JAMA | **Original Investigation**

Cardiovascular Burden of the V142I Transthyretin Variant

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IMPORTANCE Individual cohort studies concur that the amyloidogenic V142I variant of the transthyretin (*TTR*) gene, present in 3% to 4% of US Black individuals, increases heart failure (HF) and mortality risk. Precisely defining carrier risk across relevant clinical outcomes and estimating population burden of disease are important given established and emerging targeted treatments.

OBJECTIVES To better define the natural history of disease in carriers across mid to late life, assess variant modifiers, and estimate cardiovascular burden to the US population.

DESIGN, SETTING, AND PARTICIPANTS A total of 23 338 self-reported Black participants initially free from HF were included in 4 large observational studies across the US (mean [SD], 15.5 [8.2] years of follow-up). Data analysis was performed between May 2023 and February 2024.

EXPOSURE V142I carrier status (n = 754, 3.2%).

MAIN OUTCOMES AND MEASURES Hospitalizations for HF (including subtypes of reduced and preserved ejection fraction) and all-cause mortality. Outcomes were analyzed by generating 10-year hazard ratios for each age between 50 and 90 years. Using actuarial methods, mean survival by carrier status was estimated and applied to the 2022 US population using US Census data.

RESULTS Among the 23 338 participants, the mean (SD) age at baseline was 62 (9) years and 76.7% were women. Ten-year carrier risk increased for HF hospitalization by age 63 years, predominantly driven by HF with reduced ejection fraction, and 10-year all-cause mortality risk increased by age 72 years. Only age (but not sex or other select variables) modified risk with the variant, with estimated reductions in longevity ranging from 1.9 years (95% CI, 0.6-3.1) at age 50 to 2.8 years (95% CI, 2.0-3.6) at age 81. Based on these data, 435 851 estimated US Black carriers between ages 50 and 95 years are projected to cumulatively lose 957 505 years of life (95% CI, 534 475-1 380 535) due to the variant.

CONCLUSIONS AND RELEVANCE Among self-reported Black individuals, male and female V142I carriers faced similar and substantial risk for HF hospitalization, predominantly with reduced ejection fraction, and death, with steep age-dependent penetrance. Delineating the individual contributions of, and complex interplay among, the V142I variant, ancestry, the social construct of race, and biological or social determinants of health to cardiovascular disease merits further investigation.

Editorial

Multimedia

Supplemental content

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Transthyretin cardiac amyloidosis (ATTR-CA) is an increasingly recognized cardiomyopathy resulting from extracellular cardiac deposition of the misfolded transthyretin protein. ATTR-CA can occur in the presence of a detected genetic variant (ATTRv-CA, variant related) or its absence (ATTRwt-CA, wild-type related). The amyloidogenic V142I (legacy nomenclature V122I) variant of the transthyretin (TTR) gene has been reported to be present in a significant proportion of US Black individuals (3%-4%) (particularly in comparison with other ancestry groups),[1,2] is the most common cause of ATTRv-CA in the US,[3] and demonstrates age-dependent anatomic penetrance on autopsy analysis.[4] The American College of Medical Genetics recently classified the transthyretin variants as clinically actionable reportable secondary findings,[5] and individual epidemiologic studies concur that carriers face increased risk for heart failure (HF) and all-cause mortality.[1,6-10] The availability of several targeted treatments, which may be more effective earlier in the disease process, has heightened interest in identifying at-risk individuals.[11,12]

Because testing for the V142I variant is typically performed after a carrier presents with disease, precise data are needed regarding long-term, and modifiers of, risk in unselected carriers. To better define the natural history of disease in V142I carriers, data from Black participants in 4 large observational studies based in the US were combined. Pooling data from geographically diverse cohorts facilitated more precise and generalizable risk estimation across mid to late life, the ability to assess less-frequent outcomes (including subtypes of HF), analysis of effect modifiers (particularly sex, which is thought to influence disease manifestations),[2,6] and estimation of years of life lost among V142I carriers.

Methods

We included 23 338 self-reported Black participants, including 754 carriers (3.2%) who were initially free of HF with available genotyping (**Figure 1**). This study involved self-reported Black participants in keeping with prior cohort studies included in this analysis that studied risk stratification with the variant, although race is a social construct and should not be used as a proxy for ancestry.[1,8,10] Participants provided written informed consent, and institutional review board approval was received from all participating institutions. This study followed the reporting guidelines of the Strengthening the Reporting of Genetic Association Studies (STREGA, an extension of the STROBE Statement).

Cohort Studies

Atherosclerosis Risk in Communities Study
The Atherosclerosis Risk in Communities Study is a prospective study in 4 communities across the US composed of 15 792 participants, aged 45 to 64 years, recruited between 1987 and 1989.[13] A total of 3543 Black participants (including 112 participants who were heterozygous for V142I) were included for analysis.

Key Points

Question What is the natural history and cardiovascular burden of the V142I variant of the transthyretin (TTR) gene among US Black carriers across mid to late life?

Findings Across 4 cohort studies, carriers (754/23 338) faced a substantially increased risk for heart failure (by age 63 years) and death (by age 72 years), similarly in men and women, which was estimated to contribute to approximately 1 million years of life lost among US Black individuals aged ≥50 years.

Meaning These data show the large, age-dependent burden of V142I, which may guide discussions regarding the initiation and results of genetic screening, provide clinicians with risk estimates to share with patients, and inform strategies for early targeted therapy.

Multi-Ethnic Study of Atherosclerosis
The Multi-Ethnic Study of Atherosclerosis is a cohort study of 6 communities and recruited 6814 participants free of clinical cardiovascular disease aged 45 to 84 years between July 2000 and August 2002.[14] A total of 1584 Black participants, including 49 participants who were heterozygous for V142I, were included for analysis.

Reasons for Geographic and Racial Differences in Stroke
The Reasons for Geographic and Racial Differences in Stroke Study recruited 30 239 adults at least 45 years old between January 2003 and October 2007.[15] Participants were randomly selected from a commercially available list to create a sample balance on race and sex across the stroke buckle, the stroke belt, and the rest of the continental US. A total of 8527 Black participants (including 259 heterozygous and 3 homozygous for V142I) met inclusion criteria for the study.[10]
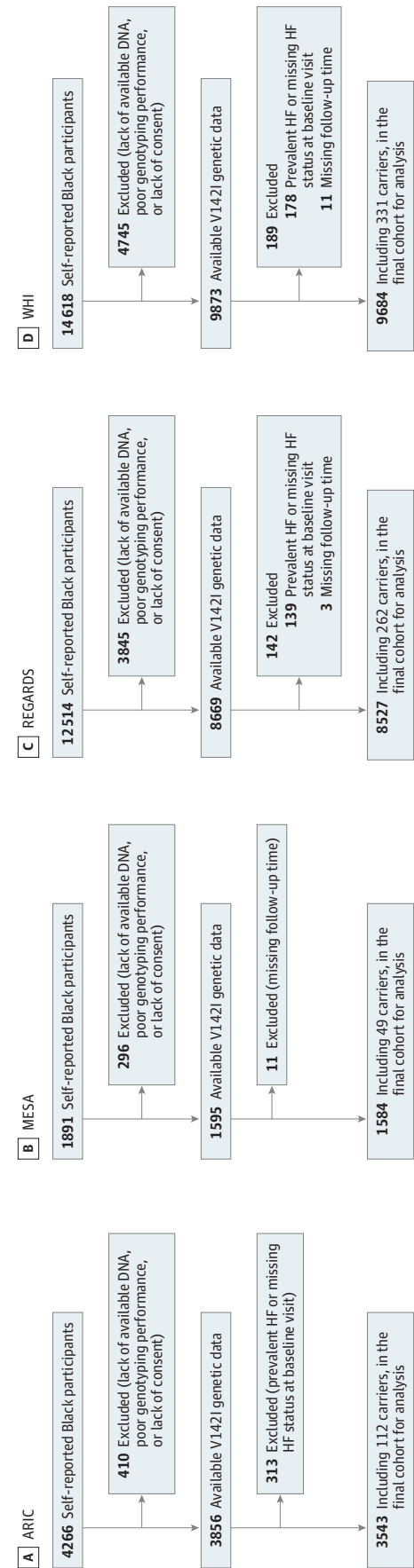
Women's Health Initiative
Women were eligible to participate in the Women's Health Initiative if they were 50 to 79 years of age, generally healthy, and postmenopausal at the time of enrollment.[16] A total of 161 808 participants were enrolled between 1993 and 1998 in the observational or clinical trial groups. A total of 9684 Black women (including 330 heterozygous and 1 homozygous for V142I) were included in this analysis.

The median African genetic ancestry percentage for each cohort was determined. Details regarding individual study cohorts, population descriptors, genotyping, ancestry analysis, comorbidities, and laboratory values are provided in the eMethods in Supplement 1.

Study Outcomes
Longitudinal outcomes included first HF hospitalization, first HF hospitalization subtypes (HF with reduced ejection fraction [HFrEF] and HF with preserved ejection fraction [HFpEF]), all-cause mortality, and a composite of HF hospitalization or all-cause mortality. HFpEF was defined by an EF of 50% or greater or qualitatively normal EF, while HFrEF was defined by an EF less than 50% or a qualitatively low EF (eMethods in Supplement 1). This EF dichotomization facilitated inclusion of qualitative reports of EF.

Figure 1. Analysis of Black Participants From 4 Large Cohort Studies

A ARIC

4266 Self-reported Black participants

→ 410 Excluded (lack of available DNA, poor genotyping performance, or lack of consent)

3856 Available V142I genetic data

→ 313 Excluded (prevalent HF or missing HF status at baseline visit)

3543 Including 112 carriers, in the final cohort for analysis

B MESA

1891 Self-reported Black participants

→ 296 Excluded (lack of available DNA, poor genotyping performance, or lack of consent)

1595 Available V142I genetic data

→ 11 Excluded (missing follow-up time)

1584 Including 49 carriers, in the final cohort for analysis

C REGARDS

12514 Self-reported Black participants

→ 3845 Excluded (lack of available DNA, poor genotyping performance, or lack of consent)

8669 Available V142I genetic data

→ 142 Excluded
139 Prevalent HF or missing HF status at baseline visit
3 Missing follow-up time

8527 Including 262 carriers, in the final cohort for analysis

D WHI

14618 Self-reported Black participants

→ 4745 Excluded (lack of available DNA, poor genotyping performance, or lack of consent)

9873 Available V142I genetic data

→ 189 Excluded
178 Prevalent HF or missing HF status at baseline visit
11 Missing follow-up time

9684 Including 331 carriers, in the final cohort for analysis

The process for inclusion and exclusion of participants is delineated for each study. A total of 23338 participants were ultimately analyzed, including 754 carriers of the V142I variant. ARIC indicates Atherosclerosis Risk in Communities; HF, heart failure; MESA, Multi-Ethnic Study of Atherosclerosis; REGARDS, Reasons for Geographic and Racial Differences in Stroke; and WHI, Women's Health Initiative.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics, stratified by carrier status. We performed Cox proportional hazards models, stratifying by age, sex, and genotype platform, while adjusting for interactions between genotyping platform and the first 10 principal components,[8,10] using time from the baseline visit as the time scale to describe the relationship between the variant and adverse outcomes. Proportional hazards were assessed via Schoenfeld residuals.

We assessed for interactions between carrier status and several variables for HF hospitalization, all-cause mortality, and the combined outcome (HF hospitalization or all-cause mortality). Given strong effect modification by age, subsequent modeling focused on using sequences of 10-year age windows (eg, beginning age 50 through 59 years), generating 10-year adjusted hazard ratios using Cox regression, stratifying by sex and genotype platform while adjusting for the interactions between genotyping platform and principal components.[9] To better visualize these resulting estimates, we applied locally weighted scatterplot smoothing (LOWESS).[9,17,18] For LOWESS, tricube weighting was used with bandwidth of 0.8 (80% of observations used at each point).[19] This process was repeated for starting years between ages 50 and 90 years for HF hospitalization and death analyses, and between 58 and 90 years for HFpEF and HFrEF hospitalization (given fewer events at the lower age range). We reported age at first nominally statistically significant risk in each outcome. We performed post hoc sensitivity analyses using nominal statistical significance at α = .01 to acknowledge multiple age ranges tested. Participants were censored if they died (for HF hospitalization analyses) or were lost to follow-up, while participants were administratively censored at the time of last follow-up. For incident HFpEF hospitalization analyses, participants experiencing HF hospitalization with undetermined EF or reduced EF were censored (with parallel considerations for incident HFrEF hospitalization).

To estimate years of life lost among carriers compared with noncarriers, we used previously validated actuarial (age-based) methods to calculate nonparametric Kaplan-Meier estimates of overall survival and HF hospitalization-free survival at every year of age specified.[17,18] This method uses age (at a given starting age and at the time of death) as the time component. The area under the survival curve reflected projected event-free survival and overall survival. For each age between 50 and 95 years, we compared survival estimates of carriers and noncarriers. Estimates of survival gains were smoothed with LOWESS.

Finally, we applied these actuarial estimates of years of life lost at each age to the US population of Black individuals. For each age between 50 and 95 years, we extracted data on the estimated number of living Black individuals from the US Census Bureau's American Community Survey 5-Year Estimates from 2022, which was then multiplied by the carrier frequency observed in the current analysis to estimate the number of carriers at each age in the US (accounting for decreasing frequency of the variant aging given increasing mortality risk). The years of life lost at each age among carriers was multiplied by the number of estimated carriers in the population to generate total years lost at each age, which was then summed to estimate the numbers of years lost among carriers at least age 50 years. Analyses were performed using Stata version 18 (StataCorp LLC). For interaction testing, a 2-sided P value <.05 divided by 9 (ie, number of subgroups) was considered significant. For other analyses, a 2-sided P value <.05 was considered significant.

Results

Baseline Characteristics

The mean (SD) age at visit 1 was 62 (9) years, 76.7% were women (due to the large sample size included from WHI), 62.9% had hypertension, and 21.9% had diabetes (**Table 1**). Carrier percentages were similar between men (3.0%) and women (3.3%). Characteristics were generally balanced across V142I carrier status.

Carrier Status and Cardiovascular Outcomes

Total events and hazard ratios are shown in **Table 2** and Kaplan-Meier event curves are displayed in eFigures 1 and 2 in Supplement 1. With a mean (SD) 15.5 (8.2) years of follow-up, carriers faced an increased risk for all study outcomes, though the association with HFpEF hospitalization did not reach statistical significance. Carrier risks for HF and death were comparable with several traditional cardiovascular risk factors (eTable 1 in Supplement 1). Risk for HF hospitalization or death was significantly increased among the 4 homozygotes compared with heterozygotes (hazard ratio, 7.75 [95% CI, 2.24-26.79]) (eTable 2 in Supplement 1). eTable 3 in Supplement 1 shows interaction P values between carrier status and select variables, including study cohort, age, sex, hypertension, diabetes, systolic blood pressure, heart rate, body mass index, and African ancestry with study outcomes. Of these, only age was identified as a significant modifier of variant risk.

To further accommodate the age-related effects on outcomes, we used 10-year rolling hazard ratios (**Figure 2**; and eFigure 3 in Supplement 1). The risk for all outcomes generally increased between middle to late life. Statistically significant increased 10-year risk was first detected at age 63 years for HF, 65 for HF or death, and 72 for death. The increased HF risk was driven predominantly by an increased risk of HFrEF, with an elevated 10-year risk detected at age 65 years that strongly increased over time, in contrast to a later modest signal for HFpEF hospitalization emerging at age 76 years. Risk for HF hospitalization or death was similar between men and women (eFigure 4 in Supplement 1), in keeping with the lack of interaction reported by sex (eTable 3 in Supplement 1). Sensitivity analyses using 99% CIs were largely similar, noting modestly longer time to statistical significance (eFigures 5-6 in Supplement 1). Within analyses using 10-year intervals, there were still some indications of proportional hazards violations with respect to age.

Expected Overall and Event-Free Survival by Age

To describe the effect of the variant on years of life lost without relying on modeling assumptions, we provided several

Table 1. Clinical Characteristics of the Pooled Study Cohorts by V142I Carrier Status at Baseline Visit

	V142I noncarriers (n = 22 584)	V142I carriers (n = 754)
Study cohort, No. (%)		
Atherosclerosis Risk in Communities	3431 (15.2)	112 (14.9)
Multi-Ethnic Study of Atherosclerosis	1535 (6.8)	49 (6.5)
Reasons for Geographic and Racial Differences in Stroke	8265 (36.6)	262 (34.7)
Women's Health Initiative	9353 (41.4)	331 (43.9)
Participant characteristics		
Age, mean (SD), y	62 (9)	61 (9)
Sex, No. (%)		
Female	17 308 (76.6)	591 (78.4)
Male	5276 (23.4)	163 (21.6)
Clinical characteristics		
Physical examination		
Systolic blood pressure, mean (SD), mm Hg [No.]	131 (18) [22 534]	131 (19) [752]
Diastolic blood pressure, mean (SD), mm Hg [No.]	78 (10) [22 527]	78 (11) [753]
Heart rate, mean (SD), beats/min [No.]	69 (19) [22 441]	68 (13) [746]
Body mass index, mean (SD) [No.][a]	30.7 (6.6) [22 435]	30.2 (6.7) [748]
Comorbidities, No./total (%)		
Hypertension	13 965/22 174 (63.0)	460/744 (61.8)
Obesity	10 789/22 435 (48.1)	326/748 (43.6)
Diabetes	4909/22 349 (22.0)	156/748 (20.9)
Coronary heart disease	1570/22 544 (7.0)	51/753 (6.8)
Laboratory testing		
Glucose, mg/dL		
Mean (SD) [No.]	109 (45) [20 670]	108 (45) [684]
>125 mg/dL, No. (%)	3249 (15.7)	99 (14.5)
Creatinine, mg/dL		
Mean (SD) [No.]	0.93 (0.59) [20 468]	0.89 (0.37) [677]
>1.5 mg/dL, No. (%)	692 (3.4)	21 (3.1)
Low-density lipoprotein cholesterol, mg/dL		
Mean (SD) [No.]	131 (41) [20 216]	131 (40) [669]
≥190 mg/dL, No. (%)	1691 (8.4)	49 (7.3)

SI conversion factors: To convert cholesterol to mmol/L, multiply by 0.0259; creatinine to μmol/L, multiply by 88.4; and glucose to mmol/L, multiply by 0.0555.

[a] Calculated as weight in kilograms divided by height in meters squared.

Table 2. Events and Hazard Ratios for Adverse Cardiovascular Outcomes by V142I Carrier Status

	No./total (%)		Absolute difference, % (95% CI)	Hazard ratio (95% CI)[a,b]	P value
Outcomes	V142I noncarrier events	V142I carrier events			
HF hospitalization	2373/22 584 (10.5)	134/754 (17.8)	7.3 (4.5 to 10.0)	1.84 (1.54 to 2.20)	<.001
All-cause death	8744/22 584 (38.7)	329/754 (43.6)	4.9 (1.3 to 8.5)	1.27 (1.13 to 1.42)	<.001
HF hospitalization or all-cause death	9290/22 584 (41.1)	355/754 (47.1)	5.9 (2.3 to 9.6)	1.31 (1.18 to 1.46)	<.001
By HF type[c]					
HFrEF hospitalization	740/21 599 (3.4)	57/721 (7.9)	4.5 (2.5 to 6.5)	2.47 (1.87 to 3.26)	<.001
HFpEF hospitalization	722/21 599 (3.3)	32/721 (4.4)	1.1 (−0.4 to 2.6)	1.43 (0.99 to 2.05)	.054

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

[a] Models adjusted for interactions between study genotyping platform and the first 10 principal components and stratified by age, sex, and the genotyping platform.

[b] No proportional hazards violations were detected.

[c] ARIC participants did not have HF events adjudicated (including ejection fraction) until 2005, leading to different participant numbers for HFrEF and HFpEF events compared with other events.

model-free estimates. **Figure 3**A shows expected overall survival at each age between 50 and 95 years by carrier status (additional details in eTable 4 in Supplement 1). Carriers lived 2

to 2.5 fewer years compared with noncarriers until approximately age 85 years, when differences in longevity began to attenuate (Figure 3B). Because the survival loss difference

Figure 2. V142I Hazard Ratios for Adverse Cardiovascular Events by Age

A | HF hospitalization

No. at risk
Carriers	584	542	263
Noncarriers	17 340	16 175	8586

B | All-cause death

No. at risk
Carriers	588	565	292
Noncarriers	17 544	16 811	9336

C | HF hospitalization or death

No. at risk
Carriers	584	542	263
Noncarriers	17 340	16 175	8586
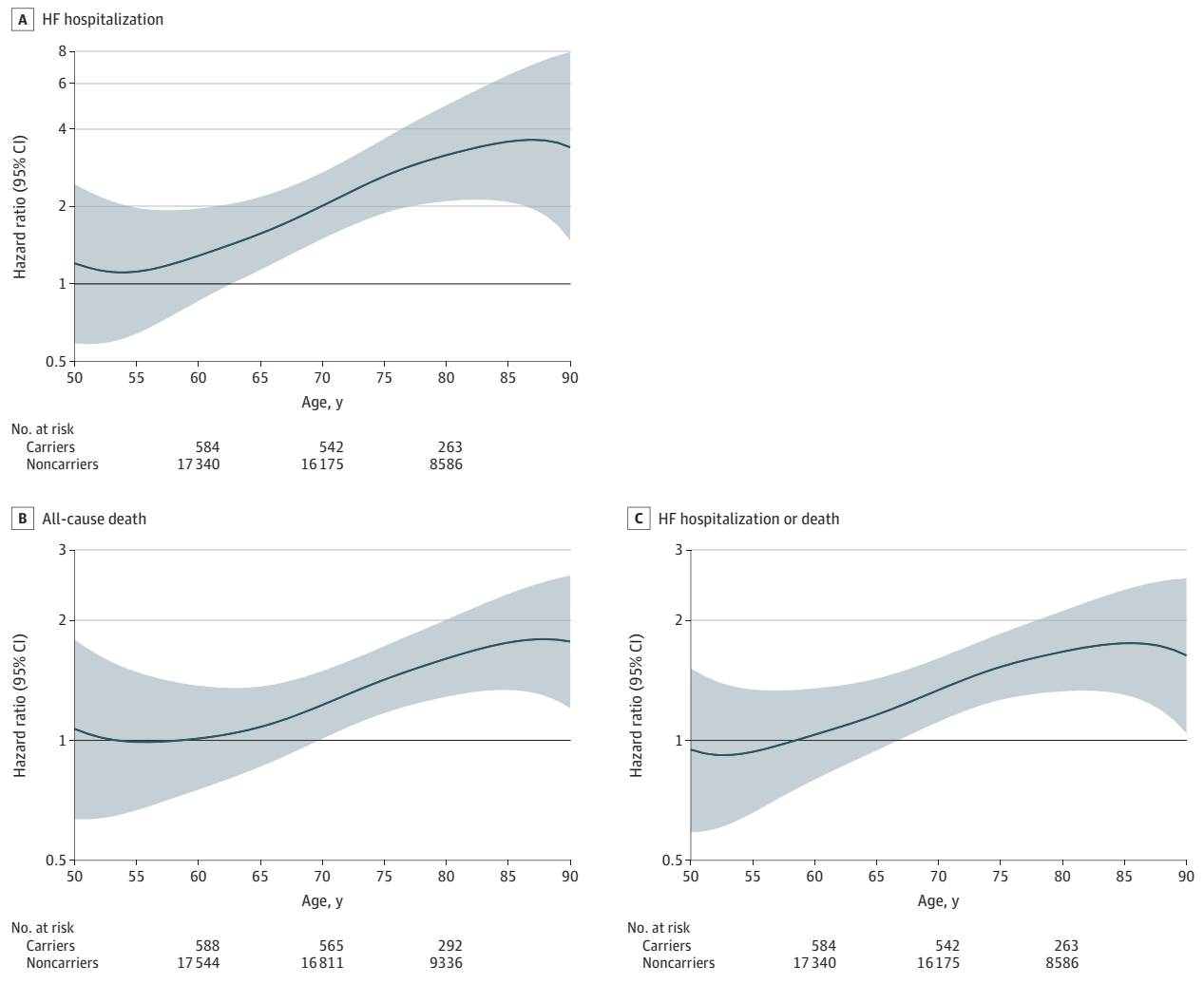
Ten-year hazard ratios and 95% CIs (shaded areas) are estimated at each age between 50 and 90 years for carriers vs noncarriers. Analyses are adjusted for interactions between study genotyping platform and the first 10 principal components, while stratified by sex and study genotyping platform. HF indicates heart failure.

between carriers and noncarriers remained relatively constant across ages 50 to 85 years, while expected survival decreased, the relative (percentage) loss in expected remaining carrier longevity generally increased over time (eFigure 7 in Supplement 1). Specifically, carriers at age 50 years subsequently lived 1.9 fewer years (95% CI, 0.6-3.1) than noncarriers, representing a 6% reduction (95% CI, 2%-10%) in expected longevity. This longevity disparity increased to a maximum of 2.8 years (95% CI, 2.0-3.6) at age 81 years. The maximum relative reduction in longevity was 34% (95% CI, 11%-56%), achieved at age 90 years. Parallel findings were demonstrated using event-free survival (eTable 5 and eFigures 8-9 in Supplement 1).

Extrapolation of Years Lost Based on Carrier Prevalence in the US Population
We applied carrier rates derived from this analysis to US population data to estimate the burden of disease in the US Black population. Among the 13 284 819 estimated Black adults aged 50 to 95 years, there are an estimated 435 851 carriers (eTable 4 in Supplement 1). Based on the expected loss of longevity at each age among carriers compared with noncarriers, US Black individuals at least 50 years old are projected to cumulatively lose 957 505 years of life (95% CI, 534 475-1 380 535) compared with noncarriers.

Discussion
Leveraging individual-level participant data from 4 large observational cohort studies facilitated several analyses highlighting risk encountered by carriers of the amyloidogenic V142I variant of the *TTR* gene. First, this study provided more precise estimates of cardiovascular risk across mid to late life (>90 years old) than were previously available. These risks strongly related to age, but were not modified by sex, suggesting

Figure 3. Effect of V142I on Overall Survival of Carriers Compared With Noncarriers
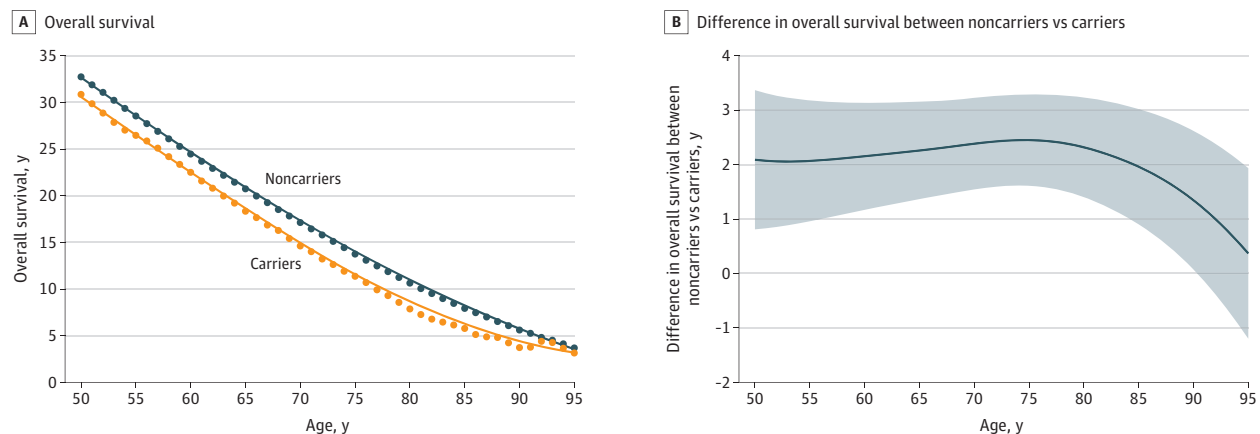
A, Estimated mean overall survival in carriers and noncarriers for every year between ages 50 and 95 years. B, The difference in mean years lost among carriers compared with noncarriers shown with the smoothed estimate (blue line), and 95% CI of the smoothed estimate (shaded area) after application of a locally weighted scatterplot smoothing procedure.

underdiagnosis of ATTRv-CA in women, as some clinical studies have reported male predominance of phenotypic penetration. Second, the earliest statistically significant increase in 10-year risk was identified at earlier ages than previously shown (age 63 years for HF hospitalization and age 72 years for mortality), likely due to the inclusion of a larger sample size.[9] Third, the risk for HF hospitalization was driven by HFrEF, in contrast with its typical HFpEF association, a more modest signal that emerged in later life. Fourth, at each age from mid to late life, carriers died 2 to 2.5 years earlier than noncarriers until age 85 years (when differences began to attenuate), leading to an overall significant decrease in percentage expected longevity with increasing age. Fifth, accounting for the age-dependent frequency of the variant, Black carriers at least 50 years old are projected to live nearly 1 million fewer years than noncarriers. Given established and emerging treatment strategies, which may be more effective earlier in disease course,[11,12] early identification and treatment of V142I carriers with ATTRv-CA may have significant public health impact.

Population studies, including several included here, individually have shown significantly higher risk among V142I carriers for HF hospitalization and death, though the risk of homozygotes in these studies has remained unclear.[1,7-10,20] The small group of homozygotes (n = 4) in this study was at substantially elevated risk even in comparison with heterozygotes (demonstrating allele dose dependence), albeit with wide confidence intervals. These findings were overall consistent with data from clinical populations.[21] Pooling data importantly allowed for greater power to evaluate for interactions between clinical characteristics and variant status that might account for incomplete phenotypic penetrance. Only age was consistently identified as a strong modifier of risk. Clinical studies have demonstrated a greater risk for ATTRv-CA among male carriers,[2,6] which has been postulated to relate to less-aggressive disease trajectory in women.[22] However, sex did not significantly modify risk in this study with very similar estimates of HF hospitalization or death in men and women, sug-gesting that previous reports may be explained by underdiagnosis of ATTRv-CA in women.[2,6,8,23,24] Women with ATTRv-CA present with thinner left ventricular walls compared with men, and not accounting for differences in body size may engender underdiagnosis.[23] Without clear alternative modifiers of risk, age may currently be the most reliable clinical marker to identify risk for progressive disease.

Additionally, this larger study enabled more precise risk estimation and earlier detection of phenotypic penetrance. Previous research in the Atherosclerosis Risk in Communities Study alone identified inflection points in 10-year risk around age 70 years for HF hospitalization and 75 years for mortality.[9] The greater sample size in the current study showed that risk increased at even earlier ages (63 and 72 years, respectively). Defining these ages is clinically impactful and relevant when considering initiation of treatments such as stabilizers, silencers, or even in vivo gene editing, where treatment prior to the onset of symptoms might be most effective, though further data are needed to clarify the impact of early treatment.[11,25,26]

Notably, the risk for HF hospitalization in this study was driven by incident HFrEF hospitalization. While ATTR-CA has traditionally been associated with HFpEF, V142I carriers are more likely to experience HFrEF events. Indeed, V142I-associated ATTRv-CA presents with greater disease severity (including lower left ventricular EF) and faster disease progression compared with both ATTRwt-CA and non-V142I ATTRv-CA.[27,28] Recent data from a clinical trial in ATTR-CA supported the presence of reduced EF in a significant proportion of patients with a tendency to progress in ATTR-CA.[29] Therefore, among Black hospitalized patients with HFrEF, suspicion for ATTR-CA should be heightened and not restricted to patients with preserved EF.[30-33] It is important to note that not all carriers with HFrEF have ATTRv-CA because carriers are at risk for other causes of cardiomyopathy as well (such as coronary artery disease), emphasizing the importance of further cardiovascular evaluation for etiology. Identification of ATTR-CA in the HFrEF population is also important because

implementation of some guideline-directed medical therapies may not be well tolerated in ATTR-CA.[34] The more modest association with increased HFpEF hospitalization in late life may represent a survivor bias, whereby those carriers who survive to late life may have an inherently more benign form of the disease.

Our actuarial analyses demonstrated that carriers die approximately 2 to 2.5 years earlier than noncarriers. Because these findings were consistent until approximately 85 years of age, the relative reduction in longevity of carriers compared with noncarriers significantly increased with aging, further reflecting the steep age-dependent penetrance of the variant. Because the variant is relatively common (3%-4% among US Black individuals), these years of life lost at the individual level translate to a substantial burden at the population level. The approximately 435 000 living carriers between ages 50 and 95 years will collectively lose nearly 1 million years of life. Because targeted therapies are either available, emerging, or promising in ATTR-CA,[11,25,26,35] these results suggest that identification of disease and implementation of efficacious therapies might extend longevity in this large population.[11] These results may be increasingly relevant with greater access to genetic testing in the population, whether accomplished through biobanks, direct-to-consumer testing, or broad population assessments (including the All of Us Research Program[36]). Additionally, these results support the inclusion of the variant as a clinically actionable secondary finding.[5]

Limitations

There are several limitations of this study. First, specific phenotypic markers or diagnoses of cardiac amyloidosis were not broadly available in these studies, and therefore understanding which individual carriers have ATTR-CA (as opposed to other causes of HF) is limited. However, at a population level, the absolute difference estimates of HF events provide understanding of the burden of ATTRv-CA. Second, despite pooling studies, interaction analyses may still be underpowered to detect modifiers of variant risk. Third, extrapolation of the current estimates to the US population assumes that the cohorts studied here are broadly representative, and these data may not accurately inform estimates in other parts of the world where variant prevalence and event rates may vary.[2] Fourth, participants who self-reported as Black were included, although race does not capture the significant genetic diversity within Black individuals in the US and worldwide. Delineating the individual contributions of, and complex interplay between, the V142I variant, ancestry, race as a social construct, and biological or social determinants of health to cardiovascular disease merits further investigation. Fifth, adjudication of HFrEF and HFpEF events varied by study and were obtained through available medical record review.

Conclusions

Among self-reported Black individuals, male and female V142I carriers faced similar and substantial risk for HF hospitalization, predominantly with reduced ejection fraction, and all-cause death later in life, with steep age-dependent penetrance. Delineating the individual contributions of, and complex interplay among, the V142I variant, ancestry, the social construct of race, and biological or social determinants of health to cardiovascular disease merits further investigation.

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