angiogenic cytokines in patients with congestive heart failure. Am Heart J. 2005; 150:137–143. [PubMed: 16084160]
11. Bancks MP, Bielinski SJ, Decker PA, et al. Circulating level of hepatocyte growth factor predicts incidence of type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis (MESA). Metabolism. 2016; 65:64–72. [PubMed: 26892517]
12. Lieb W, Safa R, Benjamin EJ, et al. Vascular endothelial growth factor, its soluble receptor, and hepatocyte growth factor: clinical and genetic correlates and association with vascular function. Eur Heart J. 2009; 30:1121–1127. [PubMed: 19223316]
13. Larson NB, Berardi C, Decker PA, et al. Trans-ethnic meta-analysis identifies common and rare variants associated with hepatocyte growth factor levels in the Multi-Ethnic Study of Atherosclerosis (MESA). Ann Hum Genet. 2015; 79:264–274. [PubMed: 25998175]
14. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–881. [PubMed: 12397006]

15. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology. 2005; 234:35–43. [PubMed: 15618373]
16. Tobin J. Estimation for relationships with limited dependent variables. Econometrica. 1958; 26:24–36.
17. Rutella S, Bonanno G, Procoli A, et al. Hepatocyte growth factor favors monocyte differentiation into regulatory interleukin (IL)-10 + + IL-12low/neg accessory cells with dendritic-cell features. Blood. 2006; 108:218–227. [PubMed: 16527888]
18. Gallo S, Gatti S, Sala V, et al. Agonist antibodies activating the Met receptor protect cardiomyoblasts from cobalt chloride-induced apoptosis and autophagy. Cell Death Dis. 2014; 5:e1185. [PubMed: 24743740]
19. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2005; 111:1313–1320. [PubMed: 15769774]
20. Lee TC, O'Malley PG, Feuerstein I, et al. The prevalence and severity of coronary artery calcification on coronary artery computed tomography in black and white subjects. J Am Coll Cardiol. 2003; 41:39–44. [PubMed: 12570942]
21. Satani K, Konya H, Hamaguchi T, et al. Clinical significance of circulating hepatocyte growth factor, a new risk marker of carotid atherosclerosis in patients with Type 2 diabetes. Diabet Med. 2006; 23:617–622. [PubMed: 16759302]
22. Gepner AD, Young R, Delaney JA, et al. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging. 2015:8.
23. Polak JF, Post WS, Carr JJ, et al. Associations of common carotid intima-media thickness with coronary heart disease risk factors and events vary with distance from the carotid bulb. J Am Soc Echocardiogr. 2014; 27:991–997. [PubMed: 24944141]
24. Rychli K, Richter B, Hohensinner PJ, et al. Hepatocyte growth factor is a strong predictor of mortality in patients with advanced heart failure. Heart. 2011; 97:1158–1163. [PubMed: 21572126]
25. Susen S, Sautiere K, Mouquet F, et al. Serum hepatocyte growth factor levels predict long-term clinical outcome after percutaneous coronary revascularization. Eur Heart J. 2005; 26:2387–2395. [PubMed: 16105849]
26. Rajpathak SN, Wassertheil-Smoller S, Crandall J, et al. Hepatocyte growth factor and clinical diabetes in postmenopausal women. Diabetes Care. 2010; 33:2013–2015. [PubMed: 20519660]
27. Yamamoto Y, Kohara K, Tabara Y, et al. Association between carotid arterial remodeling and plasma concentration of circulating hepatocyte growth factor. J Hypertens. 2001; 19:1975–1979. [PubMed: 11677362]
28. Nakamura Y, Morishita R, Nakamura S, et al. A vascular modulator, hepatocyte growth factor, is associated with systolic pressure. Hypertension. 1996; 28:409–413. [PubMed: 8794825]
29. Nakamura S, Moriguchi A, Morishita R, et al. A novel vascular modulator, hepatocyte growth factor (HGF), as a potential index of the severity of hypertension. Biochem Biophys Res Commun. 1998; 242:238–243. [PubMed: 9439642]
30. Rehman J, Considine RV, Bovenkerk JE, et al. Obesity is associated with increased levels of circulating hepatocyte growth factor. J Am Coll Cardiol. 2003; 41:1408–1413. [PubMed: 12706940]
31. Swierczynski J, Korczynska J, Goyke E, et al. Serum hepatocyte growth factor concentration in obese women decreases after vertical banded gastroplasty. Obes Surg. 2005; 15:803–808. [PubMed: 15978151]

Key questions

What is already known about this subject?

HGF has previously been associated with cardiovascular risk factors and atherosclerotic disease.

What does this this study add?

Previous studies have predominantly focused on clinical populations that were limited in scope, sample size, and racial/ethnic diversity. By using the Multi-Ethnic Study of Atherosclerosis (MESA), we observed that each standard deviation higher HGF was associated with an average increase in coronary artery calcium of 55 Agatston units for non-Hispanic white and 51 for African Americans, but was not in the other race/ethnic groups (interaction $p=0.02$). Likewise, coronary heart disease 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 standard deviation increase in HGF.

How might this impact on clinical practice?

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.

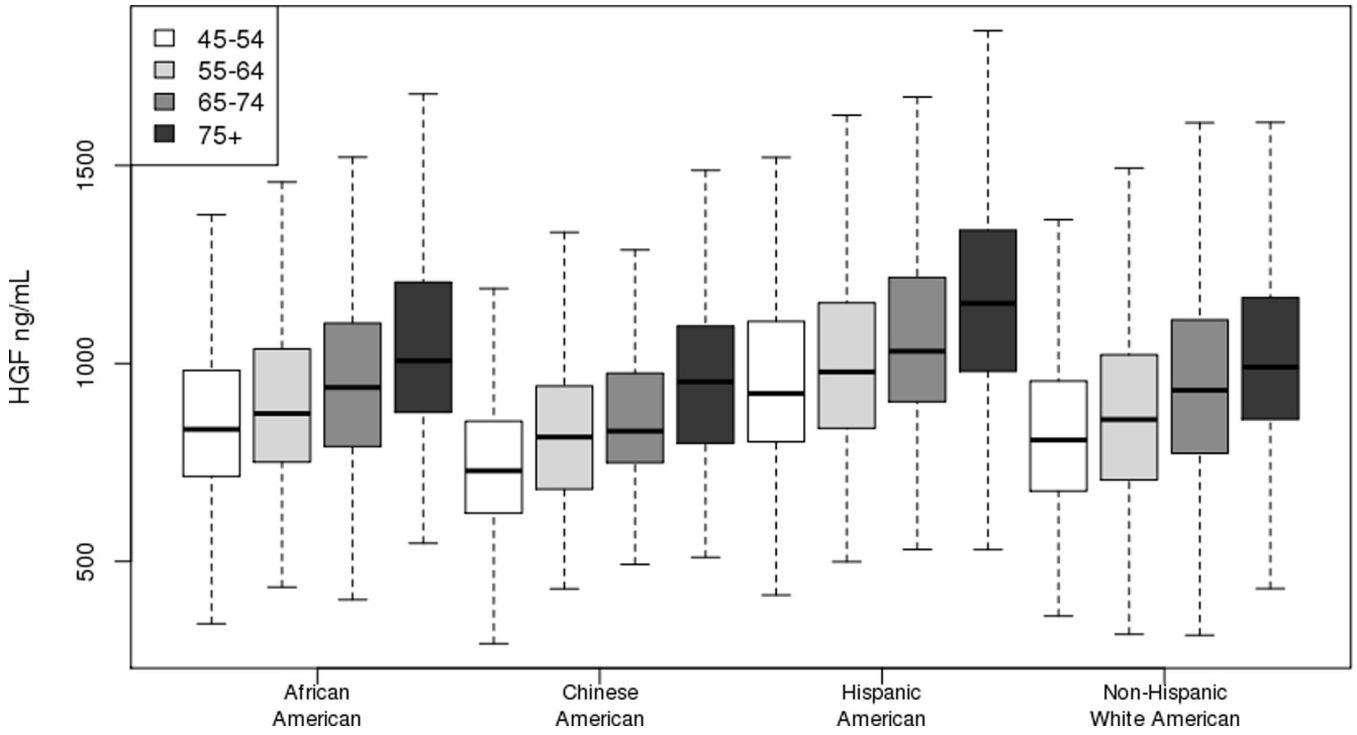

Figure 1.

Boxplot of hepatocyte growth factor by race/ethnicity and age strata. The lower and upper edges of the rectangle are the 25th and 75th percentiles and the horizontal line within the rectangle is the median. The lines extend from each rectangle to the lowest and highest values within 1.5 × interquartile range.

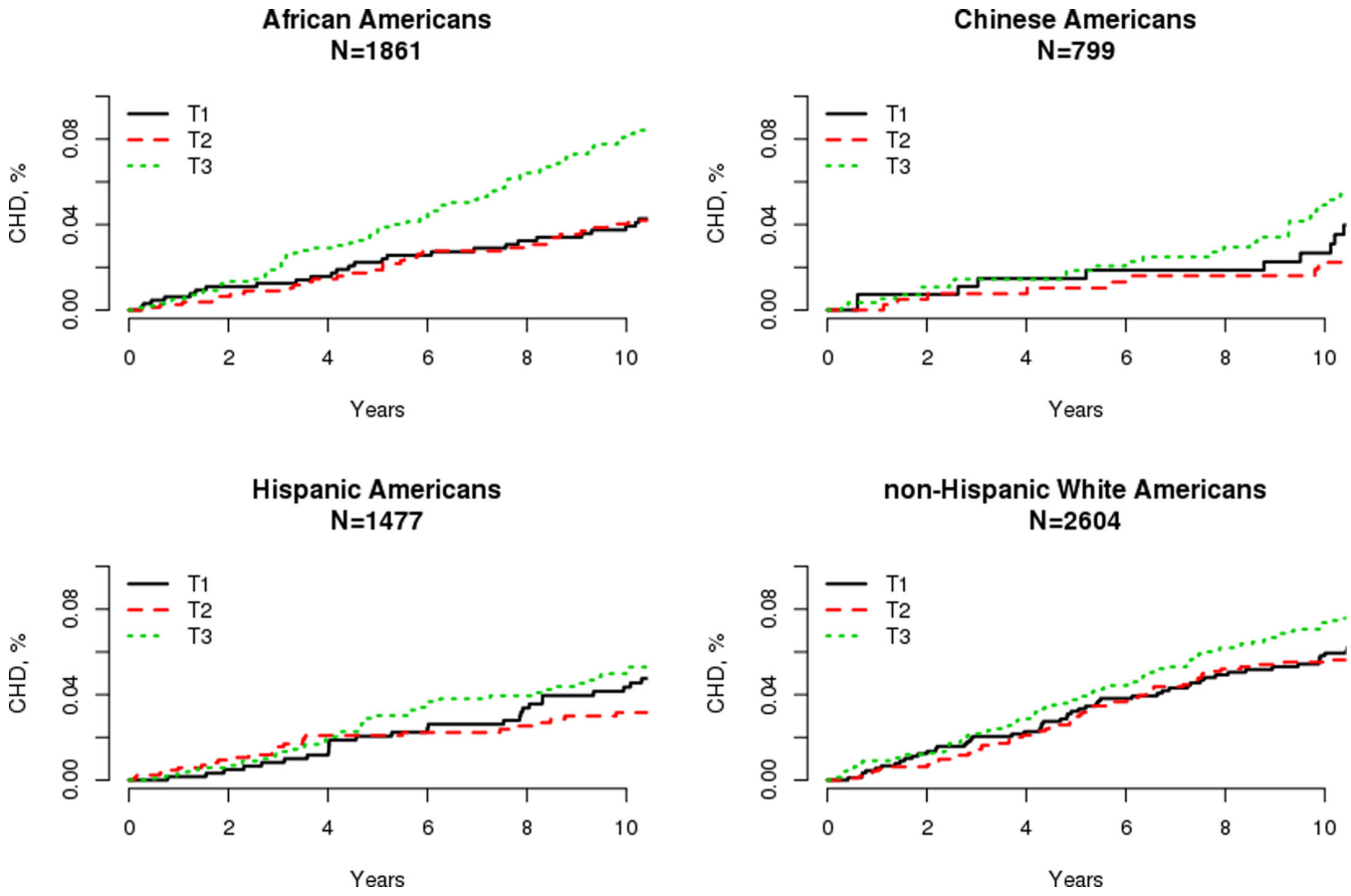

Figure 2.

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, pg/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
Education					<0.001
≤11th grade	12	25	45	5	
High school graduate	19	16	20	17	
Some college	35	20	25	28	
Bachelor's degree	17	23	6	22	
Graduate/professional school	17	16	4	28	
Income					<0.001
< $25,000	30	50	49	16	
$25,000 – $50,000	32	22	33	27	
$50,000 – $100,000	29	18	15	33	
≥ $100,000	8	10	2	25	
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

Characteristics	African American	Chinese American	Hispanic American	Non-Hispanic white American	p Value
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

CAC, coronary artery calcium; GFR, glomerular filtration rate; HDL, high-density lipoproteins; IMT, intima medial thickness; HGF, hepatocyte growth factor; LDL, low-density lipoprotein.

p Value from linear regression model for continuous variables and chi-square test for categorical variables 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 (pg/mL)	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
Education				<0.001				<0.001				0.33				<0.001
≤11th grade	9	11	15		16	26	33		39	50	46		3	5	7	
High school graduate	16	19	23		12	18	19		21	18	23		14	15	22	
Some college	35	34	36		25	16	19		30	22	24		23	29	33	
Bachelor's degree	21	19	13		28	22	18		5	7	5		27	23	17	
Graduate/professional school	20	17	13		20	18	11		6	4	3		33	29	20	
Income				0.002				0.08				0.10				<0.001
< $25,000	22	32	37		41	49	60		44	50	55		11	14	23	
$25,000 – $50,000	31	32	34		22	21	23		35	33	31		23	26	32	
$50,000 – $100,000	37	27	23		24	19	12		19	15	12		33	35	30	
≥ $100,000	10	9	6		13	11	6		3	3	2		33	25	15	
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

GFR, glomerular filtration rate; HDL, high-density lipoproteins; HGF, hepatocyte growth factor.

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 p Value	African American		Chinese American		Hispanic American		Non-Hispanic white American	
	*Beta (S.E.)	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
CAC>0, Agatston Score											
Model 1	37 (9)	<0.001	0.041	62 (20)	0.002	−3 (19)	0.87	14 (21)	0.50	46 (13)	<0.001
Model 2	23 (10)	0.016	0.028	53 (21)	0.011	−24 (19)	0.22	11 (22)	0.62	33 (15)	0.025
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
Any CAC, Agatston Score											
Model 1	1.24 (1.16–1.31)	<0.001	0.052	1.15 (1.03–1.28)	0.012	1.31 (1.07–1.60)	0.009	1.14 (1.01–1.28)	0.029	1.39 (1.26–1.53)	<0.001
Model 2	1.12 (1.05–1.19)	<0.001	0.11	1.07 (0.96–1.20)	0.22	1.13 (0.92–1.39)	0.25	1.05 (0.93–1.20)	0.43	1.23 (1.10–1.36)	<0.001
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)	**pValue**		**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

	Pooled Sample		Race/Ethnicity Interaction p Value	African American		Chinese American		Hispanic American		Non-Hispanic white American	
	*Beta (S.E.)	p Value		Beta (S.E.)	p Value	Beta (S.E.)	p Value	Beta (S.E.)	p Value	Beta (S.E.)	p Value
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

CAC, coronary artery calcium; CHD, coronary heart disease; IMT, intima medial thickness.

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

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)**	**pValue**
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

CAC, coronary artery calcium; CHD, coronary heart disease; IMT, intima medial thickness.

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.