Risk Factors for Incident Hospitalized Heart Failure With Preserved Versus Reduced Ejection Fraction in a Multiracial Cohort of Postmenopausal Women

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Background—Heart failure is an important and growing public health problem in women. Risk factors for incident hospitalized heart failure with preserved ejection fraction (HFpEF) compared with heart failure with reduced ejection fraction (HFrEF) in women and differences by race/ethnicity are not well characterized.

Methods and Results—We prospectively evaluated the risk factors for incident hospitalized HFpEF and HFrEF in a multiracial cohort of 42 170 postmenopausal women followed up for a mean of 13.2 years. Cox regression models with time-dependent covariate adjustment were used to define risk factors for HFpEF and HFrEF. Differences by race/ethnicity about incidence rates, baseline risk factors, and their population-attributable risk percentage were analyzed. Risk factors for both HFpEF and HFrEF were as follows: older age, white race, diabetes mellitus, cigarette smoking, and hypertension. Obesity, history of coronary heart disease (other than myocardial infarction), anemia, atrial fibrillation, and more than one comorbidity were associated with HFpEF but not with HFrEF. History of myocardial infarction was associated with HFrEF but not with HFpEF. Obesity was found to be a more potent risk factor for African American women compared with white women for HFpEF (*P* for interaction=0.007). For HFpEF, the population-attributable risk percentage was greatest for hypertension (40.9%) followed by obesity (25.8%), with the highest population-attributable risk percentage found in African Americans for these risk factors.

Conclusions—In this multiracial cohort of postmenopausal women, obesity stands out as a significant risk factor for HFpEF, with the strongest association in African American women.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00000611.

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Key Words: heart failure ■ hospitalization ■ prevalence ■ public health ■ risk factors

Heart failure (HF) is a major and growing public health problem in the United States that accounts for >1 million hospital admissions per year and affects close to 6 million Americans.[1] Of patients with incident HF in epidemiological studies, 40% to 71% have HF with preserved, rather than reduced, ejection fraction (HFpEF versus HFrEF), and HFpEF is more common in women.[1–7] HFpEF is increasing in prevalence[1] and as opposed to HFrEF, limited effective therapy are presently available. To guide future therapeutic considerations, there is a need to better understand the risk factors and natural history of HFpEF.

See Clinical Perspective

The epidemiology of HFpEF has largely been studied in white cohorts.[2,4–7] Some existing studies have examined incident HF

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in multiethnic cohorts but without ejection fraction data or have studied survival of those with prevalent HFpEF.[8–11] As such, there is an important need to evaluate risk factors for incident HFpEF and HFrEF, especially in women who are understudied.

The Women's Health Initiative recently readjudicated HF in a subcohort of women that differentiates acute from chronic HF and allows for the evaluation of incident hospitalized HFpEF and HFrEF.[12,13] We therefore sought to identify risk factors for HFpEF and HFrEF in women in this subcohort and to better understand the role of race/ethnicity in explaining any differences in HFpEF and its risk factors. For those HFpEF and HFrEF risk factors that were amenable to prevention, we assessed their population-attributable risk percentage (PAR%) to estimate the amount of HFpEF and HFrEF that could be theoretically reduced if these risk factors were eliminated.

Methods

Study Population

The Women's Health Initiative recruited women nationwide in 40 clinical centers between 1993 and 1998. Details of the recruitment, baseline questionnaires, and examinations performed have been published previously.[14–16] Briefly, study participants were women 50 to 79 years of age at baseline who had no terminal illness and were eligible for either the clinical trials or observational arm, completed baseline assessments, including several self-administered questionnaires of sociodemographic characteristics, medical history, reproductive and menstrual history, health behavior, and family history of selected diseases. Of the 161 808 postmenopausal women in the original cohort, a subcohort of 44 174 women were evaluated for hospitalized HF from baseline through January 13, 2015. To allow for evaluation of racial and ethnic differences with adequate statistical power, we excluded those whose self-reported race was Asian/Pacific islander, Native American, or unknown race/ethnicity (n=1042). To evaluate a disease-free cohort, we excluded 505 women with self-reported HF at baseline and 444 who had chronic HF on their first adjudication. The final analytic cohort was 42 170 women. This study received institutional review board approval, and all participants signed informed consents at all 40 clinical centers.

Outcomes

Hospitalized HF was adjudicated based on self-report of a hospitalization related to HF or coronary heart disease (CHD) by trained adjudicators.[12,13] Details of the adjudication process for acute HF are given in Appendix I in the Data Supplement. Acute HF with an ejection fraction <45% was considered HFrEF. Acute HF with an ejection fraction ≥45% was considered HFpEF. If no ejection fraction was available, it was classified as heart failure with unconfirmed ejection fraction. We performed an additional sensitivity analysis defining HFpEF as an ejection fraction of ≥50% and HFrEF as <50%.

The acute HF classification system used in this analysis has been shown to have good agreement with other HF epidemiological algorithms including Framingham (69.5%), modified Boston (63.7%), National Health and Nutrition Examination Survey (60.9%), Gothenburg (59.5%), and the International Classification of Diseases, Ninth Revision, Clinical Modification (62.9%) and demonstrates modest kappa coefficients (0.32–0.10).[12]

Clinical Covariates

Race/ethnicity was self-reported as African American, Hispanic/Latino, white (not of Hispanic origin), or other.[14,15] Clinical covariates include age, education, income, cigarette smoking, current hormone use, hypertension, diabetes mellitus, atrial fibrillation, CHD, chronic lung disease, physical activity, medication use, alcohol use, comorbid conditions, and anemia. Details can be found in Appendix II in the Data Supplement.

Statistical Methods

Baseline characteristics are reported separately by race/ethnicity and because of differences in age in the race/ethnicity groups, percentages are adjusted to the 5-year age distribution of the hormone therapy participants. Annualized event rates were also age adjusted as above, with 95% confidence intervals computed using a bootstrap method with 5000 repetitions.

Primary analyses used time-to-event methods based on the Cox regression model. Time is defined as days from randomization in the hormone therapy or from Women's Health Initiative enrollment for non-hormone therapy participants to the event or censoring. Censoring is the earliest of HF of a different type, death, end of follow-up, or January 13, 2015. All models were stratified by study component (clinical trial or observational study) and age strata used for clinical trial randomization. Cox regression models use the Wald χ^2 test to evaluate the effect of each individual variable while simultaneously adjusting for all variables in the model. Tests for interactions are based on likelihood ratio tests. PAR% were calculated using the standard definitions.[17]

Results

Of the subcohort of 42 170 women evaluated for incident hospitalized HF, 51.2% were white, 33.6% were African American, and 15.2% were Hispanic. At baseline, African American and Hispanic women were younger than white women; therefore, age-adjusted baseline comparisons have been made (Table 1). African American women had lower incomes, were more likely to be obese, less physically active, and had higher prevalence of hypertension, diabetes mellitus, CHD, myocardial infarction (MI), stroke than their white counterparts. In addition, African American women were more likely to have had a hysterectomy, have anemia, and less likely to be on aspirin. Hispanic women were less educated, had lower incomes, had less health insurance, more likely to have diabetes mellitus, and have had a hysterectomy and were less likely to be current smokers and to take aspirin than white women.

Of the 42 170 women, followed up for a mean of 13.2 years, there were 1952 cases of acute incident hospitalized HF. Of these 1952 cases, 70.7% had troponin measures, 38.9% had brain naturietic protein, and 6.1% had N terminal pro brain naturietic protein assessed. Ejection fraction was determined at the time of HF hospitalization in 1419 cases (73%). Of these, 85% were determined by transthoracic echocardiogram, 1% by radionuclideventriculogram, 11% by angiography, 1% by stress echo, and 2% by transesophageal echocardiogram.

Of the 1952 cases of acute incident hospitalized HF, 902 (46.2%) met the definition of HFpEF, 508 (26.0%) were HFrEF, 533 (27.3%) were of unknown ejection fraction, and 9 cases initially had a reduced ejection fraction that improved to normal. Annualized incidence rates were 0.35% for incident hospitalized HF, 0.16% for HFpEF, and 0.09% for HFrEF with higher incident rates for HFpEF, compared with HFrEF for all race/ethnicity groups. White women were more likely to develop both HFpEF and HFrEF compared with African American and Hispanic women, with age-adjusted annualized incidence (%) and 95% confidence interval (CI) of 0.20

Table 1. Baseline Characteristics by Race/Ethnicity in 42 170 Participants

	White (n=21 603)		African American (n=14 159)		Hispanic (n=6408)	
	n	%*	n	%*	n	%*
Age at screening, y						
50–59	6388	32.5	5939	32.5	3235	32.5
60–69	9998	45.3	6043	45.3	2491	45.3
70–79	5217	22.2	2177	22.2	682	22.2
Education						
Less than college degree	14 532	67.5	9031	65.1	4977	79.1
College degree or higher	6954	32.5	4945	34.9	1316	20.9
Family income						
<$35 000/y	10 013	48.1	7083	57.3	3540	65.8
$35 000–$49 999/y	4425	21.6	2369	17.6	926	15.6
$50 000–$74 999/y	3535	17.5	2211	15.8	726	11.4
≥$75 000/y	2543	12.8	1392	9.3	486	7.2
Body mass index, kg/m^2						
<25	6125	28.4	2271	16.6	1577	25.6
25–<30	7634	35.4	4600	33.2	2418	38.7
30–<35	4722	22.0	3771	27.0	1480	23.0
≥35	3008	14.2	3388	23.2	863	12.6
History of MI	429	1.9	437	3.4	72	1.3
History of CHD†	827	3.7	826	6.7	185	3.6
Stroke ever	196	0.9	347	2.7	100	1.9
History of hypertension (taking medicines or BP ≥140/90)	7944	38.6	8238	62.2	2118	39.2
Treated diabetes mellitus (pills or shots)	924	4.2	1626	12.1	445	7.5
History of cancer (except NMSC)	687	3.2	1112	8.3	416	7.3
Current smoker	2168	10.4	1584	10.7	452	6.4
Dyslipidemia	2495	12.4	2083	16.7	887	16.7
Hysterectomy	7872	36.3	7839	55.1	2866	45.2
Oophorectomy						
None	16 312	75.9	8451	60.1	4575	71.6
Unilateral/partial/unknown number	2140	9.9	2478	18.2	647	11.0
Bilateral	3083	14.2	3069	21.8	1094	17.4
History of atrial fibrillation	718	3.3	675	5.2	177	3.2
History of chronic lung disease	704	3.6	517	4.1	163	3.0
Anemia (Hgb <11 g/dL)	66	0.3	315	2.4	46	0.8
Comorbidity (Charlson index)						
0	14 012	66.9	7870	56.9	3970	62.9
1	4103	19.4	3373	25.4	1308	22.3
2	2192	10.3	1502	11.6	578	10.5
≥3	741	3.5	773	6.1	227	4.3
Diuretics use	2314	10.5	3268	24.1	385	6.9
β-Blocker use	1485	6.7	1068	7.9	318	5.6

(*Continued*)

Table 1. Continued

	White (n=21 603)		African American (n=14 159)		Hispanic (n=6408)	
	n	%*	n	%*	n	%*
Aspirin use, ≥80 mg	4673	21.2	1833	13.9	667	11.7
Current hormone therapy use‡						
E-alone	3908	18.0	3184	21.4	1528	23.2
E-alone placebo/nonuser	3964	18.3	4642	33.7	1332	21.9
E+P	7028	32.6	1266	8.3	1188	16.7
E+P placebo/nonuser	6703	31.1	5047	36.6	2347	38.2
Any previous hormone therapy use	5716	26.3	2127	15.5	881	14.3
Any insurance	19 894	92.2	12 646	92.7	4858	83.3
Alcohol intake						
Non/past drinker	5953	27.6	7029	51.6	2724	45.0
<1 drink/wk	7268	34.1	4384	30.7	2147	33.5
1–<7 drinks/wk	5428	25.4	1935	13.5	1123	16.8
7+ drinks/wk	2781	12.9	604	4.2	291	4.7
Total energy expenditure/wk from physical activity (MET h/wk)						
<1.25	4383	22.5	3752	27.2	1597	25.1
1.25–<6.25	4837	24.6	3560	26.2	1532	25.5
6.25–<15.3	5140	26.0	3286	24.2	1447	24.5
≥15.35	5312	26.9	3054	22.4	1468	24.9
	White (n=21603)		African American (n=14159)		Hispanic (n=6408)	
	n	Mean (SD)§	n	Mean (SD)§	n	Mean (SD)§
Age at screening	21 603	63.4 (6.7)	14 159	63.3 (6.7)	6408	63.3 (6.7)
Heart rate, beats per min	21 586	70.1 (11.8)	14 134	70.7 (13.3)	6397	69.0 (11.5)

CHD indicates coronary heart disease; Hgb, hemoglobin; MI, myocardial infarction; and NMSC, non-melanoma skin cancer.

*Percentages are age adjusted to the 5-y age distribution of the hormone trial participants.

†CHD includes MI, CABG/PCI, and angina requiring medication.

‡Current use is randomization arm for the hormone therapy trial participants or current E-alone use reported at baseline for non-hormone therapy participants with a hysterectomy or current E+P use reported at baseline for non-hormone therapy participants without a hysterectomy.

§Mean (SD) are age adjusted to the 5-y age distribution of the Hormone Trial participants.

(0.18–0.21) for HFpEF and 0.10 (0.09–0.11) for HFrEF for white women, 0.0.15 (0.13–0.17) for HFpEF and 0.10(0.08–0.12) for HFrEF for African American women, and 0.08 (0.06–0.010) for HFpEF and 0.05 (0.03–0.07) for HFrEF for Hispanic women.

Risk Factors for HFpEF Compared With HFrEF

We examined risk factors for hospitalized incident HFpEF and HFrEF (Table 2). Compared with white women, Hispanic women had a lower risk for both HFpEF and HFrEF in fully adjusted models, whereas African American women had a lower risk of HFpEF. Risk factors for both incident hospitalized HFpEF and HFrEF were older age, hypertension, diabetes mellitus at baseline and interim diabetes mellitus, current smoking, interim MI, CHD, and cancer. Anemia had a similar increased magnitude of risk for HFpEF and HFrEF but did not reach statistical significance for HFrEF. Risk factors of incident hospitalized HFpEF, but not HFrEF, were obesity, history of CHD other than MI, more than one comorbidity, and hysterectomy with partial oophorectomy but not bilateral oophorectomy and atrial fibrillation. Risk factors for HFrEF and not HFpEF were history of MI and elevated heart rate was of borderline significance.

Differences in HFpEF Between African American, Hispanic American, and White Women

We evaluated risk factors for incident hospitalized HFpEF and HFrEF stratified by race/ethnicity (Table 2). Most risk factors were similar between the 3 race groups except for a significant interaction with obesity (P=0.007). Compared with body mass index (BMI) <25 kg/m^2, BMI categories 30 to 34.9, and ≥35 kg/m^2 placed African American women at greater risk for HFpEF (hazards ratio [HR]=6.27; 95% CI, 2.49–15.77 and HR=7.50; 95% CI 2.96–18.98) compared with white women (HR=1.08; 95% CI, 0.81–1.43; HR=2.10; 95% CI,

Table 2. Risk Factors for HFpEF and HFrEF Overall and Stratified by Race/Ethnicity

Risk factor	HFpEF HR (95% CI)* Total	HFrEF HR (95% CI) Total	HFpEF HR (95% CI) white	HFrEF HR (95% CI) White	HFpEF HR (95% CI) African American	HFrEF HR (95% CI) African American	HFpEF HR (95% CI) Hispanic	HFrEF HR (95% CI) Hispanic
Age (ref=50–59 y)	†	‡	†	‡	§			
60–69	2.46 (1.95–3.10)	1.48 (1.11–1.97)	2.82 (2.05–3.87)	1.97 (1.30–2.97)	2.03 (1.40–2.94)	1.16 (0.75–1.81)	2.74 (1.25–6.04)	0.93 (0.34–2.57)
70–69	5.22 (4.05–6.73)	2.76 (2.01–3.79)	6.24 (4.49–8.67)	3.80 (2.48–5.84)	4.03 (2.61–6.21)	1.74 (1.01–3.01)	2.46 (0.75–8.02)	2.08 (0.62–6.98)
Race (ref=white)	†	‖						
African American	0.59 (0.47–0.75)	0.77 (0.57–1.04						
Hispanic	0.47 (0.32–0.69)	0.54 (0.33–0.90)						
Income (ref=$50–$75K)		‖	‖	‖	‖			
<$35 K/y	1.26 (0.99–1.60)	1.79 (1.23–2.61)	1.10 (0.84–1.45)	1.94 (1.20–3.14)‖	1.88 (1.08–3.28)‖	1.53 (0.80–2.90)	1.74 (0.47–6.48)	2.73 (0.26–29.10)
$35–<$50 K/y	0.96 (0.73–1.27)	1.59 (1.05–2.39)	0.91 (0.67–1.25)	2.01 (1.20–3.34)	1.26 (0.66–2.41)	0.88 (0.40–1.93)	0.87 (0.18–4.11)	1.64 (0.11–24.37)
≥$75 K/y	0.77 (0.53–1.13)	1.53 (0.94–2.51)	0.61 (0.38–0.96)	1.73 (0.93–3.23)	1.77 (0.86–3.66)	1.23 (0.52–2.92)	NA	2.07 (0.09–49.09)
College education (ref=less than college degree)	0.93 (0.78–1.12)	0.92 (0.72–1.18)	1.01 (0.82–1.25)	0.90 (0.67–1.22)	0.74 (0.50–1.08)	1.09 (0.69–1.72)	1.22 (0.49–3.00)	0.88 (0.16–4.77)
Hypertension (ref=no)	1.57 (1.33–1.86)†	1.99 (1.59–2.51)†	1.57 (1.30–1.90)†	2.07 (1.58–2.71)†	1.80 (1.22–2.67)§	1.60 (1.01–2.54)‖	1.22 (0.57–2.60)	4.24 (1.25–14.32)‖
Heart rate per 5 beats per min	1.00 (0.97–1.03)	1.04 (1.00–1.08)‖	0.99 (0.95–1.03)	1.05 (1.00–1.09)‖	1.02 (0.97–1.08)	1.05 (0.99–1.11)	1.09 (0.97–1.29)	0.81 (0.58–1.13)
Hx MI (ref=no)	1.08 (0.74–1.57)	2.50 (1.60–3.90)†	1.05 (0.66–1.67)	3.37 (1.91–5.94)†	0.97 (0.49–1.93)	1.95 (0.90–4.24)	4.51 (0.40–50.41)	4.12 (0.14–125.57)
Hx CHD other than MI (ref=no)	1.60 (1.17–2.19)§	1.22 (0.79–1.87)	1.57 (1.07–2.30)‖	0.93 (0.52–1.65)	1.95 (1.11–3.41)‖	1.63 (0.80–3.34)	0.50 (0.04–5.66)	3.19 (0.44–23.02)
Hx stroke (ref=no)	1.35 (0.87–2.10)	1.25 (0.68–2.29)	1.55 (0.86–2.77)	1.02 (0.41–2.57)	1.31 (0.64–2.69)	1.44 (0.61–3.43)	NA	NA
DM (ref=no)	1.84 (1.41–2.39)†	2.16 (1.49–3.14)†	1.76 (1.26–2.47)§	1.74 (1.06–2.86)‖	2.30 (1.44–3.68)‡	2.44 (1.28–4.64)§	0.12 (0.01–1.26)	25.43 (2.54–254.18)§
Dyslipidemia (ref=no)	0.91 (0.74–1.11)	1.09 (0.84–1.42)	0.91 (0.71–1.17)	1.11 (0.80–1.54)	0.89 (0.59–1.34)	0.97 (0.58–1.62)	1.81 (0.76–4.28)	0.87 (0.24–3.18)
Oophorectomy (ref=none)	‖		‖					
Unilateral/partial/ unknown number	1.40 (1.11–1.77	0.80 (0.57–1.13)	1.43 (1.08–1.91)	0.85 (0.55–1.32)	1.26 (0.82–1.95)	0.79 (0.45–1.39)	1.86 (0.64–5.38)	NA
Bilateral	1.15 (0.91–1.46)	0.85 (0.62–1.16)	1.23 (0.92–1.65)	1.03 (0.69–1.53)	0.99 (0.63–1.55)	0.62 (0.35–1.12)	0.91 (0.31–2.66)	0.63 (0.14–2.80)
Hx cancer (ref=no)	1.20 (0.82–1.74)	1.45 (0.87–2.42)	1.48 (0.93–2.36)	1.75 (0.88–3.47)	0.84 (0.40–1.74)	0.82 (0.33–2.06)	0.48 (0.08–3.02)	31.18 (1.64–593.30)‖
Comorbidity (ref=none)								
≥1	1.34 (1.10–1.63)§	1.20 (0.92–1.58)	1.30 (1.02–1.65)	1.23 (0.89–1.72)	1.67 (1.11–2.52)‖	1.21 (0.70–2.07)	0.45 (0.13–1.57)	0.24 (0.02–2.44)
BMI (ref=BMI <25 kg/m^2)	†		†		†		‖	
25–<30	1.11 (0.88–1.40)	0.91 (0.68–1.21)	1.00 (0.78–1.29)	0.87 (0.62–1.21)	3.57 (1.40–9.08)	1.10 (0.60–2.03)	1.39 (0.43–4.43)	1.10 (0.21–5.65)
30–<35	1.35 (1.06–1.72)	1.00 (0.74–1.36)	1.08 (0.81 1.43)	1.12 (0.79–1.60)	6.27 (2.49–15.77)	0.81 (0.41–1.59)	0.90 (0.23–3.44)	1.75 (0.32–9.66)
≥35	2.36 (1.84–3.03)	0.87 (0.61–1.24)	2.10 (1.57–2.80)	0.69 (0.43–1.11)	7.50 (2.96–18.98)	1.09 (0.56–2.13)	4.29 (1.24–14.90)	3.09 (0.48–19.80)
Current smoking (ref=never/past)	2.17 (1.72–2.74)†	2.14 (1.59–2.86)†	2.75 (2.09–3.61)†	2.40 (1.64–3.52)†	1.44 (0.89–2.33)	1.74 (1.04–2.91)‖	0.71 (0.09–5.53)	2.52 (0.52–12.19)
Physical activity (ref=<1.25 MET h/wk)								
1.25–<6.25	0.91 (0.75–1.11)	0.92 (0.70–1.20)	0.94 (0.74–1.20)	0.95 (0.68–1.34)	0.77 (0.52–1.13)	0.81 (0.49–1.33)	1.62 (0.53–4.12)	1.08 (0.30–3.88)
6.25–<15.3	0.81 (0.66–1.00)	0.72 (0.54–0.96)	0.83 (0.65–1.07)	0.72 (0.50–1.03)	0.73 (0.48–1.11)	0.75 (0.44–1.27)	0.87 (0.29–2.60)	0.45 (0.08–2.47)
≥15.3	0.74 (0.59–0.93)	0.74 (0.54–1.00)	0.75 (0.57–0.98)	0.77 (0.53–1.12)	0.65 (0.41–1.03)	0.59 (0.32–1.09)	1.32 (0.46–3.82)	1.34 (0.30–6.08)
Chronic lung disease (ref=no)	1.27 (0.90–1.79)	1.54 (0.98–2.41)	1.50 (1.02–2.22)‖	1.22 (0.67–2.23)	0.73 (0.31–1.72)	2.05 (0.96–4.38)	0.44 (0.05–4.06)	0.82 (0.03–21.58)

(*Continued*)

Table 2. Continued

Risk factor	HFpEF HR (95% CI)* Total	HFrEF HR (95% CI) Total	HFpEF HR (95% CI) white	HFrEF HR (95% CI) White	HFpEF HR (95% CI) African American	HFrEF HR (95% CI) African American	HFpEF HR (95% CI) Hispanic	HFrEF HR (95% CI) Hispanic
Anemia (ref=no)	1.91 (1.07–3.40)‖	1.83 (0.85–3.90)	0.73 (0.18–2.98)	NA	3.04 (1.58–5.85)‡	2.62 (1.05–6.57)‖	NA	35.19 (4.54–272.68)‡
Atrial fibrillation (ref=no)	1.39 (1.02–1.90)‖	1.08 (0.69–1.70)	1.41 (0.97–2.07)	0.94 (0.51–1.71)	1.38 (0.78–2.45)	1.38 (0.67–2.84)	0.55 (0.07–4.69)	NA
β-blocker use (ref=no)	1.21 (0.95–1.54)	0.77 (0.53–1.11)	1.19 (0.89–1.59)§	0.75 (0.48–1.17)	1.16 (0.72–1.87)	0.67 (0.30–1.50)	2.11 (0.58–7.69)	2.82 (0.54–14.83)
Aspirin use (ref=no)	1.08 (0.90–1.29)	1.28 (1.00–1.62)‖	1.12 (0.92–1.37)	1.32 (1.00–1.75)‖	0.87 (0.57–1.33)	1.05 (0.62–1.79)	0.95 (0.32–2.86)	0.77 (0.17–3.52)
Current HT use (ref=E-alone placebo/nonuse)								
E alone	1.20 (0.97–1.48)	0.76 (0.57–1.02)	1.29 (0.99–1.69)	0.75 (0.52–1.10)	1.17 (0.78–1.73)	0.88 (0.52–1.50)	0.86 (0.33–2.16)	0.34 (0.07–1.73)
E+P	0.95 (0.73–1.24)	0.67 (0.47–0.93)	1.09 (0.80–1.48)	0.77 (0.51–1.15)	0.60 (0.26–1.37)	0.52 (0.21–1.29)	0.43 (0.11–1.64)	0.11 (0.01–1.40)
E+P placebo/ nonuse	1.05 (0.83–1.34)	0.72 (0.53–0.98)	1.20 (0.88–1.63)	0.78 (0.52–1.17)	0.86 (0.55–1.34)	0.71 (0.42–1.22)	0.69 (0.24–2.03)	0.50 (0.13–1.96)
Any previous HT use (ref=none)	0.97 (0.81–1.17)	1.21 (0.95–1.53)	0.90 (0.73–1.11)	1.23 (0.93–1.61)	1.37 (0.92–2.05)	1.22 (0.72–2.08)	0.50 (0.15–1.71)	0.93 (0.22–3.96)
Alcohol (ref=1–<7 drinks/wk)								
Non/past	0.94 (0.75–1.17)	1.01 (0.75–1.37)	0.92 (0.71–1.19)	1.20 (0.84–1.71)	0.74 (0.45–1.20)	0.68 (0.38–1.23)	4.47 (1.00–20.03)	0.99 (0.17–5.90)
<1 drinks/wk	0.95 (0.76–1.18)	0.93 (0.69–1.26)	0.95 (0.74–1.21)	0.97 (0.67–1.38)	0.86 (0.52–1.42)	0.81 (0.45–1.47)	2.38 (0.51–11.08)	0.67 (0.11–4.13)
≥7 drinks/wk	1.07 (0.79–1.44)	1.08 (0.73–1.61)	1.04 (0.76–1.44)	1.10 (0.70–1.71)	0.91 (0.36–2.25)	0.90 (0.33–2.48)	NA	1.61 (0.10–26.31)
Any insurance (ref=none)	0.89 (0.64–1.24)	1.10 (0.69–1.75)	0.77 (0.51–1.16)	1.36 (0.68–2.72)	1.33 (0.66–2.66)	0.89 (0.43–1.83)	1.26 (0.45–3.54)	0.97 (0.21–4.42)
Interim MI (ref=no)	1.83 (1.28–2.62)§	2.21 (1.40–3.50)‡	1.64 (1.09–2.47)‖	1.92 (1.08–3.40)‖	3.10 (1.38–6.96)§	3.32 (1.37–8.04)§	1.98 (0.16–23.81)	6.18 (0.74–51.90)
Interim CHD not MI (ref=no)	1.39 (1.05–1.84)‖	1.85 (1.27–2.69)§	1.60 (1.16–2.19)§	1.69 (1.07–2.69)‖	0.79 (0.41–1.52)	2.20 (1.07–4.54)‖	1.40 (0.32–6.21)	4.09 (0.74–22.65)
Interim DM (ref=no)	1.61 (1.31–1.98)†	1.29 (0.95–1.75)	1.84 (1.43–2.36)†	1.60 (1.10–2.33)‖	1.24 (0.83–1.84)	0.81 (0.47–1.41)	1.80 (0.76–4.28)	2.09 (0.46–9.52)
Interim cancer (ref=no)	1.56 (1.24–1.94)‡	1.61 (1.17–2.23)§	1.59 (1.22–2.06)†	1.44 (0.97–2.15)	1.49 (0.91–2.44)	2.71 (1.52–4.84)‡	2.70 (0.89–8.18)	NA

For risk factors with >2 levels, the statistical significance applies to the inclusion of the entire term in the model. NA indicates insufficient number of cases to estimate HR. BMI indicates body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CHD, coronary heart disease (MI, CABG, PCI, or angina requiring medication); CI, confidence interval; DM, diabetes mellitus (treated with pills or shots); HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazards rate; Hx, history; MI, myocardial infarction; PCI, percutaneous coronary intervention; and HT, hormone therapy.

*All HR and 95% CI are estimated from multivariable Cox proportional hazard models stratified by study component (clinical trial or observational study) and age strata (50–54, 55–59, 60–69, 70–79) and adjusted for all listed risk factors simultaneously.

†$P<0.0001$.

‡$P<0.001$.

§$P<0.01$.

‖$P<0.05$.

1.57–2.80). Hispanic women with BMI >35 kg/m^2 also were at a significantly increased risk for HFpEF (HR=4.29; 95% CI, 1.24–14.90).

Population-Attributable Risk% for HFpEF and HFrEF

To assess the impact of potential preventive strategies for HFpEF and HFrEF, the PAR% for risk factors that are amenable to change and prevalent in the population (hypertension, obesity, diabetes mellitus, and CHD) were calculated (Figure).

For HFpEF, approximately two thirds of the PAR% is associated with hypertension and obesity, whereas diabetes mellitus and CHD make up approximately one fourth of the PAR%. For African American women, hypertension and obesity were associated with >90% of the PAR%, and for Hispanic women, the same risk factors were associated with ≈72% of the PAR%. For HFrEF, hypertension showed the strongest PAR% in all 3 race/ethnicity groups.

Discussion

This study of incident hospitalized HFpEF and HFrEF in a multiethnic cohort of women confirms previous findings that HFpEF is of greater incidence than HFrEF in postmenopausal women and that risk factors for both HFpEF and HFrEF include age, CHD, diabetes mellitus, smoking, and hypertension. Robust associations for HFpEF, but not HFrEF, include obesity, number of comorbid conditions, anemia, and atrial

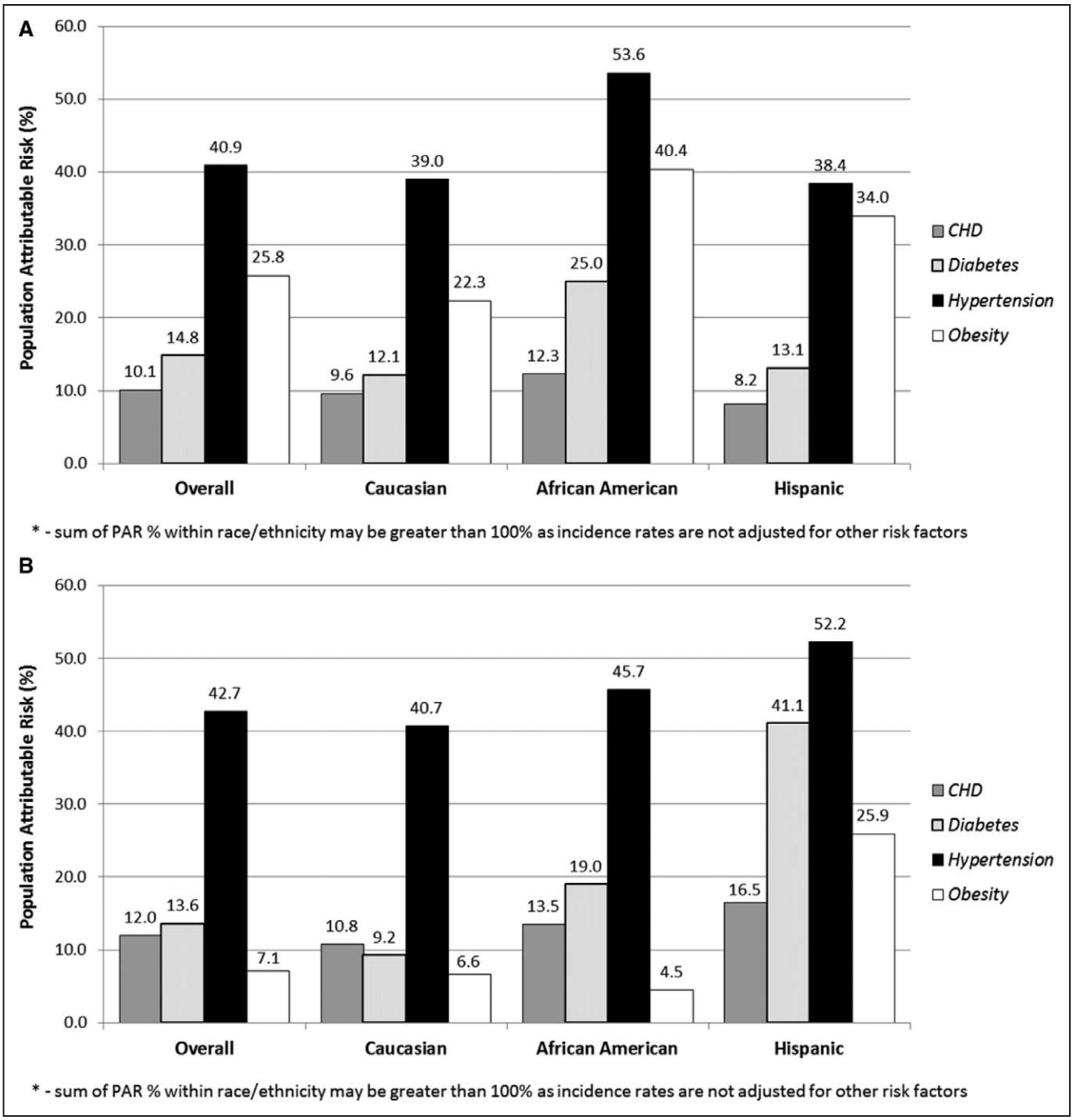

Figure. A, Population-attributable risk (PAR)* by race and ethnicity for heart failure with preserved ejection fraction. *Sum of PAR% within race/ethnicity may be >100% as incidence rates are not adjusted for other risk factors. **B**, PAR* by race and ethnicity for heart failure with reduced ejection fraction. *Sum of PAR% within race/ethnicity may be >100% as incidence rates are not adjusted for other risk factors.

fibrillation. As expected, MI is a risk factor for HFrEF. This study is unique in describing the importance of obesity as a risk factor for HFpEF and its PAR%, with special significance for African American women. Although the important role of hypertension as a risk factor for both HFpEF and HFrEF is well documented, the important role of obesity as a risk factor in women for HFpEF is less well known.

Ho et al[17] found a similar result for obesity as a risk factor for incident HFpEF in both sexes in the Framingham Heart study, as did Gupta et al[11] in the Atherosclerosis Risk in Communities study for prevalent HFpEF in African Americans. Lam et al found stronger association of obesity in women compared with that in men in the baseline assessment of participants in the I-PRESERVE trial.[18] Brouwers et al[19] in the Dutch Prevend study found obesity to be a risk factor for both HFpEF and HFrEF. The pathophysiologic mechanisms by which higher BMI levels are associated with higher rates of incident HFpEF may well be related to adverse effects on obesity on skeletal muscle, oxidative stress, inflammation, and insulin resistance, all contributors

to HFpEF.[20] Recently, Paulus and Tschöpe[21] have proposed that obesity through the above mechanisms may induce changes in the coronary microvascular endothelium, whereas Mohammed et al[22] has shown associations with coronary microvascular rarefaction with HFpEF as another potential mechanism.

Although overweight and obesity are risk factors for incident HF and for HFpEF in most studies, both Haass et al[23] and Kao et al[24] have demonstrated in the I-PRESERVE and CHARM preserved trials that HFpEF participants with either lower BMIs and higher BMIs predicted more cardiovascular events and decreased survival. This apparent paradox might be explained by cardiac cachexia and nutritional deficiencies associated with lower BMI,[25] whereas a BMI >35 kg/m^2 is associated with higher rates of glucose intolerance, metabolic syndrome, and chronic inflammation, all of which contribute to worse cardiovascular outcomes and higher levels of mortality.[20]

The importance of overweight and obesity in the potential prevention of HFpEF in women, especially in African American women, is noteworthy given its high PAR%. Why overweight and obesity places African American women at higher risk for HFpEF compared with white women even when adjusting for diabetes mellitus and hypertension is unknown, but differences in inflammatory obesity, insulin sensitivity, and visceral fat distribution might play a role in these findings. The potential synergy between weight loss and exercise in obese, sedentary women and their impact on the prevention of HFpEF are worthy of future trials. Indeed, in those with HFpEF, a recent trial showed an improvement in peak oxygen consumption with additive effects for weight loss and exercise.[26]

Our study is the largest study in postmenopausal women to evaluate clinical risk factors for incident hospitalized HF with preserved and reduced ejection fractions and allows for race/ethnicity comparisons. An additional strength of our study was that it used a well-validated classification system in defining new-onset incident hospitalized HF and its subtypes.

Our study has several important caveats to consider when evaluating its conclusions. First, it relied on hospitalized HF, and therefore, outpatient-diagnosed HF was not captured. However, outpatient-diagnosed HF is <25% of HF, is equally distributed between HFpEF and HFrEF, and leads to subsequent hospitalization within a relatively short period of time.[27] In addition, ejection fraction information while captured in the majority of HF outcomes was missing in 27%, leading to potential misclassification bias. We may have overestimated the frequency of HFrEF by using an ejection fraction of <45% compared with a more stringent ejection fraction of <40% to categorize as many participants as either HFpEF or HFrEF in our cohort. In addition, the differential association between some risk factors and type of HF could be because of dependent censoring, although unlikely. We performed a sensitivity analysis using ≥50% ejection fraction defining HFpEF and <50% defining HFrEF and found similar results. We have limited power in our comparison of risk factors for Hispanic American women because of small number of HF events in Hispanic women.

Conclusion

This study demonstrated the higher incidence rate for new-onset hospitalized HFpEF compared with HFrEF. Differential risk factors for new-onset HFpEF included obesity, number of comorbidities, anemia, and atrial fibrillation, whereas cigarette smoking, diabetes mellitus, hypertension, and CHD were risk factors for both types of HF. Obesity was found to be a more potent risk factor for African American women compared with white women for HFpEF and showed a trend in Hispanic women. Because HFpEF is growing in incidence and prevalence as the population ages, and limited effective treatment for HFpEF are presently available, preventive strategies focusing on hypertension and obesity given their high PAR% seem most promising.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Heart failure is a major and growing public health problem in the United States, especially in older women. Heart failure with preserved ejection fraction (HFpEF) is increasing in prevalence and as opposed to heart failure with reduced ejection fraction (HFrEF), limited effective therapy are presently available. To guide future therapeutic considerations, there is a need to better understand the risk factors and natural history of HFpEF compared with HFrEF. This study compared risk factors for incident HFpEF and HFrEF and explored differences by race/ethnicity in 42 170 postmenopausal women followed for 13 years. Obesity and hypertension were both highly prevalent, and extreme obesity (body mass index >35 kg/m^2) was a potent risk factors for HFpEF (HR=2.36) and not HFrEF (HR=1.00), with a stronger association in African American women (HR=7.50) compared with white women (HR=2.10). The association of obesity with HFpEF could be associated with the adverse effects of obesity on skeletal muscle, oxidative stress, inflammation, and insulin resistance, which may lead to changes in coronary microvascular endothelium or changes in coronary microvascular rarefaction. The reason for the differential association of obesity on the risk of HFpEF in African American women compared with white women needs further investigation.

Circulation
Heart Failure

Risk Factors for Incident Hospitalized Heart Failure With Preserved Versus Reduced Ejection Fraction in a Multiracial Cohort of Postmenopausal Women

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Appendix 1

Heart Failure Adjudication process

Detailed abstraction included recording evidence of new onset of symptoms, history of HF, general medical history, physical examination signs and symptoms, diagnostic tests (chest radiograph, echocardiogram, cardiac catheterization, coronary angiography, cardiac radionuclide ventriculogram, cardiac MRI, cardiac CT scan, stress test), biomarkers (brain natriuretic peptide [BNP], N-terminal prohormone BNP (NT-proBNP), cardiac troponins), and medications. This process allows adjudicators to define definite and possible acute HF, chronic HF, and unclassifiable or unknown event (no HF) and for acute HF to define HF with preserved ejection fraction (HFpEF), HF with reduced ejection fraction (HFrEF) and unknown ejection fraction HF (HFuEF). New onset acute HF required clear evidence either from symptoms, signs, imaging, or treatment of an acute exacerbation, worsening or new onset of symptoms, or other decompensated circulatory state. Evidence of a decompensated state included augmentation of therapy for worsening HF signs or symptoms, documentation of subsequent in-hospital control of symptoms by therapy, documentation of the specificity of HF for decompensated state as opposed to other comorbidities (e.g., chronic obstructive pulmonary disease [COPD], end-stage renal disease). These analyses define a case as the first occurrence of new onset acute HF and thus represent incident HF. If the first case is “HF unlikely or unclassifiable” but a subsequent case of acute HF occurred, the latter case is used. Hospitalizations were classified as no HF if the available documentation in the medical record suggested no evidence of pulmonary vascular congestion or volume overload. A designation of unclassifiable was usually used in cases were medical records were insufficient to differentiate between a classification of chronic stable HF and no HF or in the infrequent case of missing medical records. For the purposes of these analyses, cases classified as HF unlikely or determined to be unclassifiable were combined as no incident HF.

Appendix 2. Risk Factors for HFpEF and HFrEF excluding participants with a history of MI or CHD at baseline and/or during follow-up prior to heart failure

Risk Factor	HFpEF HR, 95% CI[1]	HFrEF HR, 95% CI
Number of cases in model	526	271
Age (ref=50-59)	****	**
60-69	2.74 (2.11, 3.56)	1.42 (1.02, 1.98)
70-69	6.11 (4.58, 8.15)	3.36 (2.34, 4.82)
Race (ref=Whites)	***	*
Black	0.61 (0.47, 0.79)	0.76 (0.54, 1.09)
Hispanic	0.52 (0.34, 0.79)	0.42 (0.22, 0.80)
Income (ref=$50-$75K)	*	
< $35K	1.24 (0.95, 1.63)	1.77 (1.15, 2.70)
$35-<$50K	0.96 (0.70, 1.31)	1.60 (1.01, 2.55)
≥ $75K	0.79 (0.52, 1.19)	1.55 (0.89, 2.67)
College education (ref=<college degree)	0.94 (0.77, 1.15)	0.91 (0.68, 1.20)
Hypertension (ref=No)	1.45 (1.20, 1.76)****	2.25 (1.72, 2.94)****
Heart Rate per 5 bpm	1.00 (0.97, 1.04)	1.05 (1.01, 1.09)*
Hx Stroke (ref=No)	1.39 (0.77, 2.51)	1.81 (0.87, 3.79)
DM (ref=No)	1.95 (1.42, 2.68)****	2.60 (1.62, 4.16)****
Dyslipedemia	0.94 (0.73, 1.21)	1.02 (0.72, 1.43)
Oophorectomy	**	
Unilateral/partial/unknown number	1.57 (1.20, 2.05)	0.81 (0.54, 1.22)
Bilateral	1.17 (0.88, 1.56)	0.64 (0.43, 0.96)
Hx Cancer (ref=No)	1.37 (0.90, 2.10)	0.92 (0.46, 1.84)
Co-morbidity (ref=None)	*	
1	1.43 (1.14, 1.79)	1.13 (0.81, 1.55)
2	1.26 (0.93, 1.70)	1.00 (0.65, 1.55)
≥ 3	1.45 (0.93, 2.26)	1.22 (0.64, 2.34)
BMI (ref=BMI<25)	****	
25-<30	1.02 (0.79, 1.33)	0.93 (0.66, 1.30)
30-<35	1.34 (1.02, 1.77)	1.14 (0.80, 1.62)

[1] All HR and 95% CI are estimated from multivariable Cox proportional hazard models stratified by study component (clinical trial or observational study) and age strata (50-54, 55-59, 60-69, 70-79), and adjusted for all listed risk factors simultaneously.

≥ 35	2.54 (1.92, 3.36)	1.11 (0.74, 1.67)
Current smoking (ref=never/past)	2.37 (1.83, 3.08)****	2.18 (1.54, 3.09)****
Physical Activity (ref=<1.25 METhr/wk)	**	**
1.25-<6.25	0.86 (0.68, 1.08)	0.91 (0.67, 1.24)
6.25 <15.3	0.74 (0.58, 0.94)	0.62 (0.44, 0.87)
≥ 15.3	0.64 (0.49, 0.83)	0.62 (0.44, 0.89)
Chronic lung disease (ref=No)	1.34 (0.90, 1.99)	1.62 (0.95, 2.75)
Anemia (ref=No)	2.02 (1.07, 3.83)*	1.93 (0.78, 4.76)
Atrial fibrillation (ref=No)	1.50 (1.02, 2.20)*	1.44 (0.82, 2.53)
Beta blocker use (ref=No)	1.41 (1.05, 1.88)*	0.66 (0.39, 1.12)
Aspirin use (ref=No)	1.01 (0.82, 1.25)	1.25 (0.94, 1.67)
Current HT use (ref=E-alone placebo/non-use)		
E-alone	1.23 (0.96, 1.58)	0.73 (0.51, 1.05)
E+P	0.89 (0.66, 1.22)	0.66 (0.45, 0.97)
E+P placebo/non-use	1.17 (0.88, 1.55)	0.64 (0.45, 0.92)
Any prior HT use (ref=No)	0.88 (.71, 1.09)	1.21 (0.91, 1.60)
Alcohol (ref=1-<7 dr/wk)		
Non/past	0.85 (0.66, 1.10)	1.00 (0.70, 1.42)
<1 dr/wk	0.93 (0.73, 1.19)	0.92 (0.64, 1.30)
≥ 7 dr/wk	1.08 (0.77, 1.51)	1.34 (0.87, 2.07)
Any insurance (ref=No)	0.97 (0.66, 1.44)	1.24 (0.70, 2.17)
Interim DM (ref=No)	1.58 (1.24, 2.01)***	1.13 (0.77, 1.65)
Interim Cancer (ref=No)	1.56 (1.20, 2.01)***	1.67 (1.15, 2.41)**

DM: diabetes mellitus treated with pills or shots
Hypertension: hypertension treated with medication or BP ≥ 140/90
Statistical significance indicated as follows: * p-value <0.05, ** p-value <0.01,.*** p-value < 0.001, **** p-value < 0.0001