Received Date: 07/07/2016

Revised Date: 18/08/2016

Accepted Date: 01/09/2016

Article Type: Original Article

Subject category: Preventive Cardiology

Transitions in Metabolic Risk and Long-Term Cardiovascular Health: Coronary Artery Risk Development in Young Adults (CARDIA) Study

Running title: *Murthy et al.; Transitions in Metabolic Risk in Young Adulthood*

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Word count: 3,351 (excluding abstract, references, tables, legends, acknowledgments)

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Journal Subject Terms: Epidemiology, risk factors, lifestyle

ABSTRACT (249 words)

Background: Despite evidence suggesting early metabolic dysfunction impacts cardiovascular disease (CVD) risk, current guidelines focus on risk assessments later in life, missing early transitions in metabolic risk that may represent opportunities for averting the development of CVD.

Methods and Results: In 4,420 young adults in the Coronary Artery Risk Development in Young Adults (CARDIA) study, we defined a "metabolic" risk score based on components of the ATP-III-defined metabolic syndrome. Using latent class trajectory analysis adjusted for sex, race, and time-dependent BMI, we identified six distinct metabolic trajectories over time, specified by initial and final risk: low-stable, low-worsening, high-stable, intermediate-worsening, intermediate-stable, high-worsening. Overall, individuals gained weight over time in CARDIA with statistically but not clinically different BMI trend over time. Dysglycemia and dyslipidemia over time were highest in initially high or worsening trajectory groups. Divergence in metabolic trajectories occurred in early adulthood (before age 40), with 2 in 3 individuals experiencing an increase in metabolic risk over time. Membership in a higher risk trajectory (defined as initially high or worsening over time) was associated with greater

prevalence and extent of coronary artery calcification (CAC), left ventricular (LV) mass, and decreased LV strain at Year 25. Importantly, despite similar rise in BMI across trajectories over 25 years, CAC and LV structure and function more closely tracked risk factor trajectories.

Conclusions: Transitions in metabolic risk occur early in life. Obesity-related metabolic dysfunction is related to subclinical cardiovascular phenotypes independent of evolution in BMI, including coronary artery calcification, myocardial hypertrophy and dysfunction.

Key Words: obesity; metabolic syndrome; epidemiology; risk factor

INTRODUCTION

Metabolic syndrome is a well-established risk factor for cardiovascular disease (CVD), including coronary artery disease and heart failure[1]. Alterations in metabolic risk linked to CVD may develop over decades before clinical CVD[2-5]. Prior work in large, community-based populations have defined a role for early, cumulative changes in blood pressure[6] and obesity[7] in forecasting risk of subclinical CVD in mid-life and beyond. This "life-course" perspective on cardiometabolic risk—and resulting recommendations to maintain an ideal body weight, diet, physical activity, and lipid profile—is critical to decrease incident CVD[8]. Although obesity has frequently been cited as a central pathogenic factor for CVD risk, an emerging literature suggests that cardiometabolic risk may evolve independently from body mass index (BMI)[9, 10]. Therefore, defining how cardiometabolic risk evolves during early adulthood—and how these changes are related to CVD risk independent of cumulative exposure to obesity—is critical to differentiate healthy young adult populations from at risk ones, ultimately to allow for personalized CVD prevention.

We investigated individuals from the Coronary Artery Risk Development in Young Adults (CARDIA) study to define transitions in cardiometabolic risk over 25 years independent of obesity. Furthermore, we sought to compare markers of subclinical CVD—including left ventricular mass, function, and coronary artery calcium—at 25 years after baseline visit among different groups of participants that follow distinct patterns of transition in metabolic risk. We hypothesized that individuals who experienced worsening cardiometabolic risk during young adulthood would exhibit a poorer

subclinical CVD profile at mid-life, defined by increased myocardial mass, decreased myocardial function, and coronary artery calcification.

METHODS

Study population

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a longitudinal cohort designed to study determinants of CVD among 5,115 young adults (aged 18-30) initially recruited in 1985-1986. Participants were recruited from four sites across the United States, including Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. Recruitment balanced enrollment at each site by sex, age (18-24 years old versus 25-30 years old), race, and education. Serial follow-up of participants at years 2, 5, 7, 10, 15, 20, and 25 (2010-2011) after enrollment has been performed, with 72% retention of surviving participants at year 20 and 25. All participants provided written informed consent, with annual Institutional Review Board approval. Clinical assessments were performed at each CARDIA visit as described[11-15]. From an initial cohort of 5,115 individuals, we excluded individuals with self-reported congenital heart disease, congestive heart failure, cardiomyopathy, myocarditis, rheumatic heart disease, valvular heart disease (all assessed at baseline study visit), prior myocardial infarction reported at baseline or final study visit, bariatric surgery by final study visit, or withdrawn consent for study participation, leaving 4,941 CARDIA participants (97% of the study cohort) for analysis.

Metabolic risk score for transitions

To reflect current metrics for metabolic risk assessment in the clinic[16], we defined a "metabolic risk score" by assigning +1 point for each of the following 5 high risk features, based on the ATPIII definition of metabolic syndrome[17]: (1) triglyceride concentration ≥ 150 mg/dl; (2) high-density lipoprotein concentration ≤ 40 mg/dl (males) or ≤ 50 mg/dl (females); (3) waist circumference ≥ 102 cm (males) or ≥ 89 cm (females); (4) systolic blood pressure ≥ 135 mmHg (mean of two different readings), self-reported history of hypertension, or current or former use of blood pressure medication; (5) self-reported diabetes or fasting glucose concentration ≥ 100 mg/dl. Self-reported diabetes only was used for the fifth criteria in examinations at year 2 and year 5, as glucose was not measured on these visits. The range for the metabolic risk score was therefore 0-5 points. We did not include body mass index in the metabolic risk score, as we sought to measure metabolic risk development independent of obesity status. (Cumulative body mass index adjustment was performed in logistic models; see **Statistical Analysis**, below.) The presence of each risk factor used to construct the score over all CARDIA examinations is shown in **Table S1**.

Cardiovascular imaging

We examined the coronary artery calcium score at the most contemporary CARDIA examination (year 25, 2010-2011), using a standard multi-detector CT scanner platform as described[18]. Coronary artery calcium score (CAC) was handled as "non-zero" and as a continuous

variable (with log-transformation) for positive CAC scores. Speckle tracking echocardiography and M-mode echocardiography were performed using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) using standardized protocols across all centers at Year 25, with offline imaging interpretation (Digisonics, Houston, Texas)[19]. Left ventricular mass (LVM) was derived from the Devereux formula[20], and indexed to height. Speckle tracking echocardiography images for myocardial strain measurements were analyzed for LV mid-wall layer, using Wall Motion 2-dimensional Tracking software (Toshiba Medical Systems), from three cardiac cycles for each view, recorded for offline analyses. Strain was calculated as the change in segment length relative to its end-diastolic length, and the peak systolic value from the 4-chamber images was recorded as the longitudinal strain.

Statistical analysis

Baseline clinical and demographic characteristics were compared via analysis of variance or non-parametric (Kruskal Wallis) techniques, as appropriate. From the initial 4,941 CARDIA participants, we excluded participants without a measurable metabolic risk score at baseline, less than three assessments of the metabolic risk score over 8 total CARDIA examinations, or missing body mass index, sex, or race assessment at baseline study visit, leaving 4,420 CARDIA participants (89% of initial study cohort) for trajectory analysis.

To specify transitions in metabolic risk over time, we used latent class models to identify groups of CARDIA participants that share a common trajectory of metabolic risk over time.[21] Trajectories in metabolic risk score (using a censored normal model using PROC TRAJ in SAS) were specified as a function of participant age, with baseline adjustment by sex and race (using the RISK option), and time-dependent adjustment for body mass index (using the TCOV option). We determined the optimal number of underlying trajectories (starting from 8 total trajectories modeled with second-order terms) by a composite criteria consisting of: (1) confirming visually distinct trajectories; (2) ensuring >5% membership in any single trajectory group; (3) observing improvement in the Bayesian information criterion. The average posterior probability of group membership was 0.76 (range 0.72-0.82). Metabolic score at Year 25 was calculated in 3,262 participants (74% of the initial 4,420 analytic cohort; relative to 72% overall retention in the overall CARDIA study).

We estimated the relationship between group membership and subclinical CVD using logistic regression models, with group membership entered as an independent variable. “Subclinical CVD” was defined by (1) the presence of coronary artery calcification (modeled as CAC > 0) at Year 25 or a significant extent of CAC at Year 25 (>100); (2) height-adjusted left ventricular mass at Year 25; and

(3) left ventricular longitudinal strain at Y25. Each model was adjusted for baseline age, race, sex, education, lifetime pack-years of smoking (at Year 25), and total intentional (heavy) physical activity (at Year 25). Given our central goal to separate obesity from metabolic risk, in addition to using BMI as a time-dependent covariate in defining metabolic groups, we further adjusted for a "cumulative BMI exposure" (in BMI-years), defined as the sum of each product between BMI at a given CARDIA examination and the time between that examination and the following examination. To calculate cumulative BMI exposure, we required participants to have BMI measures at Year 0 and Year 25 and a minimum of 2 BMI measures at interim exams. We calculated multivariable-adjusted least squares means for LV mass and LV strain across all trajectory groups. Because a large number of participants were missing data on the three subclinical CVD outcomes, we performed a sensitivity analysis using inverse probability of treatment weighting (IPTW) using the propensity score, as described in our previous work[22]. The propensity score for inclusion in the analysis of the subclinical CVD outcome was based on a logistic regression model containing as baseline predictors age, race, sex, systolic blood pressure, education, heavy physical activity, cigarette smoking, total cholesterol, HDL cholesterol, triglycerides, BMI, diabetes status, blood pressure medications at baseline, fasting glucose, serum creatinine, alcohol intake, and weighted life-events score. The inverse propensity probability of inclusion in the analysis was used to perform a weighted regression analysis of the outcomes, without significant change in results. Finally, we evaluated multiplicative interaction terms for sex and race.

Given that latent group modeling assigns individuals to groups in a probabilistic fashion, we generated 50 separate replicates (based on the distribution of posterior probability of group membership). We subsequently estimated logistic regression models for each outcome in every replicate, yielding a composite result across the different imputed group assignment datasets. SAS version 9.3 (SAS Institute, Cary, NC) was used for all analyses, and a two-tailed $P<0.05$ was statistically significant.

RESULTS

The six metabolic trajectories obtained through latent class trajectory modeling in this analysis to identify metabolic transitions are shown in **Figure 1**. The baseline clinical and demographic characteristics and outcomes of the 4,420 CARDIA participants stratified by metabolic trajectory are displayed in **Table 1.** Six distinct metabolic trajectories were labeled by the metabolic score at baseline study visit and Year 25 study visit: group 1 (low-stable; 17%), group 2 (low-worsening; 21%), group 3 (intermediate-stable; 17%), group 4 (intermediate-worsening; 14%), group 5 (high-stable; 23%), group 6 (high-worsening; 7%). On average, the overall CARDIA sample in this analysis (N=4,420) was evenly divided by sex (54% female), with a normal BMI (24.4±4.9 kg/m^2), normal fasting glucose (82.3±13.3 mg/dl), and minimal prevalent metabolic dysfunction (only 0.6% prevalent

diabetes). We observed very slight, clinically insignificant heterogeneity in BMI and waist circumference across trajectory groups at baseline. There was clinically and statistically significant heterogeneity in baseline pro-atherogenic dyslipidemia (triglycerides and HDL).

On average, participants who attended the final Year 25 CARDIA examination were heavier than those attending the initial study visit (initial BMI 24.4±4.9 kg/m^2 to final BMI 30.1±7.2 kg/m^2), with greater central obesity (by waist circumference), dysglycemia, and a more pro-atherogenic lipid profile. Of 4,420 participants at baseline, 1,516 (34%) were overweight or obesity (by BMI ≥ 25 kg/m^2); of the 3,274 CARDIA participants in our analytic sample at Year 25, 2,435 (74%) were overweight or obese. While individuals on average gained weight over time (with statistically significant differences in weight gain across trajectories, P<0.0001), among those participants with BMI assessed at Year 0 and Year 25 in our analytic cohort, there was an increase in BMI and central obesity, with a similar pattern across all trajectories (**Figure 2A** and **2B**). In addition, we considered waist circumference to BMI ratio (a marker of preferential visceral fat stores; **Figure 2C**). We found that individuals with worsening metabolic trajectories have a stable ratio over time, while individuals with stable trajectories have a declining ratio, suggesting that less excess weight gained over time is visceral in these individuals. Of note, waist circumference also appeared to have a similar association with baseline metabolic score in lean and overweight/obese individuals (**Figure S1**).

Despite similar trends in weight gain over time in CARDIA across metabolic trajectories, there was significant heterogeneity in fasting glucose, triglyceride, and HDL levels. Specifically, initially low or intermediate and stable trajectories of metabolic risk (group 1 and 3) had only modest worsening in these metabolic parameters over 25 years, while CARDIA participants in the most adverse trajectories (e.g., group 6: high-worsening) had the poorest metabolic indices at Year 25 (**Table 1**).

Logistic models for presence of coronary calcium and extent of coronary artery calcification, and linear models for left ventricular mass, and strain are shown in **Table 2**. After accounting for age, sex, race, education, smoking, physical activity, and obesity exposure (defined in **Methods**), all groups (except group 3: intermediate-stable) had a higher odds of subclinical coronary artery disease, as reflected by prevalent CAC and CAC score greater than 100 at Year 25, compared to the low-stable group. Similarly, after accounting for cumulative BMI and other risk factors, relative to low-stable (group 1), all other trajectory groups were associated with significantly greater height-indexed LV mass; all but group 3 were associated with poorer longitudinal strain (**Table 2**). These results were robust in sensitivity analyses using 50-fold replication over posterior group probabilities and to inverse probability weighting. Relationships between trajectory groups and CAC were similar excluding individuals with prior revascularization. In a sensitivity analysis, we considered the form of the trajectory (stable vs. worsening) as an outcome to address whether baseline characteristics would

identify metabolic progression over time; baseline characteristics only had a moderate discrimination for worsening versus stable trajectories (C-statistic 0.72, 95% CI 0.70-0.74). In addition, worsening trajectories were associated with greater subclinical CVD.

In examining the sex- and race-based heterogeneity in metabolic risk and CVD, we first observed that men were much more likely to be in metabolically worsening trajectories relative to women. We identified a significant race interaction for LV mass (P<0.0001) and LV strain (P=0.01), and a significant sex interaction for presence of coronary artery calcification (P=0.001). **Figure 3** shows the patterns of group differences by race for LV mass (**Figure 3A**) and LV strain (**Figure 3B**) and by sex for coronary artery calcification (**Figure 3C**). We found that the blacks consistently had higher LV mass and worse LV strain than whites in each group (**Figure 3**). Furthermore, the worsening metabolic trajectory had a greater impact on blacks than whites, most notably in the high-worsening group (group 6). We also found that while women generally had lower rates of coronary calcification at year 25 than men, this difference was attenuated in worse metabolic trajectories (**Figure 3C**).

DISCUSSION

In a large cohort of young adults followed over 25 years, we defined specific trajectories of metabolic risk associated with prognostic markers of subclinical CVD, including myocardial mass, function, and coronary artery calcification in mid-life. Importantly, metabolic risk diverged early, at age 20-30s, before most young adults would be eligible for modern lipid prevention guidelines[23]. We demonstrated that the evolution of metabolic risk during early adulthood may occur independently of changes in BMI: despite an overall rise in BMI by Year 25 in CARDIA (to overweight or obese on average), parameters of cardiometabolic risk (e.g., dysglycemia, diabetes risk, dyslipidemia, waist circumference) had distinct patterns of change over time in each trajectory. Moreover, we could not in general identify a trajectory to which a given individual belonged based on baseline BMI or cardiometabolic characteristics, given their similarity at baseline. While we did observe that adverse trajectories (defined by initially high or worsening metabolic risk trajectories) were associated with worse cardiovascular structure and function at late follow-up, lower risk, stable trajectories (groups 1 and 3) had a similar risk of coronary calcification and subclinical LV dysfunction. The critical finding of our work is that these associations were observed in the face of a similar pattern of increase in BMI across trajectories, suggesting that BMI may not fully explain metabolic deterioration in through young adulthood to mid-life. Collectively, despite a “healthy” profile in young adulthood (including normal BMI on average), adverse trajectories in cardiometabolic risk may evolve early in adulthood (before age 40) and are associated with subclinical cardiovascular disease by mid-life.

Metabolic syndrome, defined by abdominal obesity, pro-atherogenic dyslipidemia, hypertension, and insulin resistance, is a risk factor for incident CVD[17]. Most clinical prevention has focused on body mass index as a central arbiter of cardiometabolic risk, with screening beginning in childhood to mitigate chronic consequences of obesity[24]. Indeed, trajectories of obesity in childhood are strongly associated with CVD and diabetes in adulthood[25]. Nevertheless, the United States Preventive Services Task Force guidelines do not recommend any additional screening for dysglycemia or dyslipidemia prior to middle age (35 years old for men, 45 years old for women) in individuals not at "significant risk" for CVD or diabetes (defined as obesity, hypertension, smoking, diabetes, or personal or family history)[26]. While prior work in CARDIA has defined the importance of cumulative exposure to obesity[7, 27] on cardiovascular structure, the divergence between metabolic risk and obesity (e.g., "metabolically healthy obese" and "metabolically unwell lean" subtypes) is increasingly recognized. Previous work by our group[28] and others[29-33] has indicated that differences in metabolic susceptibility defined by visceral adiposity or inflammation may refine obesity-related cardiometabolic risk. In addition, studies involving cardiac magnetic resonance suggest that even tissue-level myocardial phenotypes may be affected in adolescent obesity, in proportion to systemic inflammation and dysglycemia[34]. These findings suggest that early detection of and focus on obesity-associated metabolic risk may provide a more nuanced conception of cardiometabolic disease early in adulthood that may directly impacts heart disease, and may help to understand heterogeneity in clinical risk in individuals across the spectrum of obesity[29].

In this context, using well-defined, clinically accessible risk factors, we found that individuals who were at low metabolic risk at baseline had already diverged in terms of metabolic risk in early adulthood (e.g., between age 20-40 years), before standard prevention guidelines urge routine screening (e.g., for dyslipidemia). Importantly, there were no clinically important differences in these groups in terms of baseline body mass index, lipid panel, fasting glucose, or other important cardiometabolic indices to facilitate their distinction. In addition, despite a similar pattern of weight gain across all metabolic risk trajectories over time in CARDIA, we observed distinct associations between metabolic trajectories and subclinical CVD. Importantly, we observed significant race and sex-based heterogeneity in the relationship between adverse metabolic risk over 25 years and subclinical CVD: African Americans exhibited a higher LV mass and poorer systolic function relative to Caucasians, potentially explaining well-described race-related differences in heart failure risk[35]. Moreover, the well-described protection from CVD enjoyed by pre-menopausal women (relative to men) was attenuated with worsening metabolic trajectory. Alongside general cardiometabolic prevention, these results suggest that focused efforts in selected populations to limit the evolution of cardiometabolic risk from young adulthood may curb later CVD and its associated cost and morbidity.

A critical step in the formulation of metabolic trajectories in this work is the metabolic score used to specify risk. We decided to use ATP-III defined metabolic syndrome components to comprise our risk score due to their clinical accessibility and previous association with cardiometabolic disease[16]. While more granular, longitudinal and direct measures of physical activity (by accelerometry), cardiorespiratory fitness (e.g., exercise duration), visceral fat[30], and dietary patterns would likely contribute to defining trajectories, we did not have access to longitudinal accelerometry, fitness, adiposity or dietary data in every examination within CARDIA. In addition, our score purposefully excluded BMI; instead, we specified a time-dependent BMI adjustment in trajectory modeling to account for longitudinal changes in BMI over time. Ultimately, these results suggest that metabolic deterioration occurs early in adulthood in parallel to (but are not necessarily explained completely by) a rise in BMI over time.

The identification of early divergence in metabolic risk independent of BMI prompts several additional questions. First, early clinical differentiation of the different metabolic trajectories would allow the identification of individuals at higher risk at an earlier stage of cardiometabolic disease for prompt prevention. Certainly, those individuals who enter young adulthood at high metabolic risk tended to remain at high metabolic risk or worsen over time, warranting aggressive, guideline-mandated surveillance and prevention. Previous seminal work has demonstrated that changes in waist circumference over time track changes in cardiometabolic risk[36, 37]. While clinical factors in our study only modestly discriminated risk of worsening metabolic trajectory over time, CARDIA was an observational (not an interventional) study. As such, directed clinical interventions based on known markers (e.g., triglycerides, low fitness or activity levels, poorer dietary quality, or enlarging waistline[36, 37]) may offer preventative benefits. Whether more sensitive markers of early metabolic dysfunction (e.g., adipokines, metabolite profiles) central to insulin resistance and cardiometabolic risk would further call attention to patients at high risk remains an area of active investigation. Moreover, it is critical to note that these results certainly do not negate the importance of BMI in standard risk prediction: obesity is a well-established marker of increased CVD risk[1], though these results suggest that it does not fully explain CVD risk. Ultimately, these results suggest that a “life-course” approach to risk assessment that begins early and integrates BMI, known risk factors (e.g., waist circumference) with metabolic risk will be critical in halting CVD progression.

The limitations of this study must be viewed in the context of its design. While the use of self-report to exclude participants with CVD may introduce bias, the overall reduction in study population was modest (5,114 to 4,941). With subject dropout over time, 3,262 participants (74% of the initial 4,420 analytic cohort) had quantified metabolic scores at Year 25. However, we adjusted for known CVD risk factors (smoking, self-reported physical activity) in our final models to reduce the impact of biases related to systematic differences in characteristics of retained subjects[6]. Furthermore, while not

all participants had metabolic scores assessed at every CARDIA study visit, the median number of metabolic score assessments was 7 (interquartile range 6-8 of 8 total CARDIA visits, similar across trajectory groups (between 7-8 across all groups) and suggested that any systematic patterns in missing data are unlikely to impact trajectory assignments. Given the absence of *a priori* weighting schemes, we weighted each metabolic component equally, ascribing an equivalent degree of cardiometabolic risk to each component. Finally, serial dietary and physical activity assessments were not available at every exam in CARDIA, and represent a potential area of future study.

CONCLUSIONS

Transitions in metabolic risk occur in early adulthood, are not be completely explained by increases in BMI over time, and are associated with coronary artery calcification and myocardial hypertrophy and dysfunction. Targeting therapeutic interventions focused on weight, body composition, and physical activity maintenance early in life alongside regular cardiometabolic surveillance are critical to halt heart disease.

Acknowledgments: Drs. Murthy and Shah had full access to the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Shah, Murthy, Abbasi and Lima are responsible for the conception and study design. Dr. Murthy, Siddique, Abbasi, Colangelo, and Shah conducted statistical analysis. Dr. Murthy and Shah supervised the analysis. Dr. Lima, Carr, Mr. Terry, and C. Lewis were responsible for acquisition of data. Drs. Murthy, Abbasi, Reis, Venkatesh, Jerosch-Herold, de Ferranti, Das, Freedman, Carnethon, C. Lewis, Lima and Shah were responsible for drafting of the manuscript. All authors were responsible for critical revision of the manuscript. This manuscript has been reviewed by CARDIA for scientific content.

Funding Sources: This research was supported by 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 95168, N01 HC 95169 , and HL098445-05 (to JJC) from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-RR-025005 from NCRR. Dr. Shah is supported by an American Heart Association Fellow-to-Faculty Award and the Thrasher Research Foundation. The Coronary Artery Risk Development in Young Adults Study (CARDIA) is supported by contracts HHSN268201300025C, HHSN268201300026C, HHSN268201300027C, HHSN268201300028C, HHSN268201300029C, and HHSN268200900041C from the National Heart, Lung, and Blood Institute

(NHLBI), the Intramural Research Program of the National Institute on Aging (NIA), and an intra-agency agreement between NIA and NHLBI (AG0005).

DISCLOSURES: Dr. Lewis has received a research grant from Novo Nordisk. There are no other disclosures relevant to the content of this manuscript. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

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Table 1. Characteristics of 4,420 CARDIA participants by metabolic trajectory group. Abbreviations: standard deviation, SD; interquartile range, IQR; body mass index, BMI; myocardial infarction, MI; high density lipoprotein, HDL; Int, intermediate. Educational attainment is defined as years of education attained by initial CARDIA study examination. Psychosocial stress scores (e.g., life events, hostility scores) are as described in prior work in CARDIA[15].

Covariate	Study population (N=4,420)	Metabolic Trajectory Groups						P value
		Group 1 (Low-Stable) (N=759)	Group 2 (Low-Worsening) (N=934)	Group 3 (Int-Stable) (N=753)	Group 4 (Int-Worsening) (N=637)	Group 5 (High-Stable) (N=1033)	Group 6 (High-Worsening) (N=304)	
BASELINE DEMOGRAPHICS								
Age, mean (SD), y	24.9 (3.6)	25.2 (3.6)	25.0 (3.6)	24.7 (3.6)	25.0 (3.7)	24.7 (3.7)	25.2 (3.4)	0.01
Male sex, n (%)	2020 (45.7)	284 (37.4)	612 (65.5)	204 (27.1)	418 (65.6)	306 (29.6)	196 (64.5)	<0.0001
Black race, n (%)	2210 (50.0)	371 (48.9)	487 (52.1)	387 (51.4)	332 (52.1)	538 (52.1)	95 (31.3)	<0.0001
Educational attainment at Y0, mean (SD), y	13.9 (2.3)	14.3 (2.3)	14.1 (2.3)	13.9 (2.2)	13.6 (2.2)	13.6 (2.2)	13.6 (2.3)	<0.0001
Current smoker, n (%; N=4392)	1289 (29.4)	148 (19.6)	235 (25.4)	200 (26.7)	240 (37.9)	357 (34.7)	109 (36.3)	<0.0001
Physical activity (moderate and vigorous), median at baseline (IQR), exercise units								
Y0 (N=4419)	365 (198, 577)	380 (209, 620)	426 (246, 645)	328 (185, 545)	396 (208, 620)	305 (156, 500)	347 (192, 559)	<0.0001
Y25 (N=3251)	279 (134, 493)	328 (168, 556)	312 (146, 522)	266 (120, 494)	272 (144, 482)	231 (108, 410)	247 (112, 456)	<0.0001
Alcohol consumption, median (IQR), ml/day (N=4403)	4.8 (0.0, 14.6)	4.8 (0, 14.3)	7.6 (0, 19.8)	2.4 (0, 10.6)	7.2 (0, 17.7)	2.4 (0, 12.1)	4.8 (0, 14.5)	<0.0001
Medication use ever, n (%)								
Anti-hypertensive	1077 (24.4)	49 (6.5)	234 (25.1)	102 (13.6)	227 (35.6)	307 (29.7)	158 (52.0)	<0.0001
Lipid-lowering	614 (13.9)	41 (5.4)	119 (12.7)	71 (9.4)	140 (22.0)	145 (14.0)	98 (32.2)	<0.0001
CARDIOMETABOLIC RISK FACTORS								

Mean BMI, kg/m^2 (SD)								
Baseline (Y0)	24.4 (4.9)	23.5 (3.9)	24.1 (3.7)	25.4 (6.8)	24.0 (4.0)	24.7 (5.2)	24.5 (4.4)	<0.0001
Follow-up (Y25)(N=3274)	30.1 (7.2)	28.6 (6.3)	29.7 (5.4)	31.3 (10.3)	29.0 (5.1)	31.1 (7.5)	30.4 (5.3)	<0.0001
Waist circumference, mean (SD)								
Baseline (Y0)	77.6 (11.2)	73.9 (9.2)	78.0 (9.1)	77.5 (13.8)	78.9 (10.4)	77.7 (11.8)	82.0 (11.4)	<0.0001
Follow-up (Y25) (N=3271)	94.3 (15.9)	88.2 (14.1)	95.5 (13.3)	92.6 (19.6)	96.4 (13.3)	96.1 (16.9)	101.1 (13.1)	<0.0001
Glucose, mean (SD), mg/dl,								
Baseline (Y0) (N=4278)	82.3 (13.3)	79.7 (6.9)	82.2 (7.6)	81.2 (9.9)	83.8 (11.6)	82.6 (16.4)	87.9 (27.9)	<0.0001
Follow-up (Y25) (N=3146)	99.3 (27.5)	91.0 (16.0)	101.6 (26.2)	92.0 (15.3)	109.8 (38.6)	97.3 (22.4)	119.1 (46.3)	<0.0001
Diabetes, n %								
Baseline (Y0)	25 (0.6)	0 (0)	1 (0.1)	5 (0.7)	4 (0.6)	5 (0.5)	10 (3.3)	<0.0001
Follow-up (Y25)(N=3272)	456 (13.9)	20 (3.5)	88 (12.4)	43 (7.5)	114 (24.2)	113 (15.1)	78 (38.6)	<0.0001
TG, mean (SD), mg/dL								
Baseline (Y0)	72.6 (47.5)	54.7 (21.4)	63.2 (26.4)	66.6 (40.0)	78.7 (49.9)	78.5 (46.1)	128.4 (93.1)	<0.0001
Follow-up (Y25) (N=3147)	113.8 (86.1)	76.0 (30.5)	111.2 (71.3)	84.7 (33.8)	151.7 (106.6)	112.8 (58.7)	229.5 (185.0)	<0.0001
HDL mean (SD)								
Baseline (Y0) (N=4322)	53.2 (13.1)	62.6 (11.8)	57.2 (11.2)	53.7 (12.1)	51.1 (11.9)	47.1 (11.4)	40.5 (9.2)	<0.0001
Follow-up (Y25) (N=3269)	57.8 (17.8)	70.2 (17.5)	58.6 (17.1)	63.1 (14.6)	51.4 (19.0)	52.4 (14.0)	40.5 (8.6)	<0.0001
Systolic Blood pressure, mean (SD), mmHg								
Baseline (Y0)	110.4 (10.9)	106.8 (9.6)	111.5 (9.5)	108.6 (10.8)	112.7 (10.2)	110.0 (11.5)	117.0 (12.9)	<0.0001
Follow-up (Y25)(N=3276)	118.7 (15.3)	112.9 (12.7)	120.2 (14.7)	116.2 (15.1)	123.4 (16.6)	118.7 (15.4)	125.3 (15.2)	<0.0001
Diastolic Blood pressure, mean (SD), mmHg								
Baseline (Y0)	68.6 (9.6)	66.4 (8.3)	69.2 (8.8)	67.5 (8.7)	69.1 (10.1)	68.4 (10.2)	73.9 (11.3)	<0.0001
Follow-up (Y25)(N=3275)	74.0 (10.9)	70.0 (9.8)	75.0 (10.7)	72.4 (11.0)	76.7 (11.1)	74.4 (10.5)	78.0 (10.9)	<0.0001
PSYCHOSOCIAL RISK FACTORS								
Number of life events at Year 0, mean (SD) (N=4418)	8.3 (4.6)	7.9 (4.4)	8.3 (4.8)	8.3 (4.8)	8.5 (4.6)	8.3 (4.5)	8.3 (4.9)	0.31

Weighted life events score at Year 0, mean (SD) (N=4418)	2363 (1397)	2281 (1316)	2377 (1463)	2361 (1460)	2437 (1398)	2350 (1331)	2415 (1450)	0.42
Cook Medley Hostility Score at Year 0, mean (SD) (N=4261)	19.4 (8.6)	18.0 (8.1)	20.0 (8.5)	19.1 (8.9)	20.8 (8.5)	19.3 (8.7)	19.5 (8.5)	<0.0001
MARKERS OF SUBCLINICAL CARDIOVASCULAR DISEASE								
CAC score at Year 25, median (IQR; N=2997)	0 (0, 3.9)	0 (0, 0)	0 (0, 4.7)	0 (0, 0)	0 (0, 18.7)	0 (0, 3.1)	1.6 (0, 60.7)	<0.0001
Presence of any CAC at Year 25, n % (N=2997)	834 (27.8)	86 (17.0)	188 (29.1)	105 (19.7)	169 (39.1)	190 (27.5)	96 (50.8)	<0.0001
LV mass index, mean (SD), $g/m^{2.7}$								
Year 5 (N=3868)	35.1 (9.2)	34.0 (9.1)	35.8 (8.7)	35.2 (9.8)	34.5 (8.2)	35.1 (9.2)	36.2 (10.7)	0.0008
Year 25 (N=2932)	39.7 (11.6)	36.6 (9.4)	40.2 (10.4)	39.8 (13.6)	40.1 (11.5)	40.3 (11.8)	43.6 (13.4)	<0.0001
LV longitudinal strain at Year 25, mean (SD), % (N =2849)	-15.1 (2.4)	-15.7 (2.3)	-14.9 (2.3)	-15.4 (2.4)	-14.6 (2.3)	-15.1 (2.4)	-14.1 (2.4)	<0.0001

Table 2. Multivariable models for coronary artery calcification, left ventricular mass and strain. Abbreviations: Y25, year 25; LV, left ventricular; BMI, body mass index. P values for groups are for comparisons with referent (group 1, low-stable).

Covariate	Presence of coronary artery calcification at Y25 (N=2941)		Coronary artery calcium score at Y25 > 100 (N=2941)		Height-indexed LV mass at Y25 (N=2882)		LV strain at Y25 (N=2796)	
	Odds ratio	P	Odds ratio	P	β	P	β	P
Age, year 25 (per year)	1.15 (1.12-1.18)	<0.0001	1.24 (1.19-1.30)	<0.0001	0.12	0.02	0.03	0.007
Sex								
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	3.34 (2.74-4.06)	<0.0001	3.48 (2.53-4.78)	<0.0001	1.89	<0.0001	0.75	<0.0001
Race								
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	0.80 (0.65-0.97)	0.03	0.97 (0.72-1.31)	0.86	2.05	<0.0001	0.89	<0.0001
Smoking (per pack-year)	1.03 (1.02-1.04)	<0.0001	1.02 (1.01-1.04)	<0.0001	0.06	0.002	0.004	0.36
Physical activity, year 25 (heavy intensity, per 1 standard deviation)	1.13 (1.04-1.24)	0.007	1.09 (0.95-1.25)	0.23	0.36	0.07	-0.042	0.35
Education, year 25 (per year)	0.97 (0.93-1.00)	0.07	0.93 (0.88-0.98)	0.01	-0.30	0.0001	-0.01	0.48
Cumulative BMI (per 1 standard deviation in BMI-years)	1.41 (1.28-1.55)	<0.0001	1.43 (1.24-1.64)	<0.0001	5.47	<0.0001	0.37	<0.0001
Metabolic Trajectory Groups								
Group 1: low-stable	1.00 (Ref)	-	Ref	-	Ref	-	Ref	-

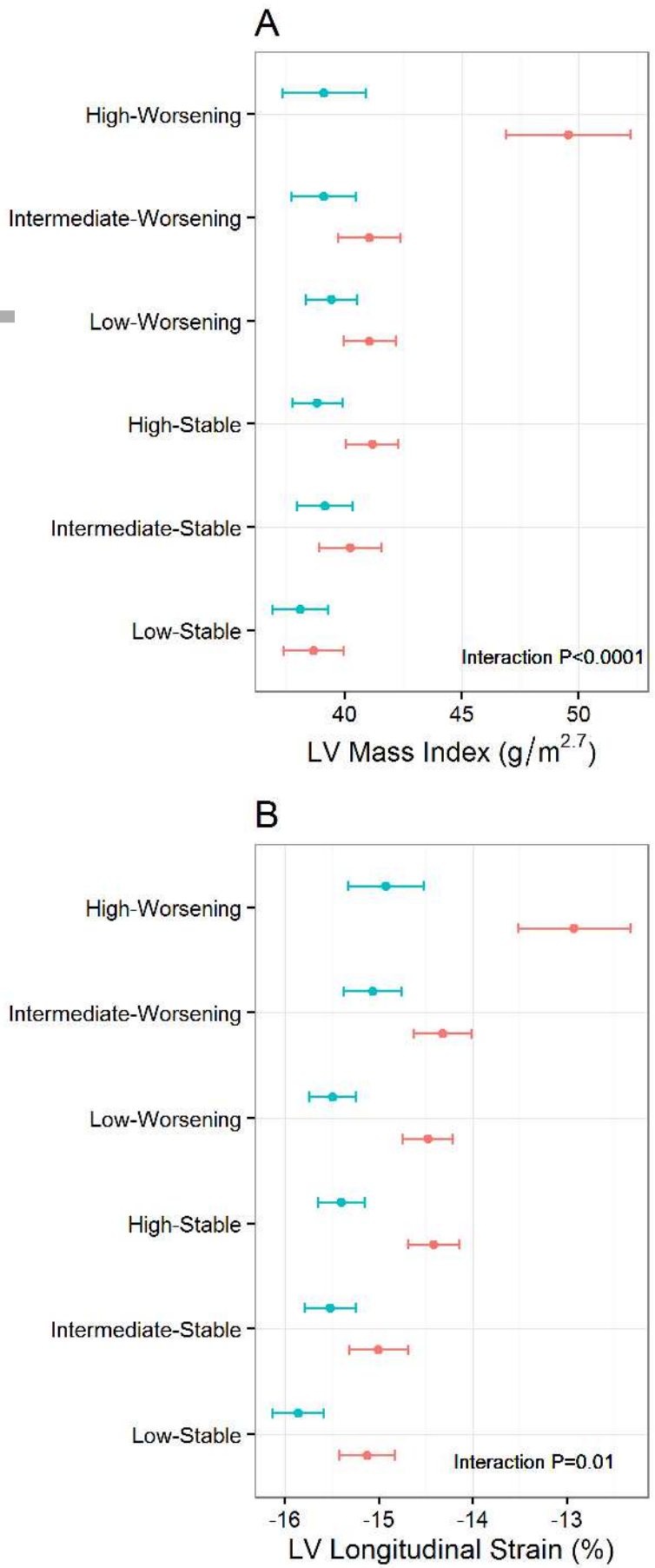
Group 2: low-worsening	1.50 (1.10-2.04)	0.01	1.67 (0.99-2.83)	0.057	1.85	0.002	0.51	0.0002
Group 3: intermediate-stable	1.24 (0.89-1.77)	0.20	1.69 (0.94-3.04)	0.08	1.28	0.04	0.25	0.08
Group 4: intermediate-worsening	2.47 (1.78-3.42)	<0.0001	2.57 (1.50-4.39)	0.0006	1.67	0.01	0.80	<0.0001
Group 5: high-stable	1.95 (1.43-2.67)	<0.0001	1.80 (1.05-3.10)	0.03	1.56	0.009	0.58	<0.0001
Group 6: high-worsening	3.61 (2.41-5.41)	<0.0001	3.66 (2.00-6.69)	<0.0001	4.34	<0.0001	1.36	<0.0001

Figure Legends:

Figure 1. Metabolic trajectories over time in CARDIA. Each trajectory is represented by a different color, with shaded bands representing 95% confidence intervals.

Figure 2. Trends in body mass index [BMI] (A), waist circumference [WC] (B) and ratio of WC / BMI over time in CARDIA, stratified by trajectory group computed using linear mixed effects models with discrete time points for each CARDIA exam and exam*trajectory group interaction terms. Over time, all groups had similar increases in BMI and WC. While worsening groups had stable WC / BMI ratios ($P \geq 0.29$ for exam 1 vs. exam 8), the stable groups all had declining WC / BMI ratios ($P \leq 0.0005$ for exam 1 vs. exam 8), suggesting greater proportionate increases in abdominal adiposity in the metabolically worsening groups.

Figure 3. Effect modification by race and sex. Left ventricular (LV) mass index (A) and longitudinal strain (B) across metabolic trajectories by race. Points represents the adjusted least-squares means with 95% confidence intervals. (C) Rate of coronary artery calcification (CAC) score >0 by metabolic trajectory and sex. Differences by sex are significant ($P<0.0001$) in each group except high-worsening ($p=0.06$) with evidence of effect modification of metabolic trajectory by sex (interaction $P=0.001$).



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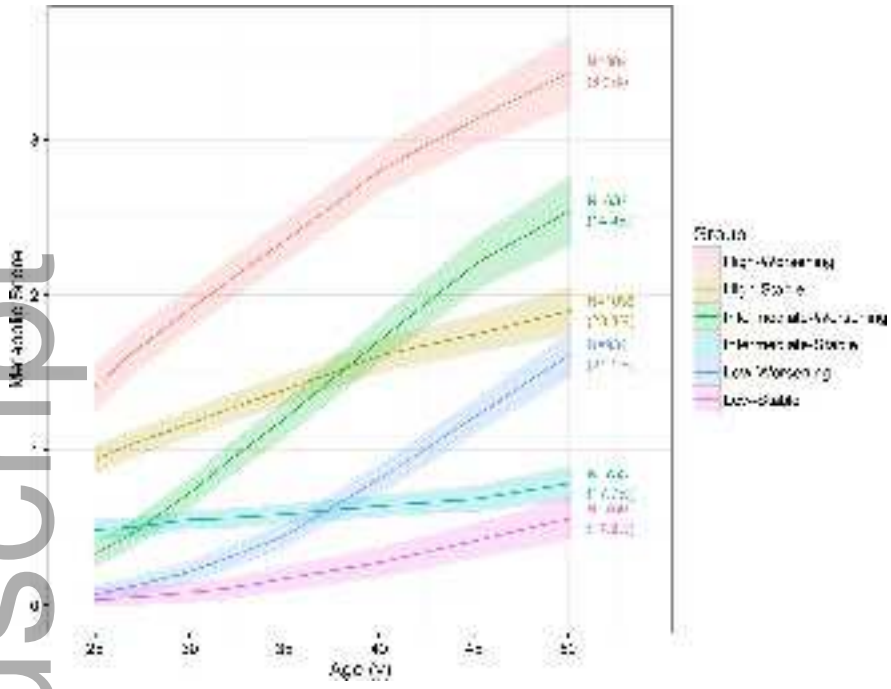

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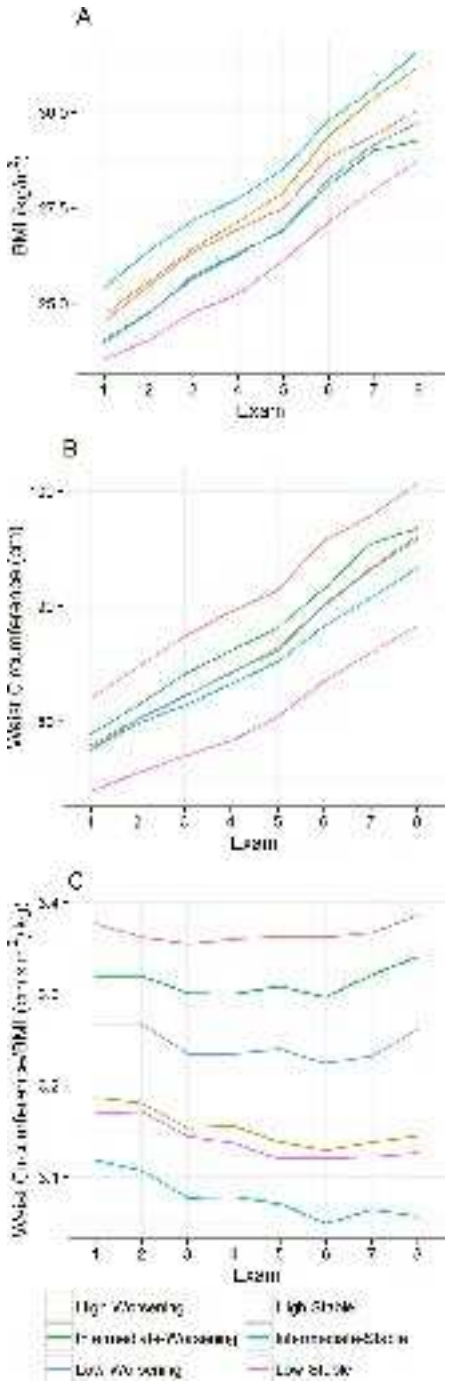

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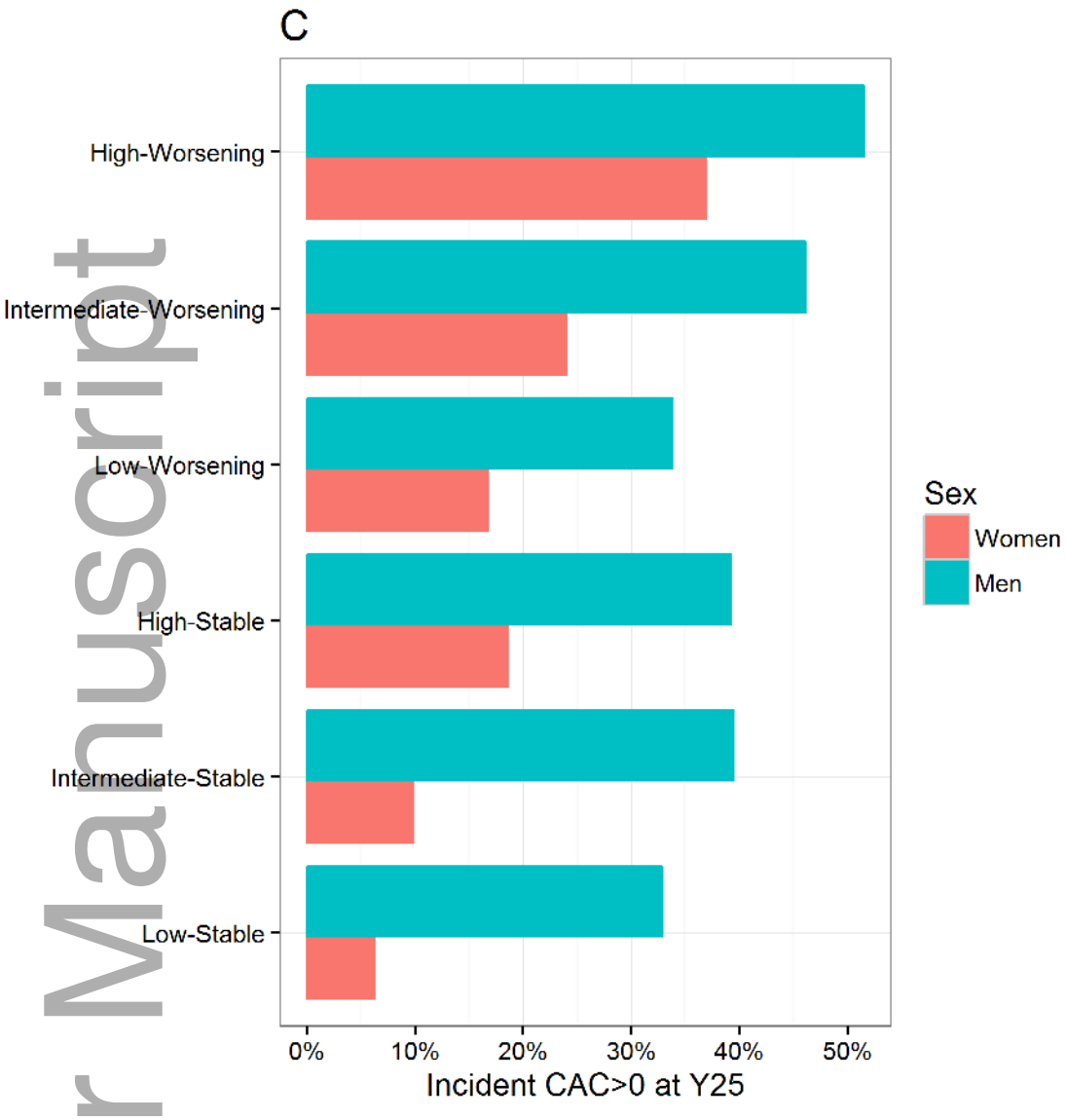

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