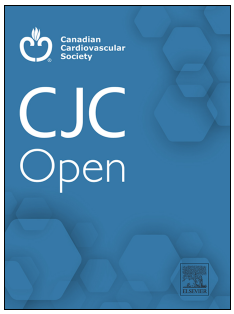

Hepatocyte Growth Factor and 10-year Change in Left Ventricular Structure: The Multi-Ethnic Study of Atherosclerosis

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Hepatocyte Growth Factor and 10-year Change in Left Ventricular Structure: The Multi-Ethnic Study of Atherosclerosis

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ABSTRACT

Background: Hepatocyte growth factor (HGF) is a cytokine linked to incident heart failure (HF), particularly HF with preserved ejection fraction (HFpEF). Increases in left ventricular (LV) mass and concentric remodeling defined by increasing mass-to-volume ratios are imaging risk markers for HFpEF. We aimed to determine if HGF was associated with adverse LV remodeling.

Methods: We studied 4,907 participants of the Multi-Ethnic Study of Atherosclerosis, free of cardiovascular disease (CVD) and HF at baseline, who had HGF measured and cardiac magnetic resonance imaging (CMR) performed at baseline. Of these, 2,921 completed a 2nd CMR at 10 years. We examined the cross-sectional and longitudinal associations of HGF and LV structural parameters using multivariable-adjusted linear mixed effect models, adjusting for CVD risk factors and NT-proBNP.

Results: The mean (SD) for age was 62 (10) years; 52% were female. Median (IQR) for HGF level was 890 pg/mL (745-1070). At baseline, the highest HGF tertile, compared to the lowest, was associated with greater mass-to-volume ratio [relative difference 1.94 (95% CI, 0.72, 3.17)] and lower LV end diastolic volume [-2.07 mL (-3.72, -0.42)]. In longitudinal analysis, the highest HGF tertile was associated with increasing mass-to-volume ratio [10-year difference: 4.68 (2.64, 6.72)] and decreasing LV end diastolic volume [-4.74 (-6.87, -2.62)].

Conclusions: In a community-based cohort, higher HGF levels were independently associated with a concentric LV remodeling pattern of increasing mass-to-volume ratio and decreasing LV end diastolic volume by CMR over 10 years. These associations may reflect an intermediate phenotype explaining the association of HGF with HFpEF risk.

Key Words Heart failure, Heart failure with preserved ejection fraction, Cardiac Imaging, Cardiac MRI

Abbreviations and Acronyms

CVD: Cardiovascular Disease

eGFR: Estimated Glomerular Filtration Rate

HF: Heart Failure

HFpEF: Heart Failure with Preserved Ejection Fraction

HFrEF: Heart Failure with Reduced Ejection Fraction

HGF: Hepatocyte Growth Factor

LV: Left Ventricle

LVEDV: LV End-diastolic Volume

LVM: LV Mass

M:V: Mass-to-Volume

MRI: Magnetic Resonance Imaging

NT-proBNP: N-Terminal Pro B-type Natriuretic Peptide

Registration: The MESA cohort is registered at : clinicaltrials.gov/ct2/show/NCT00005487

INTRODUCTION

Among chronic diseases, heart failure (HF) is a major and growing threat to the healthcare system.[1, 2] Although there have been significant advances in HF treatment over the years,[3, 4] therapeutic developments fall far behind the growing incidence of new HF cases. Two subtypes dominate current diagnoses and dictate subsequent treatment: HF with reduced ejection fraction (HFrEF), generally determined by an left ventricular (LV) ejection fraction ≤50%, and HF with preserved ejection fraction (HFpEF), determined by HF symptoms alongside an ejection fraction ≥50%.[4] It should be acknowledged that recent HF guideline organizations have further sub-typed a third HF group for those with a moderately reduced ejection fraction of 40-49% as an important clinical entity (HFmrEF), thus re-categorizing HFrEF as being ejection fraction <40% and HFpEF with ejection fraction ≥50%.[5, 6] Nomenclature aside, HFrEF and HFpEF are derived from very different pathophysiologic mechanisms, despite often leading to a similar set of symptoms consistent with clinical HF (i.e., dyspnea, orthopnea, lower extremity edema).

Hepatocyte Growth Factor (HGF) is a mesenchymal cytokine essential to the embryonic development of epithelial and endothelial cell lines.[7] HGF is thought to have many potentially favorable attributes, such as being anti-apoptotic, angiogenic, and anti-fibrotic.[8] Despite these favorable properties, in epidemiologic studies, circulating HGF levels have been associated with incident cardiovascular disease (CVD), including coronary heart disease,[9] stroke,[10] peripheral artery disease,[11] and HF[12]. This suggests that release of HGF into circulation may reflect compensatory mechanisms in response to vascular injury that ultimately have failed in disease states such as HF. Recent work from our group has shown that HGF was significantly associated with the incident HF overall, and when adjudicated for HF subtype, HGF levels were found to be associated with incident HFpEF but not HFrEF.[12] Given these findings, changes in cardiac

structure and function may be an intermediary step linking HGF and the pathogenesis of HF, though this has not been well studied.

Cardiac magnetic resonance imaging (MRI) is an important tool in the evaluation of cardiac size and function, allowing for precise measurement and differentiation of HF and its various precursors, such as chamber dilation or hypertrophy.[13-16] Increased LV hypertrophy and concentric remodeling (increased mass-to-volume (M:V) ratio), for example, are risk markers for incident HFpEF.[17-19] Given important physiologic differences in LV size and function that predispose to the development of HFrEF versus HFpEF, further studies on LV remodeling in association with HGF are warranted.

Our aim was to examine the association of HGF with baseline and 10-year change in LV mass, volume, and their ratio via cardiac MRI with the goal of understanding any potential pathophysiological impacts or associations of this biomarker with cardiac structure and function.

MATERIAL AND METHODS

Transparency and Openness Policy

The Multi-Ethnic Study of Atherosclerosis (MESA) data are available through the National Heart, Lung, Blood Institute (NHLBI) Biologic Specimen and Data Repository Coordinating Center (BioLINCC). Requests for access to the data can be made through their website: https://biolincc.nhlbi.nih.gov/studies/mesa/. Via the methods described in this manuscript, our findings should be easily reproducible.

Study Population

MESA is a prospective, multi-center study of 6,814 participants who were aged 45-84 years old at baseline and represented 4 self-reported racial or ethnic groups.[20] All participants were free of clinical CVD or HF at Exam 1 (2000-2002), and were followed for up for a total of

6 exams. Institutional review board agreement at each study site was required, and written consent was obtained for all participants.

We included all MESA participants with HGF measurement from exam 1 as well as a baseline cardiac MRI assessment. Participants were excluded if they were missing LV parameters (n=1797), missing HGF (n=36), or missing covariates in our primary model (n=74). This left a total sample size of 4,907 for cross-sectional analysis, and a sample size of 2,921 who had a 2nd cardiac MRI that enabled longitudinal analysis (**Figure 1**).

HGF Measurement

Fasting blood samples were obtained from all participants, separated by centrifugation within 30 minutes of sample collection and then stored at -70°C in serum until samples were ready to be thawed for analysis.[21] HGF levels were assessed via a sandwich enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN).[22] At mean concentrations of 687, 2039, and 4080 pg/mL, the interassay coefficients of variations were 12%, 8%, and 7.4%, respectively, for manufacturer controls. Pooled serum controls exhibited a mean concentration of 688 pg/mL and a coefficient of variation of 10.4%.[21]

Cardiac MRI Analysis

LV structure was assessed using cardiac MRI at visit 1 (2000-2002) and visit 5 (2010-2012), as previously described.[23, 24] The MRI Core Lab performed harmonization to account for technical changes, including the MRI scanners and sequences, over this 10-year period.[23] The LV parameters considered in this analysis included LV mass (LVM), LV end-diastolic volume (LVEDV), mass-to-volume (M:V) ratio, and LVM and LVEDV indexed to body surface area. Left atrial maximum and minimum volume was additionally included for further analysis. Inter-reader reliability of cardiac MRI variables within MESA has previously been reported, and was

shown to be excellent for LVEDV and LVM. As a point of reference, mean LVEDV and LVM values in the cohort were 119.2 mL and 120.6 g, respectively.[25]

Covariate Assessment

Participants underwent standardized questionnaires, physical exam, and laboratory testing at exam 1, as previously described.[20] For this analysis we considered sociodemographic factors (age, sex, race/ethnicity, MESA site, and education), body size and physiologic factors (height, weight, heart rate, systolic blood pressure, estimated glomerular filtration rate (eGFR)), other lifestyle and cardiovascular risk factors (smoking status, physical activity, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and diabetes status), and use of modifying pharmacotherapy agents (anti-hypertensive and lipid-lowering medications). N-terminal pro b-type natriuretic peptide (NT-proBNP) was included in an additional model to determine if the association of HGF and change in LV parameters was independent of NT-proBNP.

Medication use was captured by an inventory. Education was dichotomized as < or ≥bachelor's degree. Physical activity was quantified as the total amount of moderate and vigorous physical activity in metabolic equivalent minutes per week obtained from a typical week Physical Activity questionnaire.[26] Height and weight were measured on exam in standardized fashion, and body mass index (BMI) was calculated as the weight divided by the height squared (kg/m^2). Systolic and diastolic blood pressure were measured while participants were seated using a Dinamap automated device, and the 2nd and 3rd measurements were averaged. Diabetes was classified as present if the fasting blood glucose level was ≥126 mg/dL, if there was a self-reported diagnosis of diabetes, or use of diabetes medications. NT-proBNP was measured by an Elecsys proBNP immunoassay (Roche Diagnostics Corporation,

Indianapolis, IN).[27] Estimated GFR was calculated using the CKD Epidemiology Collaboration formula.[28]

Statistical Analysis

LV parameters used in this this analysis were LVM, LVEDV, M:V ratio, LVM/body surface area, and LVEDV/body surface area. We examined cross-sectional and longitudinal association of HGF and each of the LV parameters separately using multivariable-adjusted linear mixed effect models with an independent covariance structure between random intercept and random slope. Mixed effect linear regression models were used to leverage MRI measurements from all available time points while simultaneously taking into account baseline and longitudinal changes in LV parameters from same model. Covariates in the model were time-varying and updated at subsequent visit. We have previously used this method before for evaluating change in LV parameters by cardiac MRI.[14, 15]

We subsequently adjusted the models in progressive fashion. Model 1 was adjusted for exam 1 age, race/ethnicity, sex and MESA site. Model 2 adjusted for variables in Model 1 along with education, exam 1 and exam 5 measures of physical activity, smoking status, height, and weight (height and weight are excluded from models in which LV parameters are indexed to body surface area). Model 3 adjusted for variables in Model 2 plus exam 1 and exam 5 measures of systolic blood pressure, use of anti-hypertensive medication, total cholesterol, HDL-C, use of lipid lowering medication, and diabetes mellitus status. Model 4 adjusted for variables in Model 3 plus baseline log-transformed NT-proBNP and eGFR.

In a sensitivity analysis, we excluded individuals with reduced LVEF (<50%) at baseline who may be influential outliers, leaving a sample size of 4,753. We used STATA version 15.0

(StataCorp LP, College Station, TX) for the analysis. P values were two-sided, with statistically significant values considered at $p<0.05$.

RESULTS

In our study population of 4,907 participants, the mean age was 62 ± 10 years. 52% were women, 39% of participants were non-Hispanic White, 25% Black, 22% Hispanic, and 13% Chinese Americans (**Table 1**). Median interquartile range (IQR) for HGF level was 890 pg/mL (745-1070), and HGF levels were significantly different between the highest and lower tertiles. A higher percentage of Hispanic participants were found in highest tertile (32%) as compared to the lowest (13%) and middle tertile (23%), while the highest percentage of Chinese American participants were found in the lowest tertile (20%) as compared to the middle (13%) and highest (7%) tertiles. There was no significant difference in the distribution of Black or non-Hispanic White Americans among HGF tertiles. Additionally, participants with higher HGF were more likely to have older age, be current smokers, have prevalent diabetes mellitus, higher systolic blood pressures, higher heart rates, lower HDL-C, and were more likely to use antihypertensive as well as lipid lowering therapy. NT-proBNP levels were significantly greater in the highest versus lowest HGF tertiles (63 vs 45 pg/mL, $p<0.001$).

In cross-sectional analysis of 4,907 participants with exam 1 assessment of LV structure, the unadjusted median (IQR) values of the LV parameters by HGF tertile is shown via box plot in **Figure 2**. **Table 2** shows the adjusted associations of HGF in tertiles with these same LV parameters. In the fully adjusted model including CVD risk factors, eGFR and NT-proBNP (model 4), the highest HGF tertile compared to the lowest was associated with greater M:V ratio (1.94 (95% CI: 0.72, 3.17)), lower LVEDV (-2.07 (-3.72, -0.42)), and lower LV volume indexed

to body surface area (-1.25 (-2.12, -0.39)). While higher HGF by tertiles was significantly associated with LVM in limited adjusted analysis (model 1), this was no longer the case following covariate adjustment. When stratified by race/ethnicity, higher HGF tertiles were only significantly associated with LV volume in White participants (**Supplemental Table S1**). There was no significant association between left atrial volume and HGF upon adjustment for CVD risk factors in cross-sectional analysis (**Supplemental Table S2**).

Out of 4,907 participants with MRI performed at exam 1, there were 2,921 who also had cardiac MRI performed at visit 5 (approximately 10-years later) to allow for longitudinal analysis of LV parameters in relation to baseline HGF measurement. Differences in baseline characteristics between participants included only in cross-sectional assessment versus those in longitudinal assessment are shown in **Supplemental Tables S3 and S4**, respectively. Participants with available data for longitudinal assessment were younger, more likely to be White, more likely to have a bachelor's degree or higher, and exhibited greater physical activity, while being less likely have a diagnosis of diabetes mellitus or to be on anti-hypertensive medications compared to participants who contributed to the cross-sectional analysis only.

In longitudinal analysis, the highest baseline HGF tertile was significantly associated with increased M:V ratio (4.68 (95% CI: 2.64, 6.72)), reduced LVEDV (-4.74 (-6.87, -2.62)), and LV volume indexed to body surface area (-2.25 (-3.37, -1.13)) over 10-year follow-up in the most fully adjusted model (**Table 3,** model 4). As with cross-sectional analysis, there was no significant association seen between HGF tertile and changes in LVM alone in any model of covariate adjustment. When stratified by race/ethnicity, HGF was only significantly associated with LVEDV in the third tertile for White participants (**Supplemental Table S5**). Higher HGF was associated with increased left atrial minimum volume in a model adjusted for CVD risk

factors (model 3); however, no significant association between HGF and left atrial volume was found on longitudinal assessment in the fully adjusted model (model 4) (**Supplemental Table S6**).

In sensitivity analysis excluding those with LV ejection fraction <50% at baseline, findings were similar in both cross-sectional analysis (**Supplemental Table S7**) and longitudinal analysis (**Supplemental Table S8**).

DISCUSSION

In this multicenter study comprising a diverse participant population, we found that baseline HGF was significantly associated with markers of concentric remodeling on cross-sectional evaluation. We further show that these changes are continued on longitudinal assessment, with baseline HGF levels correlating with decreasing LV volume and increasing M:V ratio on analysis of serial cardiac MRIs. To our knowledge, the relationship of HGF with cardiac remodeling has not been previously reported.

Prior work from MESA has linked LV geometry to future CVD events among individuals who were initially asymptomatic. Specifically, increased LV hypertrophy was associated with future HF events, and increased M:V ratio (i.e., concentric LV remodeling) was linked to incident coronary heart disease events and stroke.[16] Other studies have specifically linked concentric LV remodeling with HFpEF risk.[18, 19] Thus, the detection of structural heart disease via cardiac imaging in asymptomatic individuals may represent an intermediate phenotype at risk for HF (i.e. stage B pre-heart failure) and still within a physiologic window where interventions may be beneficial to prevent or delay the progression to clinical symptomatic HF.[4]

HFpEF represents approximately 50% of HF cases, with rising incidence in both HFpEF cases and associated mortality.[29] Until recently, no pharmacotherapies had been shown to decrease the risk of HFpEF hospitalizations, and there remains an urgent need to identify novel therapeutic strategies that might benefit this population.[30] Recently, new classes of medications, such as the sodium-glucose transport protein 2 inhibitors[31] and the neprilysin inhibitor/ angiotensin receptor blocker combination of sacubitril/valsartan[32], have shown benefit in HFpEF populations. Despite these recent exciting developments in treatment options available for HFpEF patients, available therapeutics continue to be limited and of variable effect across phenotypes, generally providing the greater benefit for those at the lower ejection fraction end of the HFpEF spectrum, with perhaps more physiologic similarity to HFrEF.[31, 32] As a result, an increased awareness of and attention to HFpEF and its etiologic predicates is crucial to improving outcomes in this population.

Given few options available for established HFpEF, appropriate evaluation and targeted preventive efforts directed at patients at risk for or in the process of developing HFpEF may prove a vital option for patients. Just as in patients with HFrEF, biomarkers may act as a crucial tool to this effect, with HGF acting as one potential biomarker. Among patients with established HF, HGF is a marker for increased risk of mortality.[33] Additionally in populations initially free of clinical HF, HGF is a marker of increased risk for the development of incident hospitalized HF, and HFpEF in particular, as we showed in a prior MESA analysis.[12] The relationship of HGF with the intermediary imaging phenotype of ventricular remodeling, however, has not been previously established.

Our current data build on prior work and show that in a diverse, multicenter cohort HGF is associated with markers of LV concentric remodeling such as a decrease in LV volume and an

increase in M:V ratio. Notably, while LVM alone was also associated with higher HGF tertile, this relationship was not significant when considering other risk factors, while the M:V ratio was more strongly associated with elevated HGF levels even in the most fully adjusted models accounting for CVD risk factors and NT-proBNP. This suggests that while factors traditionally associated with HFpEF (such as type 2 diabetes mellitus, obesity, and hypertension) may be driving an increase in cardiac mass, there may be important pathophysiologic differences mediated by alternative pathways leading to the LV volume changes seen here. The degree to which HGF is a key factor in these processes, or alternatively a confounder representative of more important risk factors, requires additional study. Indeed, when stratified by race/ethnicity, many of the observed relationships between HGF and LV parameters are significant only in specific racial/ethnic groups, though sample sizes and power are notably smaller when participants are grouped as such. It is notable that baseline HGF levels, for example those of Chinese American and Hispanic cohorts, differ as well, and incorporating these differences in future studies may be important to better understand the pathophysiology of HGF. Finally, there are clear differences between participants that attended exam 1 for cross-sectional assessment only versus those with data available for longitudinal assessment at both exams 1 and 5. This may lead to the longitudinal data being less representative of the population. Nevertheless, both our cross-sectional and longitudinal results showed consistent relationships between HGF with greater M:V ratio and lower LVEDV.

Interestingly, recent data in cardio-oncology have shown HGF to be a biomarker associated with cardiac amyloidosis, differentiating the disease from HFrEF or LV hypertrophy, and acting as a prognostic maker in identifying those patients with amyloidosis at greater risk for poor cardiovascular outcomes.[34] Given the similarity of HFpEF and cardiac amyloidosis with

respect to decreases in LV volume and M:V ratios, this may support the postulated role of HGF as a cytokine released in response to cardiac stress that is either overwhelmed by the disease state – not dissimilar to NT-proBNP – or acts in a deleterious manner upon long-term stimulation subsequently exacerbating the disease state. Further studies are necessary to delineate exactly how HGF is acting in these varying phenotypes and patient populations, or if HGF is one mediator in a more extensive pathway of disease progression.

Strengths and Limitations

As the first study to assess the relationship of HGF with cardiac remodeling, we believe this paper has a number of strengths and adds to important knowledge to potential HFpEF pathophysiologic agents via cardiac MRI assessment. As studied in a large and diverse cohort, we further believe this work is more broadly applicable than more narrow and/or homogenous cohorts. Regardless, there are several limitations to this analysis. First, this study is limited by the use of a single assessment of HGF at baseline. There was a subset of individuals in MESA who did have a repeat HGF at Exam 2, but as no cardiac MRI was performed at that visit, change in HGF was not considered in this analysis. Second, there was significant drop-out of participants receiving a 2nd cardiac MRI at visit 5; however, the longitudinal analysis was consistent with the cross-sectional findings at exam 1. Third, while we did index for BSA, sex differences with respect to BSA-adjusted LV mass were not included due to the power constraints of our cohort. Future studies may benefit from analyzing this in greater detail. Fourth, as this study does not include echocardiographic data, we are unable to comment on diastology alongside markers of cardiac remodeling via cardiac MRI, though our data did notably include left atrial size which is an important piece in the characterization of diastolic function. Additional

studies utilizing echocardiography may help in characterizing this further. Finally, this is an observational study, and as such a causal role of HGF in cardiac remodeling cannot be determined. Although we adjusted for a number of covariates, the associations demonstrated may in part be due to residual confounding. It is not possible to know if the association of baseline HGF with concentric remodeling and decreased LV volume is driven or mediated by an unknown factor aside from HGF. Additional studies are required to further evaluate the mechanisms and pathways in which HGF operates within these associations.

CONCLUSIONS

In a community-based cohort, higher baseline HGF levels were independently associated with a concentric LV remodeling pattern of increasing M:V ratio. It was also associated with decreasing LVEDV over 10 years longitudinal assessment. These associations may suggest an intermediate phenotype explaining the association of HGF with HFpEF risk. Further work is needed to determine the mechanisms, viability and potential of targeting HGF-associated pathways in HF prevention.

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Disclosures

Outside of this work, Dr. Michos reports consulting for Amarin, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Edwards Life Science, Esperion, Medtronic, Novo Nordisk, Novartis, and Pfizer. None of the other authors report any disclosures.

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Table 1. Characteristics of study participants at the MESA baseline exam (2000-2002) by HGF tertiles.					
	Overall	Tertile 1	Tertile 2	Tertile 3	P-value
	N= 4,907	n= 1,636	n= 1,636	n= 1,635	
Age, year	62 (10)	59 (9)	61 (10)	65 (10)	<0.001
Female	2,566 (52%)	793 (48%)	869 (53%)	904 (55%)	<0.001
Race/Ethnicity					<0.001
White	1,912 (39%)	708 (43%)	598 (37%)	606 (37%)	
Chinese-American	651 (13%)	329 (20%)	206 (13%)	116 (7%)	
Black	1,246 (25%)	390 (24%)	458 (28%)	398 (24%)	
Hispanic	1,098 (22%)	209 (13%)	374 (23%)	515 (32%)	
Education					<0.001
≥ bachelor's degree	1,843 (38%)	782 (48%)	628 (38%)	433 (26%)	
< bachelor's degree	3,064 (62%)	854 (52%)	1,008 (62%)	1,202 (74%)	
Physical activity, MET-min/wk	4,080 (2,040-7,545)	4493 (2,220-8,040)	4,215 (2,149-7,635)	3,705 (1,635-7,080)	<0.001
Smoking status					<0.001
Never	2,522 (51%)	900 (55%)	889 (54%)	733 (45%)	
Former	1,762 (36%)	597 (36%)	561 (34%)	604 (37%)	
Current	623 (13%)	139 (9%)	186 (11%)	298 (18%)	
Height, cm	166 (10)	168 (10)	166 (10)	165 (10)	<0.001
Weight, lb	170 (36)	164 (35)	171 (36)	174 (36)	<0.001
Heart rate, beats/min	63 (9)	61 (9)	63 (9)	65 (10)	<0.001
Systolic Blood Pressure, mmHg	125 (21)	121 (19)	126 (21)	130 (22)	<0.001
Diastolic Blood pressure, mmHg	72 (10)	72 (10)	72 (10)	72 (10)	0.376
Use of antihypertensive medication	1,724 (35%)	421 (26%)	585 (36%)	718 (44%)	<0.001
Total cholesterol, mg/dL	194 (35)	195 (35)	196 (36)	193 (36)	0.042
HDL cholesterol, mg/dL	51 (15)	53 (16)	51 (15)	49 (14)	<0.001
Use of lipid-lowering medication	781 (16%)	214 (13%)	258 (16%)	309 (19%)	<0.001
Diabetes mellitus	569 (12%)	93 (6%)	192 (12%)	284 (17%)	<0.001
NT-proBNP, pg/mL	51 (23-104)	45 (20-85)	50 (22-96)	63 (28-137)	<0.001
eGFR, mL/min/1.73 m^2	78 (16)	80 (14)	78 (15)	76 (18)	<0.001
Median HGF, pg/mL	890 (745-1,070)	693 (615-745)	890 (846-943)	1,154 (1,070-1,293)	-

LV mass, g	120 (30)	118 (29)	120 (29)	123 (31)	<0.001
LV EDV, mL	129 (30)	131 (30)	128 (30)	126 (31)	<0.001
LV EF, %	62 (6)	62 (6)	63 (6)	62 (7)	0.232
LV mass indexed to BSA, g/m^2	65 (12)	64 (11)	64 (12)	66 (13)	<0.001
LV EDV indexed to BSA, mL/m^2	69 (13)	71 (12)	69 (12)	68 (14)	<0.001
LAVmin, mL/m^2	12 (7)	12 (6)	12 (6)	13 (7)	<0.001
LAVmax, mL/m^2	30 (10)	30 (9)	30 (10)	31 (11)	0.097
Abbreviations: BSA, body surface area; EDV, end diastolic volume; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; HGF; hepatocyte growth factor; LAV, left atrial volume; LV, left ventricle; MESA, Multi-Ethnic Study of Atherosclerosis; MET, metabolic equivalent of task; NT-proBNP, N-terminal pro b-type natriuretic peptide. Data were presented as mean (standard deviation) or number (percentage) or median (interquartile range). Sample size for LAmin and LAmax = 4,145.					

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Table 2. Cross-sectional association between baseline HGF and left ventricular parameters, N= 4,907					
	LV Mass (g)	LV End Diastolic Volume (ml)	LV Mass: Volume Ratio	LV Mass (g) indexed to BSA	LV Volume (g) Indexed to BSA
Model 1					
HGF					
Tertile 1	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Tertile 2	**2.94 (1.38, 4.51)**	-0.32 (-2.08, 1.45)	**2.44 (1.29, 3.60)**	0.23 (-0.49, 0.95)	**-1.66 (-2.50, -0.82)**
Tertile 3	**6.33 (4.69, 7.98)**	-0.14 (-1.99, 1.71)	**5.34 (4.13, 6.56)**	**1.38 (0.62, 2.14)**	**-2.24 (-3.12, -1.36)**
Model 2					
HGF					
Tertile 1	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Tertile 2	-0.14 (-1.51, 1.23)	**-2.60 (-4.19, -1.01)**	**1.65 (0.50, 2.81)**	0.11 (-0.61, 0.83)	**-1.67 (-2.50, -0.83)**
Tertile 3	1.32 (-0.15, 2.80)	**-3.27 (-4.97, -1.56)**	**3.58 (2.34, 4.82)**	**1.08 (0.32, 1.84)**	**-2.18 (-3.07, -1.29)**
Model 3					
HGF					
Tertile 1	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Tertile 2	-0.62 (-1.90, 0.67)	**-2.00 (-3.54, -0.46)**	0.79 (-0.34, 1.92)	-0.33 (-1.01, 0.34)	**-1.22 (-2.03, -0.41)**
Tertile 3	0.76 (-0.63, 2.16)	**-1.76 (-3.43, -0.09)**	**1.90 (0.68, 3.13)**	0.45 (-0.28, 1.17)	**-1.14 (-2.02, -0.27)**
Model 4					
HGF					
Tertile 1	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Tertile 2	-0.55 (-1.82, 0.72)	**-1.92 (-3.44, -0.40)**	0.77 (-0.36, 1.90)	-0.28 (-0.94, 0.39)	**-1.14 (-1.94, -0.34)**
Tertile 3	0.53 (-0.86, 1.91)	**-2.07 (-3.72, -0.42)**	**1.94 (0.72, 3.17)**	0.37 (-0.35, 1.09)	**-1.25 (-2.12, -0.39)**

Abbreviations: BSA, body surface area; HGF, hepatocyte growth factor; LV, left ventricle.
Results reflect the differences [Beta (95% CI)] in baseline left ventricular parameters comparing the 2nd and 3rd tertiles of hepatocyte growth factor to the 1st tertile in men and women. We obtained results from multilevel linear mixed effect models that accounted for baseline left ventricular parameters. Results in bold font are statistically significant at $p < 0.05$.
Models were adjusted as follows:
Model 1 adjusts for baseline age, race/ ethnicity, sex and study site.
Model 2 adjusts for variables in Model 1 along with baseline education, physical activity, smoking status, height and weight (height and weight are excluded from models in which LV parameters are indexed to BSA).

Model 3 adjusts for variables in Model 2 plus baseline heart rate, systolic blood pressure, use of anti-hypertensive medication, total cholesterol, HDL cholesterol, use of lipid lowering medication and diabetes mellitus status.
Model 4 adjusts for variables in Model 3 plus baseline N-terminal pro b-type natriuretic peptide and eGFR.

Table 3. Longitudinal association between baseline HGF and 10-year change in left ventricular parameters from MESA Exam 1 (2000–2002) to Exam 5 (2010–2012)

	LV Mass (g)	LV End Diastolic Volume (ml)	LV Mass: Volume Ratio	LV Mass (g) indexed to BSA	LV Volume (g) Indexed to BSA
Model 1					
HGF					
Tertile 1	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Tertile 2	-1.61 (-3.30, 0.08)	-1.65 (-3.66, 0.35)	1.04 (-0.85, 2.94)	-0.35 (-1.23, 0.53)	-0.30 (-1.37, 0.77)
Tertile 3	-0.46 (-2.24, 1.32)	**-4.51 (-6.61, -2.40)**	**4.88 (2.88, 6.87)**	0.36 (-0.56, 1.29)	**-1.75 (-2.87, -0.62)**
Model 2					
HGF					
Tertile 1	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Tertile 2	-0.85 (-2.52, 0.81)	-1.37 (-3.38, 0.64)	1.35 (-0.55, 3.25)	-0.27 (-1.16, 0.61)	-0.25 (-1.32, 0.82)
Tertile 3	0.33 (-1.43, 2.09)	**-4.08 (-6.20, -1.96)**	**5.05 (3.04, 7.06)**	0.49 (-0.44, 1.42)	**-1.61 (-2.73, -0.48)**
Model 3					
HGF					
Tertile 1	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Tertile 2	-0.72 (-2.35, 0.92)	-1.45 (-3.45, 0.56)	1.55 (-0.35, 3.45)	-0.20 (-1.06, 0.67)	-0.42 (-1.48, 0.65)
Tertile 3	0.17 (-1.56, 1.91)	**-4.14 (-6.28, -2.01)**	**5.01 (2.99, 7.02)**	0.42 (-0.49, 1.34)	**-1.74 (-2.86, -0.61)**
Model 4					
HGF					
Tertile 1	[Reference]	[Reference]	[Reference]	[Reference]	[Reference]
Tertile 2	-0.98 (-2.58, 0.62)	-1.69 (-3.68, 0.30)	1.48 (-0.43, 3.39)	-0.42 (-1.26, 0.43)	-0.64 (-1.69, 0.41)
Tertile 3	-0.76 (-2.47, 0.95)	**-4.74 (-6.87, -2.62)**	**4.68 (2.64, 6.72)**	-0.22 (-1.12, 0.69)	**-2.25 (-3.37, -1.13)**

Abbreviations: BSA, body surface area; HGF, hepatocyte growth factor; LV, left ventricle.

Results reflect the differences [Beta (95% CI)] in changes in left ventricular parameters during 10 years of follow-up comparing the 2nd and 3rd tertiles of hepatocyte growth factor to the 1st tertile in men and women. We obtained results from multilevel linear mixed effect models that accounted for baseline left ventricular parameters. Results in bold font are statistically significant at $p < 0.05$.

Models were adjusted as follows:

Model 1 adjusts for follow-up time, baseline age, race/ ethnicity, sex, and study site.

Model 2 adjusts for variables in Model 1 along with education, baseline and 10-year measures of physical activity, smoking status, height, and weight (height and weight are excluded from models in which LV parameters are indexed to BSA).

Model 3 adjusts for variables in Model 2 plus baseline heart rate, baseline and 10-year measures of systolic blood pressure, use of anti-hypertensive medication, total cholesterol, HDL cholesterol, use of lipid lowering medication and diabetes mellitus status.
Model 4 adjusts for variables in Model 3 plus baseline and 10-year changes in N-terminal pro b-type natriuretic peptide and eGFR.

Figure legends:

Figure 1. Flowchart of study participants

Figure 2: Box plots of LV parameters by HGF tertiles. Panel A: LV mass; Panel B: LV end diastolic volume; Panel C: LV mass-to-volume ratio

The lower and upper boundaries of the rectangles denote the 25th and 75th percentiles while the horizontal line within the rectangles is the median. Lines extend from the rectangles to the smallest and largest values within 1.5 × interquartile range.

Supplemental Materials

Supplemental Table S1. Cross-sectional association between baseline HGF and left ventricular parameters, stratified by race/ethnicity.

Supplemental Table S2. Cross-sectional association between baseline HGF and left atrial volume, N= 4,145

Supplemental Table S3. Characteristics of study participants with baseline exam (2000-2002) MRI only by HGF tertiles

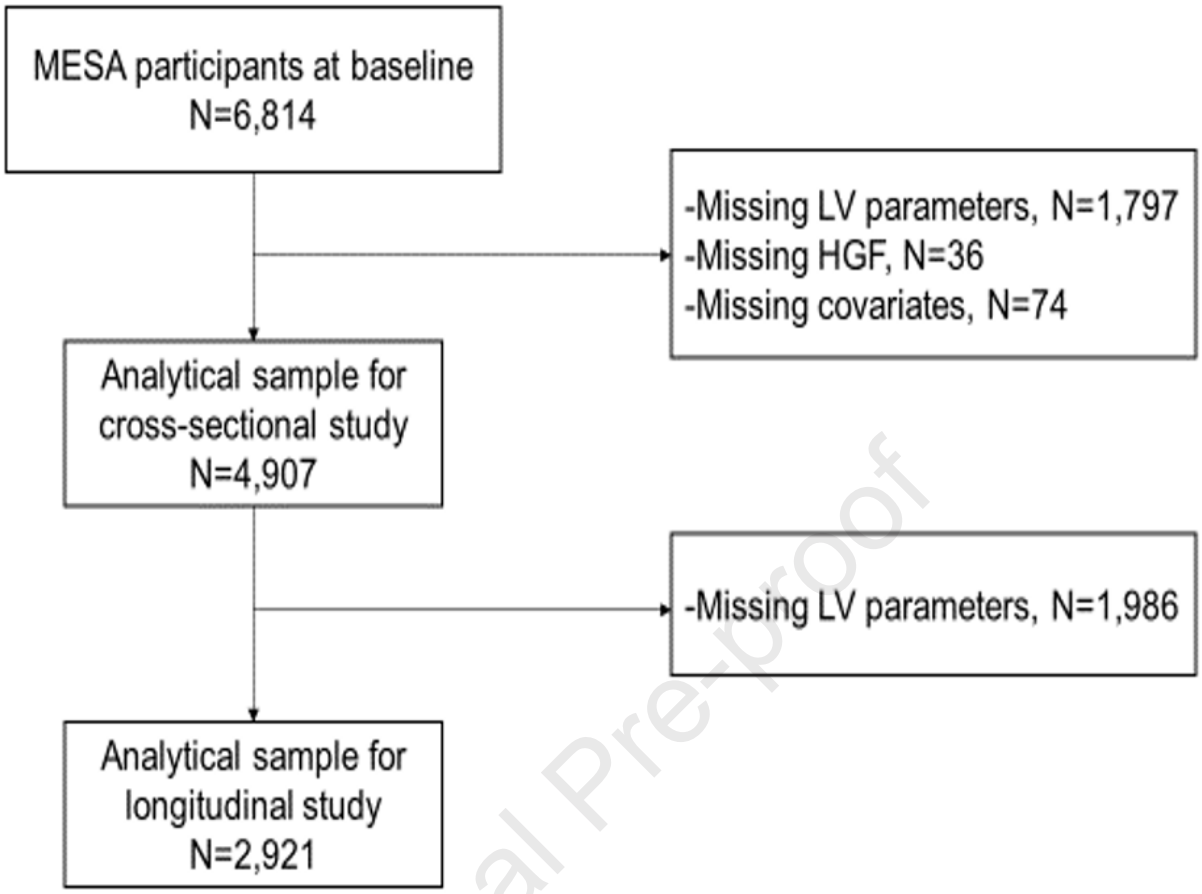
Supplemental Table S4. Characteristics of study participants with longitudinal baseline (2000-2002) and exam 5 (2010-2012) MRI by HGF tertiles

Supplemental Table S5. Longitudinal association between baseline HGF and 10-year change in left ventricular parameters, stratified by race/ethnicity.

Supplemental Table S6. Longitudinal association between baseline HGF and 10-year change in left atrial volume from MESA Exam 1 (2000–2002) to Exam 5 (2010–2012), N= 4,145

Supplemental Table S7. Cross-sectional association between baseline HGF and left ventricular parameters excluding participants with LVEF <50%.

Supplemental Table S8. Longitudinal association between baseline HGF and 10-year change of left ventricular parameters from MESA Exam 1 (2000–2002) to Exam 5 (2010–2012) excluding participants with LVEF <50%.



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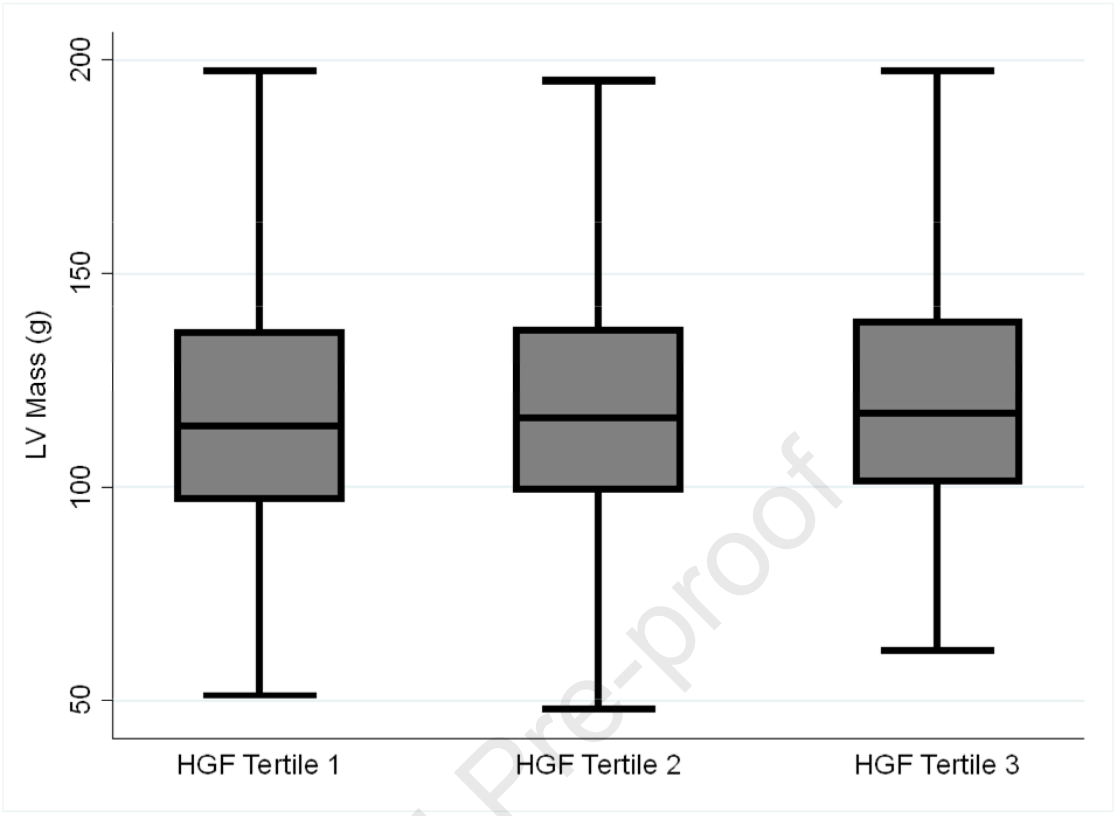

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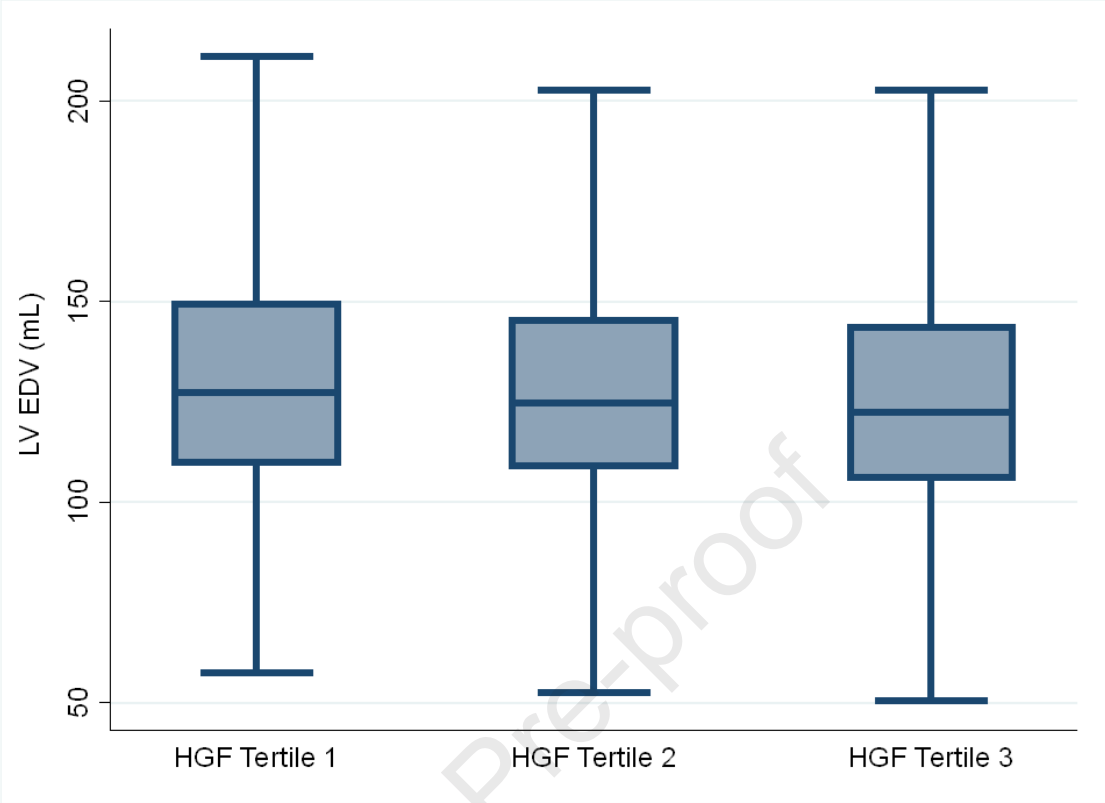

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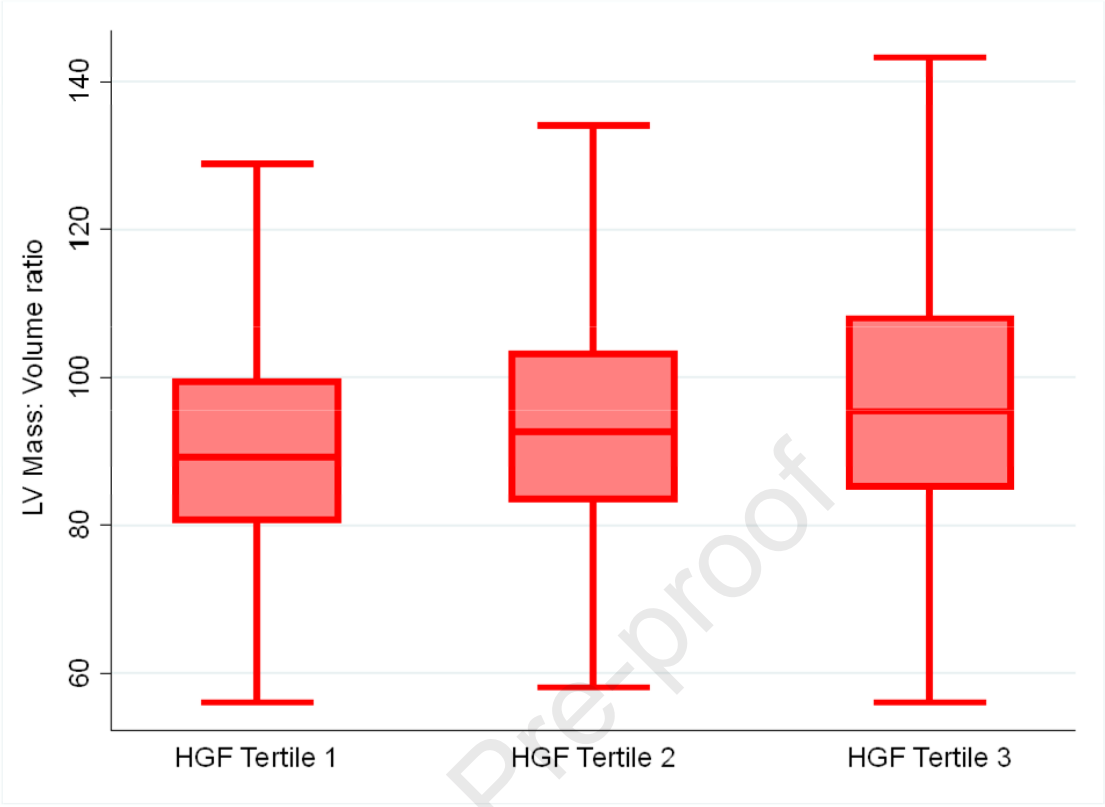

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Erin Michos reports a relationship with Dr. Michos reports Advisory Boards for Astra Zeneca, Bayer, Boehringer Ingelheim, Esperion, Novo Nordisk, Novartis, and Pfizer. that includes: consulting or advisory. The MESA study was supported by contracts HHSN268201500003I, 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), and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences. The HGF measurement was funded by R01 HL98077. Drs. Michos was funded by the Amato Fund for Women's Cardiovascular Health Research at Johns Hopkins University.