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Authors

Cohen, Laura P
Vittinghoff, Eric
Pletcher, Mark J
et al.

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Association of Midlife Cardiovascular Risk Factors with Risk of Heart Failure Subtypes Later in Life

Laura P. Cohen, MD, MPP[a], **Eric Vittinghoff, PhD**[b], **Mark J. Pletcher, MD, MPH**[b], **Norrina Allen, PhD**[c], **Sanjiv Shah, MD**[c], **John T. Wilkins, MD, MS**[c], **Patricia P. Chang, MD, MHS**[d], **Chiadi E. Ndumele, MD, MHS**[e], **Anne B. Newman, MD, MPH**[f], **Diane Ives, MPH**[f], **Mathew S. Maurer, MD**[a], **Elizabeth C. Oelsner, MD**[a], **Andrew E. Moran, MD, MPH**[a], **Yiyi Zhang, PhD**[a]

[a]Columbia University Irving Medical Center, Columbia University, New York, NY

[b]University of California, San Francisco, San Francisco, CA

[c]Northwestern University Feinberg School of Medicine, Northwestern University, Chicago, IL

[d]University of North Carolina School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[e]Johns Hopkins University Medical Center, Johns Hopkins University, Baltimore, MD

[f]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania.

Abstract

Background: Independent associations between cardiovascular risk factor exposures during midlife and later life development of HF with preserved ejection fraction (HFpEF) vs. reduced EF (HFrEF) have not been previously studied.

Methods: We pooled data from four US cohort studies (ARIC, CHS, Health ABC, and MESA) and imputed annual risk factor trajectories for body mass index (BMI), systolic and diastolic blood pressure (SBP, DBP), LDL and HDL cholesterol, and glucose starting from age 40 years. Time-weighted average exposures to each risk factor during midlife and later life were calculated and analyzed for associations with the development of HFpEF or HFrEF.

Results: A total of 23,861 participants were included (mean age at first in-person visit 61.8 ±10.2 years; 56.6% female). During a median follow up of 12 years, there were 3,666 incident HF events, of which 51% had EF measured, including 934 with HFpEF and 739 with HFrEF. High midlife SBP and low midlife HDL were associated with HFrEF, and high midlife BMI, SBP, pulse pressure, and glucose were associated with HFpEF. After adjusting for later life exposures, only midlife pulse pressure remained independently associated with HFpEF.

Address for Correspondences: Yiyi Zhang, PhD, Columbia University Medical Center, Division of General Medicine, 622 W. 168th Street, PH9-109A, New York, NY 10032, Tel: (212) 305 6787, yz3160@cumc.columbia.edu.

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Conclusions: Midlife exposure to cardiovascular risk factors are differentially associated with HFrEF and HFpEF later in life. Having a higher pulse pressure during midlife is associated with a greater risk for HFpEF but not HFrEF, independent of later life exposures.

Keywords

Heart failure subtype; heart failure with reduced ejection fraction; heart failure with preserved ejection fraction; risk factors; midlife

Introduction

About 6.5 million adults in the United States are living with heart failure (HF).[1, 2] Fifty-percent of new cases are diagnosed with HF with preserved ejection fraction (HFpEF) and the remaining are diagnosed with HF with reduced ejection fraction (HFrEF).[3] The American College of Cardiology (ACC) / American Heart Association (AHA) HF guideline recommends prevention of all HF by lifestyle modification and treatment of hypertension, dyslipidemia, obesity, and diabetes.[4, 5] While these prevention guidelines do not distinguish between HF subtypes, it has been well-recognized that different clusters of risk factors are associated with HFpEF vs. HFrEF. HFpEF is associated with older age, obesity, hypertension, diabetes, and multiple comorbidities, while HFrEF is more strongly associated with hypertension and coronary artery disease, among other risk factors.[3, 6, 7] However, most of these studies were based on cross-sectional data and few studies examined the association between risk factors and the development of incident HF subtypes.[8–10]

Additionally, the risk for HF increases with age and individuals age ≥65 years account for over 80% of prevalent HF cases.[11] Some studies suggest mitigating risk factors for HF is most important in elderly adults, while others demonstrate a 10-15 year lag time between risk factor exposure and disease onset, suggesting risk factor exposures during middle age are more important for HF prevention and should be the focus of preventative efforts.[7, 12–15] However, few studies have evaluated the independent associations between midlife vs. later life risk factors with the development of HF subtypes, and it remains unknown if there is a critical time period during the adult life course for prevention of HFpEF or HFrEF.

In this study, we pooled data from four US cohort studies with repeated risk factor measurements and examined the independent associations of cumulative risk factor exposures during midlife (age 40 to 64 years) and later life (age ≥65 years) with future risk of HF subtypes (HFrEF and HFpEF).

METHODS

All data used in this study were obtained from each study coordinating center. Limited versions of the datasets may be available through the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) from NHLBI. Our analytic code is available to interested researchers from the corresponding author upon reasonable request.

Study Design and Population

This analysis was based on data from four large prospective cohort studies: 1) the Atherosclerosis Risk in Communities (ARIC) Study,[16] 2) Cardiovascular Health Study (CHS),[17] 3) Health, Aging and Body Composition (Health ABC) Study,[18] and 4) Multi-Ethnic Study of Atherosclerosis (MESA) Study.[19] The design details of each of these studies are reported in Supplemental Materials (Supplemental Table 1). All studies were approved by the Institutional Review Boards at participating institutions; all study participants provided written informed consent prior to enrolling. The data for pooling were centralized at Columbia University where they were further harmonized and analyzed, as part of the larger NHLBI Pooled Cohorts project.[20] Harmonization is the process of creating a new data set from a homogenized set of variables used across different data sets. This method has been previously described and full information on the harmonization of individual variables can be found at: http://columbiamedicine.org/pcs/files/Public_Web_Resource1.pdf. The current analysis was restricted to participants >18 years of age without known clinical CVD (defined as history of coronary heart disease, stroke, or HF, determined by either self-report of adjudicated events) at baseline, with at least one non-missing value for each of six HF risk factors evaluated, and with follow up for HF events after age 65 years (Supplemental Figure 1).

Clinical data collection

Demographic characteristics and CVD risk factors were evaluated based on standard protocols for each study.[16–19] CVD risk factors were measured at most study visits using standardized and validated methods. The primary risk factors of interest in the current analysis included body mass index (BMI), systolic and diastolic blood pressures (SBP and DBP), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and fasting blood glucose.

Follow-up and HF events

The primary outcome was incident HF subtype. All studies prospectively obtained incident HF events. HF was defined by each cohort's internal definition of heart failure (Supplemental Table 2).[19, 21–23] Diagnosis of HF generally required HF symptoms, or physician diagnosis and medical treatment for HF. To ensure consistency across cohorts, we defined HF subtypes in our analysis based on the definitions provided by the ACC/AHA 2013 HF guideline, which were reiterated in the 2016 European Society of Cardiology guidelines.[5, 24] HFrEF was defined as clinical HF and an ejection fraction ≤40% and HFpEF as clinical HF and an ejection fraction ≥50%. Those with clinical HF and an EF between 41-49% were categorized as "borderline" and those with clinical HF and without a quantitative EF measured were categorized as "unclassified" HF. Of note, individual cohort's classification systems for HF subtype, where present, were not used in our classification system of HF subtype; we used quantitative EF to divide clinical HF into subtypes across studies.

Imputation of CVD risk factors across the life course

The restricted age range for enrollment into each cohort study limits the direct measurement of CVD risk factors throughout the adult life periods (e.g., CHS participants were enrolled after age 65, therefore their CVD risk factor levels before age 65 were not observed). We previously reported our method to impute risk factor trajectories across the adult life course using data from pooled cohorts.[25–27] In brief, we pooled data from multiple cohort studies which together provided observations that span the adult life course, and leveraged observed risk factor patterns to impute unobserved risk factors for each individual. We used linear mixed models to estimate latent trajectories underlying the observed values for each participant, and imputed risk factor levels annually from age 18 years until the end of follow-up for each participant.

Statistical Analyses

Using imputed trajectories, we calculated period-specific time-weighted averages (TWAs) of BMI, SBP, DBP, LDL, HDL, and fasting glucose as summary measures of midlife (ages 40-64) and later life (ages 65+). The TWAs were categorized according to clinically relevant groupings (BMI: <18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2; SBP: <120, 120-129, 130-139, ≥140 mm Hg; DBP: <70, 70-79, 80-89, ≥90 mm Hg; LDL: <100, 100-129, 130-159, ≥160 mg/dL; HDL: ≥65, 50-64, 35-49, <35 mg/dL, fasting glucose: <100, 100-125, ≥126 mg/dL). We assessed the correlation between young adult, midlife and later life exposures, and compared the difference between these correlation coefficients using the Fisher's z transformation.[28]

We used Cox proportional hazards models to evaluate the associations between midlife TWA risk factor exposures and each HF subtype. We used age as the time scale, with the origin for time to event set at 65 years. The basic models for each risk factor were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, smoking status, use of lipid-lowering, anti-hypertensive, or anti-diabetes medications, as well as midlife TWAs of other CVD risk factors. For example, the model for midlife LDL cholesterol was simultaneously adjusted for midlife exposures to BMI, SBP, DBP, HDL, and fasting glucose, as well as for current values of other time-varying covariates mentioned above. To further assess whether the associations between midlife risk factor exposures were independent of later life exposures, in a second step we additionally included TWAs of later life risk factors simultaneously in the model with midlife exposures. We also examined whether risk factor exposures during young adulthood (age 18-39 years) were associated with subsequent development of HF subtypes, independent of midlife exposures. Tests for linear trends across the categories of each risk factor were conducted by including a variable with the median level of each category in the models.

To account for estimation error in imputed risk factors trajectories and TWAs, we used multiple imputation techniques to obtain 30 imputed datasets. Survival analyses of the associations between risk factors and HF outcomes were performed on each imputed dataset, and summary hazard ratio (HR) and corresponding 95% confidence interval (CI) were calculated across all 30 imputations using established methods (the summary HR and 95% CI can be interpreted the same way as those generated from a standard Cox model).[29]

To examine the robustness and consistency of our findings, we performed several secondary and sensitivity analyses. These included examining the associations of pulse pressure instead of DBP, and waist circumference or waist-to-height ratio instead of BMI, with HF subtypes; using alternative EF cut-point for defining HFrEF (EF <45%) and HFpEF (EF ≥45%); using alternative age cut-point for defining midlife (age 40-59 years) and later life (age ≥60 years) periods; multiply imputing missing EF measurement for participants with unclassified HF and re-categorizing them into HFrEF or HFpEF based on the imputed EF; repeating analyses by cohort, as well as leaving out one cohort at a time to confirm that our findings were not driven by any single study. All analyses were performed using STATA version 14 (StataCorp LP, College Station, Texas).

Results

Among a total of 23,861 participants pooled from ARIC, CHS, Health ABC, and MESA who met the inclusion criteria for our analysis, the average age (SD) at enrollment was 61.8 (10.2) years, ranging from a mean of 54.2 (5.8) years in ARIC to 73.5 (2.8) years in Health ABC (Table 1). Women comprised 56.6% of participants; 24.4% self-reported as black and 4.7% were of Hispanic ethnicity. The majority of participants (96%) contributed >1 direct measurement of each cardiovascular risk factor over time (mean 4.4 visits per person; Table 2). Baseline characteristics of the study participants by HF subtype are shown in Supplemental Table 3. There was a stronger correlation between young adult and midlife exposures (Pearson correlation coefficients 0.9 to 1.0), compared to midlife and later life exposures (Pearson correlation coefficients 0.5 to 0.8; all P-values comparing the young adult and midlife vs. midlife and later life correlation coefficients <0.001) (Supplemental Table 4).

During a median follow-up of 12 years, 739 (20%) participants developed HFrEF, 934 (25%) developed HFpEF, 188 (5%) developed HF with borderline EF, and 1,805 (49%) had HF but without a specified EF (“unclassified”) (Table 2). When midlife CVD risk factor exposures were evaluated alone, midlife low BMI (<18.5), high SBP (≥140 mm Hg), and low HDL cholesterol (<35 mg/dL) were associated with an increased risk of HFrEF (Figure 1). Conversely, high BMI (≥30), high SBP (≥140 mm Hg), and high fasting glucose (≥126 mg/dL) were associated with later life HFpEF. After adjusting for later life risk factor exposures, none of the midlife risk factor exposures were statistically significantly associated with HFrEF or HFpEF, although the pattern of associations remained similar to that observed without adjustment for later life exposures (Figure 2). Only later life exposure to elevated SBP was associated with HFpEF when midlife and later life exposures were included simultaneously in the models. The associations between midlife CVD risk factors and unclassified HF subtype (i.e. EF data not available) were shown in Supplemental Figure 2.

Given a persistent pattern of higher SBP and lower DBP associated with the development of HFpEF, we separately evaluated the association between midlife and later life pulse pressure and the development of HF subtypes (Figure 3). A higher pulse pressure (≥60 mm Hg) in midlife was independently associated with HFpEF (HR = 2.04; 95% CI 1.21 to 3.41, compared to a pulse pressure <45 mm Hg), after accounting for later life exposures.

In secondary analyses, none of the risk factors during young adult (18-39 years) or midlife period were significantly associated with HF subtypes when simultaneously adjusting for midlife or young adult periods, respectively, except for a borderline association between midlife SBP and HFpEF (p-trend = 0.03) (Supplemental Figure 3). There were no significant associations between waist-to-height ratio (Supplemental Figure 4) or waist circumference (Supplemental Figure 5) in midlife or later life and HF subtype development. There were also no associations between midlife risk factor exposures when using alternative EF cut-points for HF subtypes (i.e., defining HFrEF as EF <45% and HFpEF as EF ≥45%; Supplemental Figure 6) or when changing the definition of midlife from 40-64 years to 40-59 years (Supplemental Figure 7). After imputing missing EF measurement for those with unclassified HF, there was an inverse association between midlife DBP and HFpEF, and a positive association between midlife glucose and HFrEF, after adjusting for later life exposures (Supplemental Figure 8).The analyses by each cohort are shown in Supplemental Figures 9 & 10, and the analyses leaving out one cohort are shown in Supplemental Figures 11 & 12; the results found no evidence that the study findings were driven by any single cohort.

Discussion

In this analysis, pooling participants from four large US cohort studies, we found that low BMI, high SBP, and low HDL in midlife were associated with an increased risk of HFrEF, whereas high BMI, high SBP, and high glucose in midlife were associated with HFpEF. However, after accounting for later life exposures to these risk factors, midlife risk factor exposures were no longer statistically significantly associated with the development of HF subtypes, although the pattern of associations remained similar. However, high pulse pressure during midlife was independently associated with an increased risk of HFpEF, even after adjusting for later life exposures.

Prior studies have shown that exposure to high BP during midlife is associated with the development of HF.[11, 30, 31] In the Framingham Heart Study, hypertension was the most common risk factor associated with HF and elevation in midlife SBP (20 years and 10 years prior to HF development) was independently associated with HF development.[32] An analysis of 4,408 participants in CHS and Health ABC also found a continuous positive relationship between SBP levels and HF risk in the elderly.[33] Two studies showed that midlife elevation in BP is associated with increased left ventricular mass index (a precursor to both HFrEF and HFpEF) and diastolic dysfunction (a precursor to HFpEF) in later life.[34, 35] Although it is well-accepted that hypertension is a common risk factor in both HFrEF and HFpEF, there is scarce evidence specifically evaluating the association between BP elevation in midlife and HF subtype development.

Our study found that midlife SBP was positively associated with both HFrEF and HFpEF, and midlife DBP was inversely associated with HFpEF, when not adjusting for later life risk factor exposures. The J-shaped association between midlife DBP and HFpEF in our analysis may signal early development of increased arterial stiffness that progresses during later life, leading to a higher peripheral SBP, a lower DBP, and a wider pulse pressure.[36–38] Arterial stiffness has been associated with HFpEF development, progression and prognosis.[39, 40]

Indeed, in a secondary analysis where we replaced DBP with pulse pressure, midlife pulse pressure was strongly and independently associated with HFpEF. This is consistent with prior results from Framingham Heart Study, where a 16 mm Hg increase in pulse pressure was associated with 55% increased risk of HF.[32, 41–43]

After accounting for later life BP levels, midlife SBP and DBP were no longer statistically significantly associated with HF subtypes, although the pattern of associations remained similar. This may be partly due to the high correlation between midlife and later life BP levels. Additionally, despite a very large sample size, our study only observed ~700 incident HFrEF and ~900 HFpEF cases, which may not provide enough power to delineate and quantify the independent contributions of midlife vs. later life BP to future development of HF subtypes. Conversely, midlife pulse pressure remained strongly associated with HFpEF even after adjusting for later life pulse pressure, suggesting that long-standing or more severe hypertension with resultant arterial stiffness is an important predictor for HFpEF. Long-term exposure to some risk factors can lead to end-organ damage, as is the case with high BP and arterial stiffness. This end-organ damage is less likely to be reversible and more likely to be associated with HF development than an absence of end-organ damage. Among the risk factors we evaluated, only pulse pressure directly represents end-organ damage, and is the only risk factor that is independently associated with later life HFpEF when present in midlife.

In addition to hypertension, obesity and diabetes are established risk factors for HFpEF and are implicated in the pathophysiology of its development.[6, 31, 44, 45] Our analysis found that high BMI and high glucose in midlife were associated with an increased risk for HFpEF, when not adjusting for later life exposures. Previous studies have also shown that BMI is more strongly associated with risk of HFpEF compared to HFrEF, and obesity is associated with left ventricular diastolic dysfunction, the foundation for symptomatic HFpEF.[46] Insulin resistance, which is highly associated with obesity, is also a more common risk factor in HFpEF compared to HFrEF.[46] Approximately 30-40% of those with HFpEF also have diabetes and this proportion is increasing.[47, 48]

Main strengths of our study include the unique study design which pools data from multiple large cohorts and allows us to model risk factors trajectories across the adult life course and evaluate if there is an independent risk associated with exposure to cardiovascular risk factors during specific lifetime periods. Using data from these cohort studies ensures high quality risk factor and outcome assessments and long follow-up duration for specific HF subtypes.

This study also has several limitations. We defined HF subtypes by EF evaluated at the time of an echocardiogram closest to the HF diagnosis and cannot ensure the EF was stable over time. HFpEF is often difficult to diagnose and may have been missed as a clinical diagnosis in earlier cohort studies. We did not use additional parameters to further define HFpEF, such as echo and laboratory markers that may aid in the diagnosis of HFpEF, as they were not available across all studies. As we excluded prevalent HF cases that occurred prior to age 65, our HF population may be skewed towards HFpEF or to a relatively healthier HF population. Additionally, we did not have information on hereditary and acquired cardiomyopathies,

including hypertrophic, dilated, viral, and infiltrative cardiomyopathies, which may have different risk factor patterns. Despite a large sample size and many HF events observed in our study, almost 50% of participants did not have a specified EF, limiting our ability to detect an association between midlife risk factors and HF subtypes, particularly when accounting for later life exposures. Differences in the adjudication processes between cohorts may lead to differences in the accurate recognition of HF events.[49] We used imputation methods to estimate risk factor trajectories, as majority of the cardiovascular cohort studies are restricted in age range and did not measure risk factors across the adult life course. The risk factor trajectories are subject to imputation error; however, imputation error in our study is likely non-differential and trajectory estimates for individuals with relatively fewer observed measurements are subject to extra "shrinkage" towards the sample means.[25] Therefore, our estimates of the association between risk factors and HF subtypes are likely conservative and biased towards the null. Finally, as is common with all cohort studies, there may be confounding from variables not accounted for in our HF risk modeling.

Conclusions

By pooling data from four US cohorts with over 23,000 participants, our study found that high midlife SBP and low HDL were associated with HFrEF, and high midlife BMI, SBP, pulse pressure, and glucose were associated with HFpEF. After further accounting for later life exposures, only midlife pulse pressure remained independently associated with HFpEF. These findings suggest that arterial stiffness, for which pulse pressure is a surrogate marker, is perhaps the most important early risk factor for HFpEF development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations list:

CVD	cardiovascular disease
DBP	diastolic blood pressure
HDL	high-density lipoprotein
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
LDL	low-density lipoprotein
SBP	systolic blood pressure
TWA	time-weighted average

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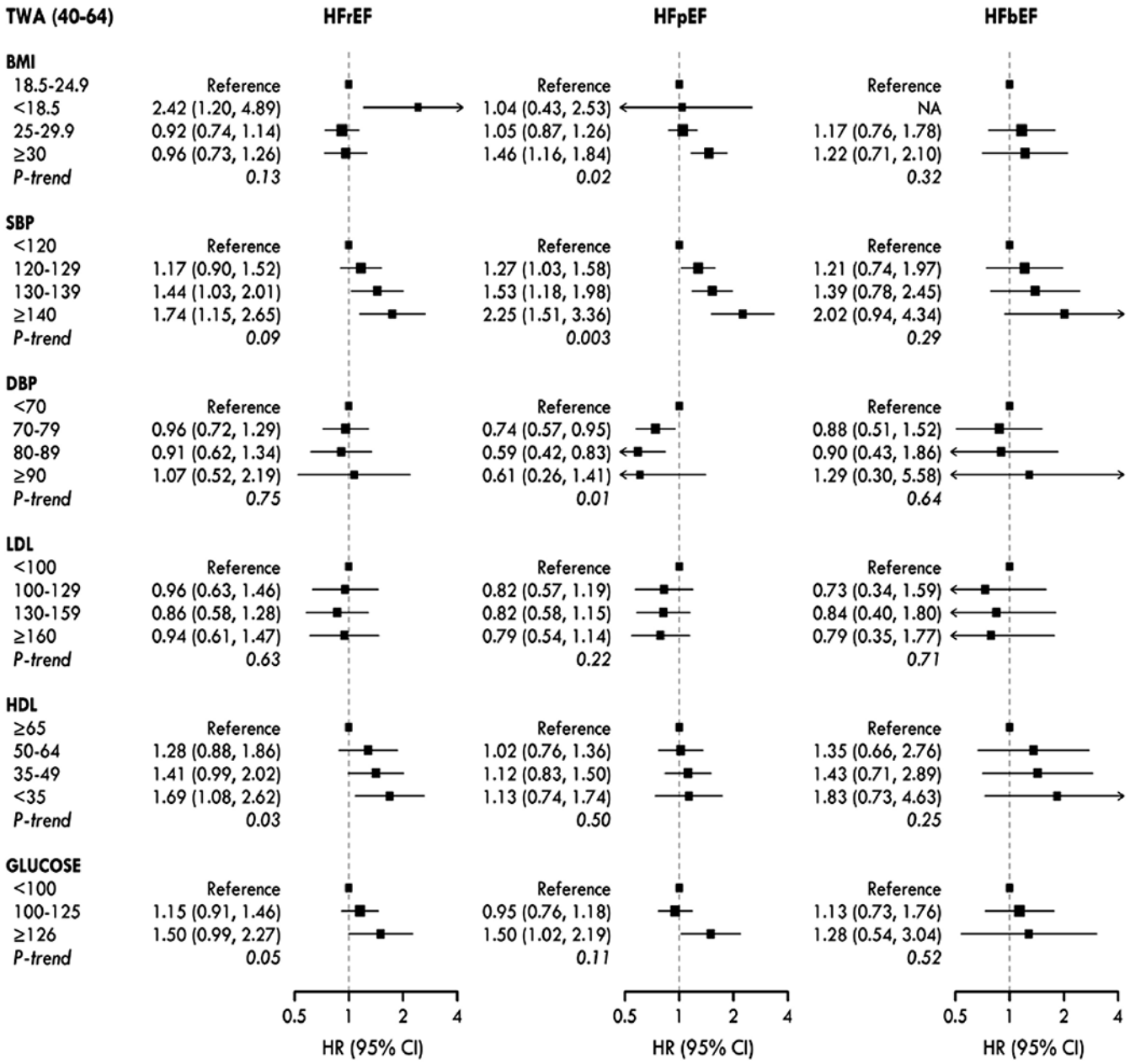

Figure 1. Associations between midlife (age 40-64 years) cardiovascular risk factor exposures and development of heart failure subtypes later in life.

Models for each risk factor were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, smoking status, use of lipid-lowering, anti-hypertensive, and anti-diabetic medications, and midlife time-weighted average (TWA) exposures to other risk factors. BMI = body mass index, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, HFbEF = heart failure with borderline ejection fraction, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, HR = hazard ratio, LDL = low-density lipoprotein cholesterol, SBP = systolic blood pressure.

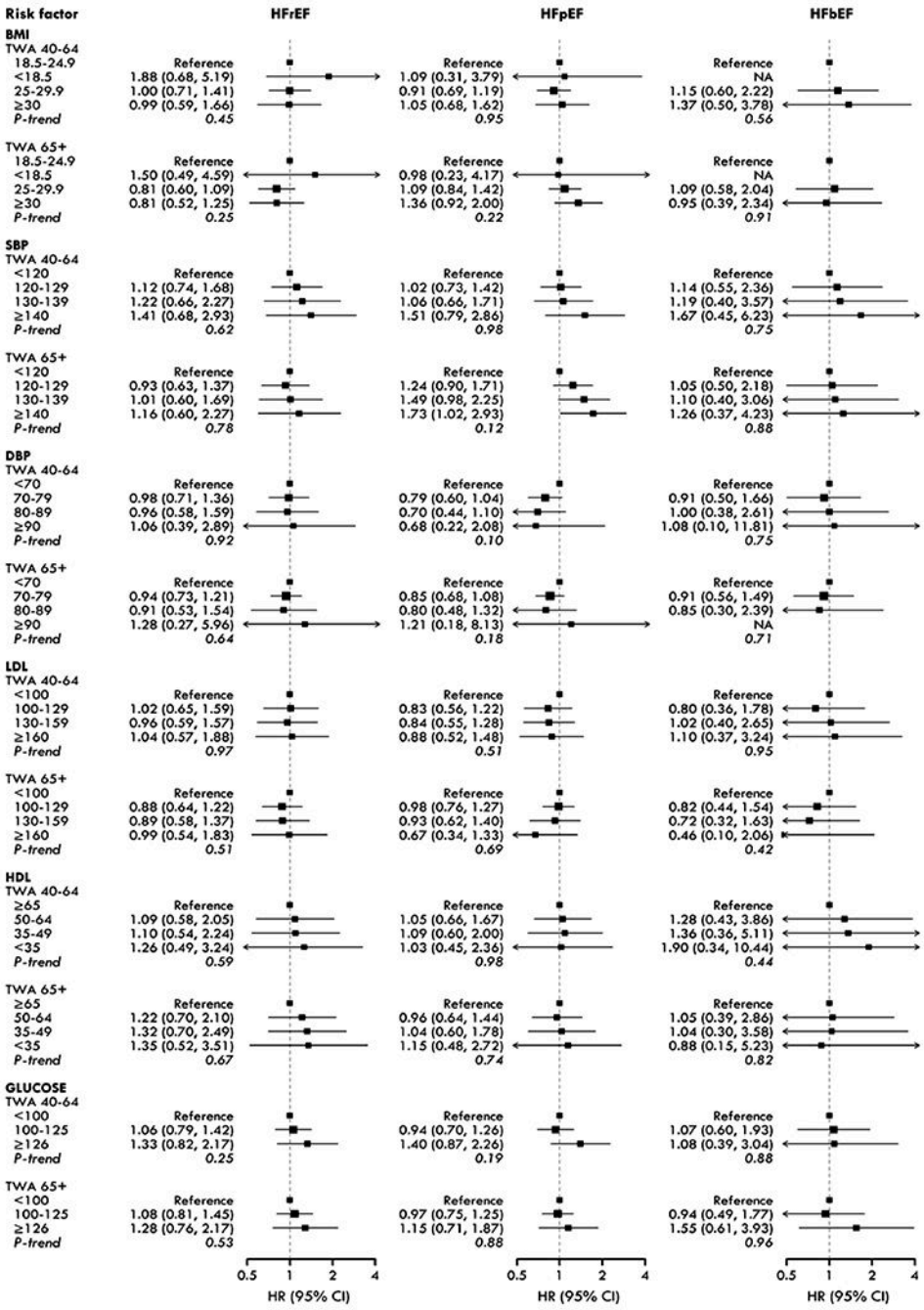

Figure 2. Associations between midlife (age 40-64 years) risk factor exposures and development of heart failure subtypes later in life, adjusted for later life (age ≥65 years) exposures.

Time-weighted average (TWA) exposures to risk factors from midlife (age 40-64 years) and later life (age ≥65 years) were included simultaneously in the same model. Models for each risk factor were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, smoking status, use of lipid-lowering, anti-hypertensive, and anti-diabetic medications, and midlife time-weighted average (TWA) exposures to other risk factors. BMI = body mass index, DBP = diastolic blood pressure, HDL = high-density lipoprotein cholesterol, HFbEF = heart failure with borderline ejection fraction, HFpEF = heart failure with preserved

ejection fraction, HFrEF = heart failure with reduced ejection fraction, HR = hazard ratio, LDL = low-density lipoprotein cholesterol, SBP = systolic blood pressure.

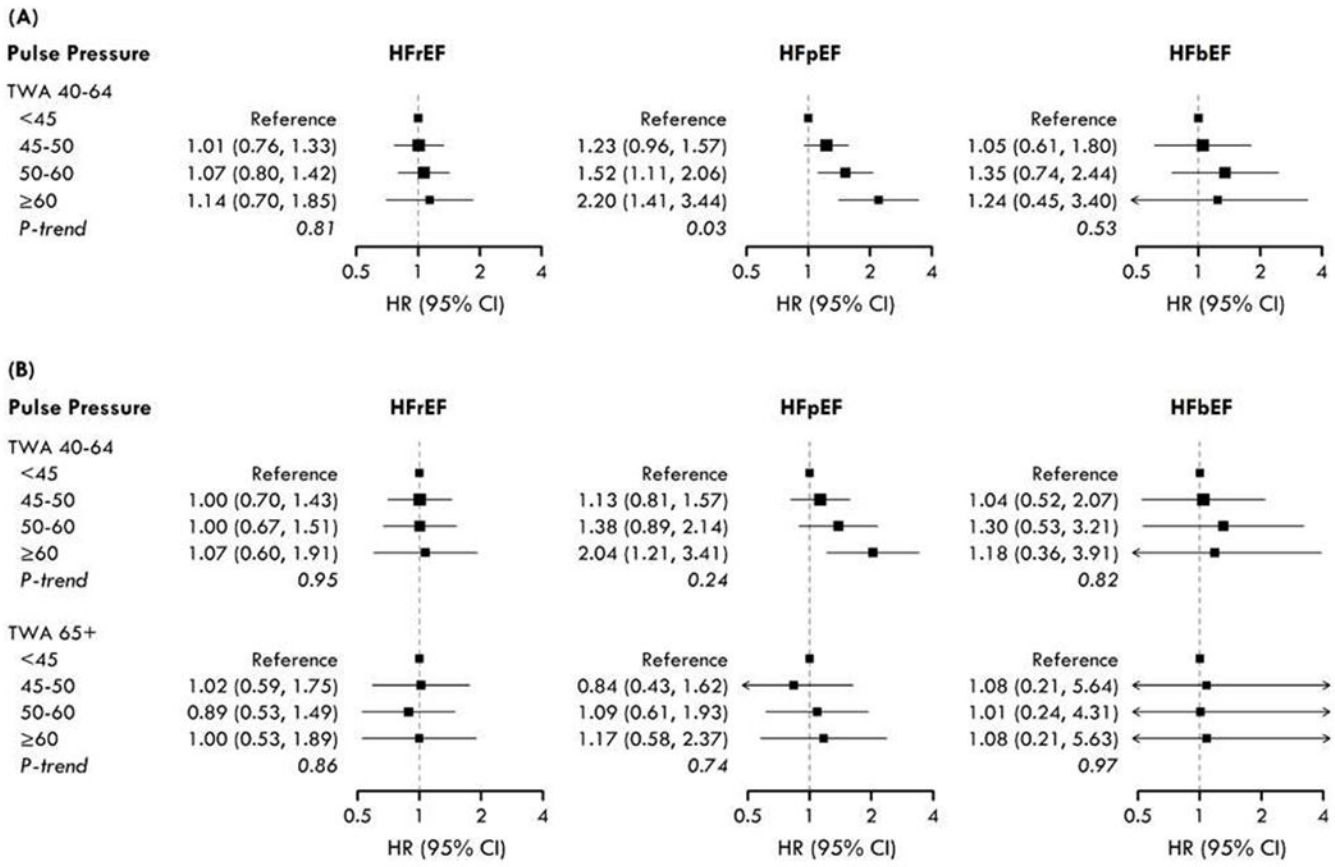

Figure 3. Associations between (A) midlife (age 40-64 years) and (B) later life (age ≥65 years) pulse pressure and development of heart failure subtypes.

(A) Time-weighted average (TWA) exposures to risk factors from midlife (age 40-64 years) were evaluated alone, and (B) simultaneously in the model with later life (age ≥65 years) TWA exposures to risk factors. Models for each risk factor were stratified by study cohort and adjusted for race/ethnicity, sex, birth year, smoking status, use of lipid-lowering, anti-hypertensive, and anti-diabetic medications, and midlife time-weighted average (TWA) exposures to other risk factors.

HFbEF = heart failure with borderline ejection fraction, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, HR = hazard ratio.

Table 1.

Characteristics of study participants at the first in-person examination

Characteristics*	Total (n = 23,861)	ARIC (n = 12,109)	CHS (n = 4,301)	Health ABC (n = 2,135)	MESA (n = 5,316)
Year of enrollment		1987–1989	1989-1990	1997-1998	2000-2002
Age range at study enrollment		45-64	≥65	70-79	45-84
Age (year)	61.8 ± 10.2	54.2 ± 5.8	72.4 ± 5.4	73.5 ± 2.8	65.6 ± 8.5
Race					
White	16,209 (67.9)	9,206 (76.0)	3,644 (84.7)	1,258 (58.9)	2,101 (39.5)
Black	5,828 (24.4)	2,867 (23.7)	630 (14.6)	877 (41.1)	1,454 (27.4)
Hispanic	1,111 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	1,111 (20.9)
Other	713 (3.0)	36 (0.3)	27 (0.6)	0 (0.0)	650 (12.2)
Sex					
Female	13,502 (56.6)	6,859 (56.6)	2,628 (61.1)	1,193 (55.9)	2,822 (53.1)
Male	10,359 (43.4)	5,250 (43.4)	1,673 (38.9)	942 (44.1)	2,494 (46.9)
Smoking					
Never	11,178 (46.8)	5,379 (44.4)	2,090 (48.6)	1,009 (47.3)	2,700 (50.8)
Former	8,520 (35.7)	3,889 (32.1)	1,685 (39.2)	910 (42.6)	2,036 (38.3)
Current	4,155 (17.4)	2,836 (23.4)	523 (12.2)	216 (10.1)	580 (10.9)
Body mass index (kg/m^2)	27.4 ± 5.1	27.4 ± 5.1	26.6 ± 4.6	27.4 ± 4.9	28.2 ± 5.4
Waist circumference (cm)	96.6 ± 13.7	96.2 ± 13.5	93.9 ± 13.3	99.3 ± 13.5	98.5 ± 14.2
Systolic blood pressure (mm Hg)	126.6 ± 20.9	120.4 ± 18.1	136.4 ± 21.4	135.7 ± 20.7	129.1 ± 21.7
Diastolic blood pressure (mm Hg)	72.5 ± 11.0	73.3 ± 10.9	71.3 ± 11.5	71.6 ± 11.7	71.9 ± 10.3
LDL cholesterol (mg/dl)	130.1 ± 37.1	137.1 ± 38.6	130.0 ± 35.5	123.0 ± 34.4	117.0 ± 31.3
HDL cholesterol (mg/dl)	53.1 ± 16.4	52.4 ± 16.9	55.6 ± 15.7	55.4 ± 17.1	51.5 ± 15.1
Glucose (mg/dl)	97 (90, 106)	98 (92, 107)	100 (94, 110)	94 (87, 104)	91 (94, 100)
Hypertension medication use	7,953 (33.3)	3,051 (25.2)	1,679 (39.0)	989 (46.3)	2,234 (42.0)
Lipid medication use	1,717 (7.2)	300 (2.5)	194 (4.5)	221 (10.4)	1,002 (18.8)
Diabetes medication use	1,527 (6.4)	453 (3.7)	281 (6.5)	215 (10.1)	578 (10.9)

*Values are mean ± SD, number (%), or median (25^{th}, 75^{th} percentile) based on baseline observed data.

Table 2.

Study observation period and number of events

Study characteristics	Total	ARIC	CHS	Health ABC	MESA
Number of participants	23,861	12,109	4,301	2,135	5,316
Median follow-up (year)	12	13	14	14	10
Number of in-person exams *	4.4 ± 2.1	4.1 ± 1.0	3.0 ± 0.9	9.4 ± 2.6	4.4 ± 1.1
Number of events					
HF reduced EF (EF <40%)	739 (20%)	250 (15%)	280 (19%)	114 (33%)	95 (37%)
HF preserved EF (EF ≥50%)	934 (25%)	295 (18%)	419 (29%)	125 (36%)	95 (37%)
HF borderline EF (EF 40-49%)	188 (5%)	56 (3%)	85 (6%)	26 (7%)	21 (8%)
Unclassified (EF not available)	1,805 (49%)	1,017 (63%)	660 (46%)	82 (24%)	46 (18%)

*Values are mean ± SD and column percentages

EF = ejection fraction, HF = heart failure.