Sudden Cardiac Death Risk Distribution in the United States Population (from NHANES, 2005 to 2012)

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Sudden cardiac death (SCD) accounts for more than half of all deaths from cardiovascular disease and is the first manifestation of heart disease in 50% of these subjects. We aimed to describe the distribution of predicted SCD risk in the general US population using a recently developed risk score. We previously developed a population-based, 10-year risk score for SCD using data from the multiracial Atherosclerosis Risk in Communities cohort, validated in the Framingham Study. We now estimate 10-year predicted SCD risk in National Health and Nutrition Examination Survey participants (pooled from cycles in 2005 to 2012) and evaluate the clinical profile of participants in lower risk (0 to 80th percentile of risk) or high risk (81st to 100th percentile of risk) strata. A total of 10,811 participants were included; the mean age of participants was 48 years, and 50% were women. The average predicted 10-year risk of SCD was 3.6% in high-risk participants (81st to 100th percentile), and 0.37% in low-risk participants (0 to 80th percentile). High-risk participants were older, had higher blood pressure, total cholesterol and body mass index, lower high-density lipoprotein, and were more likely to be men, black, smokers, and diabetic. In US adults free of cardiovascular disease, the majority of SCD risk appears confined to 10% to 20% of the population. This risk score, comprised of readily available clinical variables, identifies a subset of individuals in the population who are at an appreciably higher risk of SCD. This enriched cohort represents candidates for additional nuanced and selective screening techniques to further quantify SCD risk. **(Am J Cardiol 2019;123:1249−1254)**

Sudden cardiac death (SCD) accounts for 15% to 20% of all deaths.[1] The majority of those who suffer SCD do not have known severe left ventricular dysfunction or cardiovascular disease (CVD).[2−5] A straightforward risk prediction tool is needed to identify those in the general population who are at elevated risk for SCD. We recently developed a population-based 10-year risk score that exhibits promise in identifying individuals at risk for SCD.[6] The score, derived in the Atherosclerosis Risk in Communities (ARIC) cohort and subsequently validated in the Framingham Heart Study, incorporates 11 variables that are widely available in the electronic health record. Subjects in the top decile of risk based on this risk score had a predicted 10-year risk of SCD of roughly 5%. We aimed to determine the distribution of predicted SCD risk across various strata of age, gender, and race/ethnicity categories by applying our previously validated SCD risk score to the National Health and Nutrition Examination Survey (NHANES) 2005 to 2012 dataset.

Methods

Individual-level data from 4 cycles (2005 to 2006, 2007 to 2008, 2009 to 2010, 2011 to 2012) of NHANES were used. Detailed methods and protocols for NHANES have been previously described.[7] We included CVD-free, noninstitutionalized, nonpregnant, nonlactating subjects who had completed a mobile examination. Subjects ages 30 to 70 years were included for purposes of consistency with the original Framingham validation cohort. We defined participants as having CVD if they answered "yes" when asked if a doctor or health professional ever told them they had coronary heart disease, heart attack, stroke, or congestive heart failure. We excluded participants with a body mass index (BMI) >50 kg and total cholesterol >500 mg/dl because of their effect on the stability of estimates. Due to the nature of the NHANES study, informed consent was not required.

Methods for measuring sociodemographic, medical history, medication use and anthropometric data are described elsewhere.[7] Briefly, data were collected during an interview and medical evaluation, which included anthropometric

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measurements and laboratory testing. Age, race/ethnicity, education, income, hypertension medication use, lipid-lowering medication use, and smoking status were ascertained during the interview. Current smoking was defined as a self-report of smoking every day or some days and having smoked ≥100 cigarettes over a lifetime. Diabetes mellitus was determined by either self-reported previous diagnosis by a health professional, use of oral diabetic medication or insulin, or a hemoglobin A1c ≥6.5%. Obesity was defined as BMI ≥ 30 kg/m^2. Blood pressure measurements were performed by trained and certified physicians using previously described procedures and a mercury manometer; the average of the last 2 measurements was used whenever available, although single measurements were used if they were the only available measurements. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or treatment for hypertension.

Our recently developed population-based SCD risk prediction model yields a predicted 10-year risk of SCD using data on various risk factors.[6] The model was derived in the ARIC cohort and validated in the Framingham Heart Study. Variables included are age, gender, race/ethnicity, total cholesterol, lipid-lowering medication use, hypertension medication use, systolic blood pressure, diastolic blood pressure, smoking status, diabetes mellitus, and BMI. In ARIC, SCD was defined as death resulting from fatal myocardial infarction or definite or possible fatal coronary heart disease where the time between symptom onset and death is less than 1 hour or where the time between hospital admission and death is less than 1 hour. Deaths were reviewed using coroner records, death certificates, and through contacting kin or primary physician. In Framingham, SCD was defined as death resulting from coronary heart disease within 1 hour of symptom onset with no other probable cause of death suggested from the medical record and interview of relatives. Suspected SCD events were adjudicated by a panel of 3 trained physicians who applied criteria for SCD.

The model was originally derived and validated in whites. We then recalibrated the risk score to yield a best fit model for the black ARIC participants. See online Table 1 in the Supplement for details of the race-specific risk scores. The recalibrated black model was then applied to black NHANES participants, and the original white model was applied to participants of all other races/ethnicities.

The SCD risk prediction score was applied to NHANES participants (from exam cycles 2005 to 2012) to obtain a predicted 10-year risk for SCD for each individual participant. We then stratified participants as being at either lower predicted risk (0 to 80th percentile of predicted 10-year risk) or high risk (81st to 100th percentile).

We used survey procedures in SAS statistical software (version 9.1, SAS Institute, Cary, North Carolina) to generate accurate frequencies and variances accounting for the complex, multistage design of NHANES. Analyses were performed for all eligible adults and were stratified by age, gender, race/ethnicity, and socioeconomic subgroups to assess the relation between these demographic variables and SCD risk burden. We used the survey weights to estimate the number of subjects at high versus lower predicted SCD risk across the various demographic strata.[7] Analysis of variance, 2-sample *t* tests, or chi-square tests used as appropriate to analyze differences in baseline characteristics by race/ethnicity and risk status. A 2-tailed p value <0.05 was considered statistically significant. Dr. Olson and Dr. Lloyd-Jones had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Results

We included 10,811 CVD−free, noninstitutionalized, and nonpregnant subjects ages 30 to 70 years, representing approximately 120 million US adults (Table 1). The mean age of participants was 48 years, and 50% of the sample

Table 1
Baseline participant characteristics for overall sample, and stratified by race/ethnicity*

Variable	Overall (n = 10,811)	Non-Hispanic Whites (n = 4,706)	Non-Hispanic Blacks (n = 2,250)	Hispanic (n = 3,009)	Other (n = 846)
Age (years)	47.6 (0.2)	48.5 (0.2)	46.6 (0.3)	43.9 (0.3)	45.9 (0.5)
Female sex	50.3%	50.2%	54.0%	47.9%	51.4%
Total cholesterol (mg/dl)	203.0 (0.6)	204.1 (0.7)	196.1 (0.9)	203.5 (0.9)	201.3 (2.2)
HDL (mg/dl)	53.3 (0.2)	53.7 (0.3)	56.2 (0.3)	49.6 (0.4)	52.1 (0.8)
Dyslipidemia†	67.0%	67.2%	59.0%	72.1%	66.2%
Lipid-lowering medication use	13.4%	14.4%	12.3%	9.1%	12.4%
Systolic blood pressure (mm Hg)	120.4 (0.3)	120.3 (0.3)	124.9 (0.5)	119.1 (0.4)	118.4 0.7)
Diastolic blood pressure (mm Hg)	72.9 (0.2)	72.9 (0.3)	74.2 (0.4)	71.6 (0.4)	72.6 (0.5)
Hypertension‡	28.8%	27.9%	40.3%	19.3%	22.2%
Hypertension medication use	18.9%	19.4%	28.2%	11.2%	13.7%
Smoker	21.9%	22.2%	26.6%	17.0%	20.5%
Diabetes mellitus	8.5%	6.9%	12.8%	12.6%	10.7%
BMI (kg/m^2)	28.7(0.1)	28.5 (0.1)	30.3 (0.2)	29.5 (0.1)	26.6 (0.3)
Obesity§	35.0%	33.8%	46.1%	39.5%	21.8%

* All values given are mean (SE) unless otherwise specified.
† Dyslipidemia defined as total cholesterol ≥200 mg/dl or HDL <40 mg/dl for a man or <50 mg/dl for a woman or treatment for dyslipidemia.
‡ Hypertension defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg or treatment for hypertension.
§ Obesity defined as BMI ≥30 kg/m^2.BMI = body mass index; HDL= high-density lipoprotein.

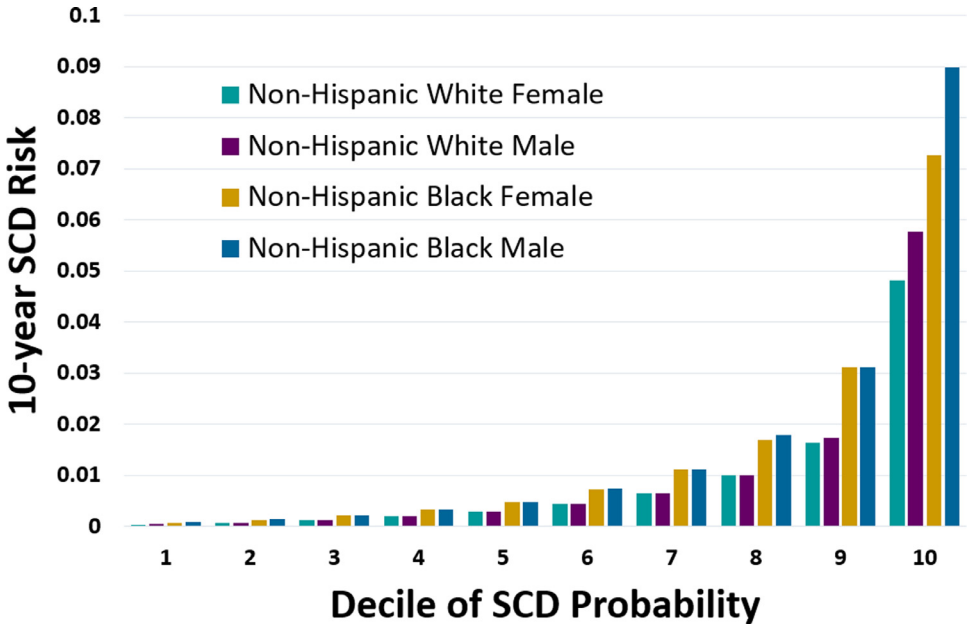

Figure 1. Predicted 10-year risks of sudden cardiac death in a representative sample of the US population, stratified by race/ethnicity, and gender. The deciles of estimated risk in 4 different race/ethnicity and gender groups are noted on the x axis and corresponding sudden cardiac death risk estimates are noted on the y axis.

were women. Sixty-seven percent of participants had dyslipidemia, 28.8%% had hypertension, 21.9% were current smokers, 8.5% had diabetes, and 35.0% were obese.

Predicted SCD risk increased in an exponential fashion across increasing deciles of risk (Figure 1). As observed in the derivation and validation cohorts, the majority of predicted SCD risk was concentrated in the top 2 deciles. The average predicted 10-year risk of SCD was 3.6% in predicted high risk participants, and 0.37% in lower risk participants.

When compared with lower risk participants, high risk participants were older and more likely to be men (Table 2, Figure 2). High risk participants also had higher blood pressure, total cholesterol, and BMI, lower high-density lipoprotein, and were more likely to be smokers and diabetic. When the subgroup of high risk participants under age 60 was examined, rates of dyslipidemia, smoking, obesity, and diabetes were further heightened (online Table 2 in the Supplement), highlighting the role of these conditions in driving predicted risk when age-related risk is deemphasized.

Compared with 16.4% of non-Hispanic whites, 12.4% of Hispanics, and 12.4% of those in the "other" race/ethnicity category, 18.0% of non-Hispanic black US adults were predicted to be high risk (Table 3). The US adults with less

Table 2
Baseline characteristics for high versus lower predicted risk participants*

Variable	Risk			
	Overall (n = 10,811)	High (top 2 deciles) (n = 2,162)	Low (bottom 8 deciles) (n = 8,649)	p value†
Age (years)	47.6 (0.2)	58.7(0.2)	45.5 (0.2)	<.001
Female sex	50.3%	23.6%	55.3%	<.001
Total cholesterol (mg/dl)	203.0 (0.6)	210.9 (1.4)	201.5 (0.6)	<.001
HDL (mg/dl)	53.3 (0.2)	48.5 (0.4)	54.2 (0.3)	<.001
Dyslipidemia‡	67.0%	72.2%	66.0%	<.001
Lipid-lowering medication use	13.4%	38.2%	8.7%	<.001
Systolic blood pressure (mm Hg)	120.4 (0.3)	133.4 (0.7)	118.0 (0.2)	<.01
Diastolic blood pressure (mm Hg)	72.9 (0.2)	73.3 (0.5)	72.8 (0.3)	0.30
Hypertension§	28.9%	65.8%	20.1%	<001
Hypertension medication use	18.9%	49.1%	13.2%	<.001
Smoker	21.9%	29.1%	20.5%	<.001
Diabetes mellitus	8.5%	31.8%	4.1%	<.001
BMI (kg/m^2)	28.7(0.1)	32.4 (0.2)	28.0 (0.1)	<.001
Obesity¶	35.0%	60.2%	30.3%	<.001

* All values listed are mean (SE) unless otherwise specified.

† Significance tests for comparisons by risk status based on 2 sample *t* test for continuous subject characteristics and Pearson's chi-square test for categorical subject characteristics.

‡ Dyslipidemia defined as total cholesterol ≥200 mg/dl or HDL <40 mg/dl for a man or <50 mg/dl for a woman or treatment for dyslipidemia.

§ Hypertension defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg or treatment for hypertension.

¶ Obesity defined as BMI ≥ 30 kg/m^2.BMI = body mass index; HDL = high density lipoprotein.

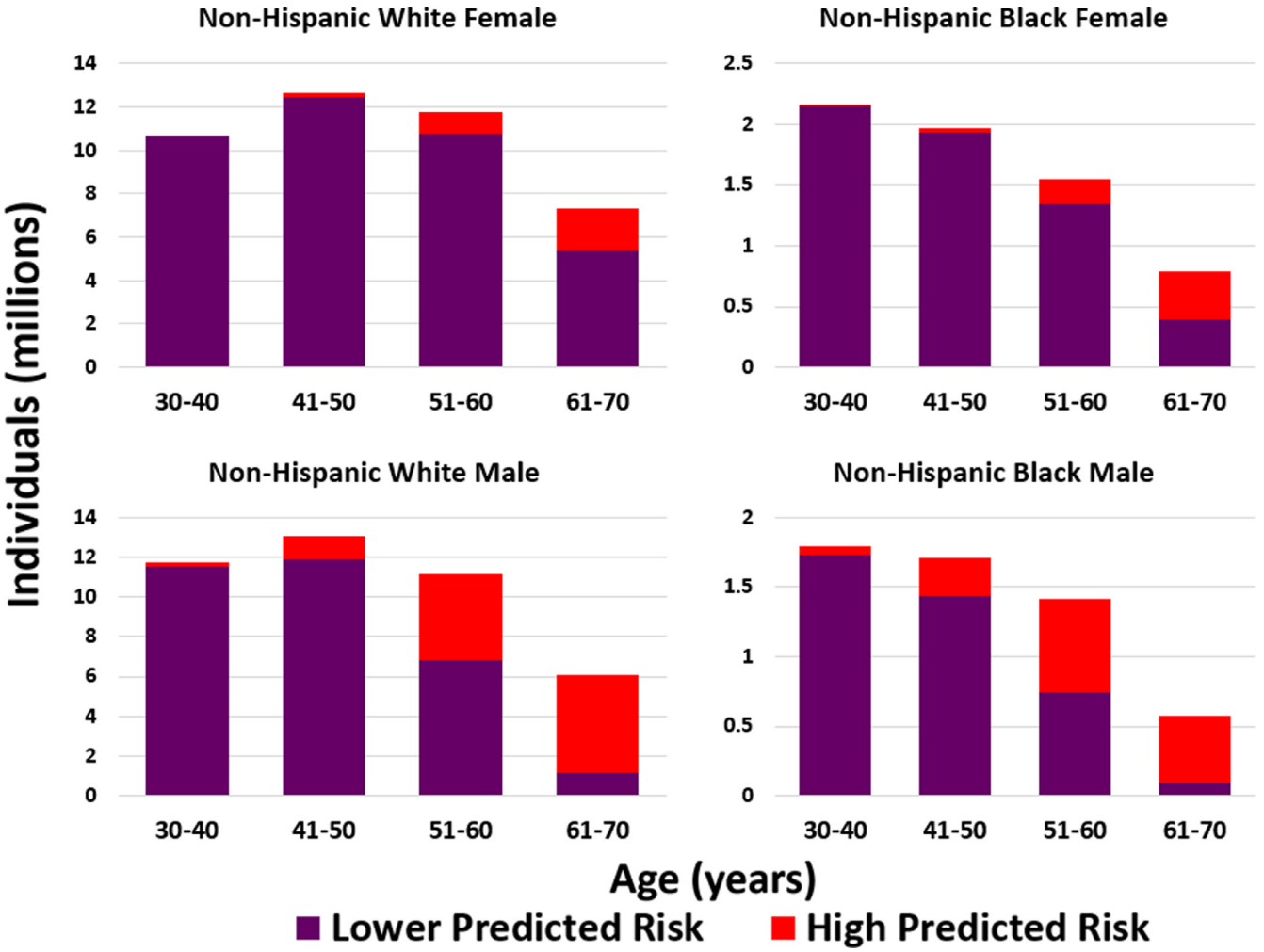

Figure 2. Sudden cardiac death risk status by age, gender, and race. Gender, race/ethnicity, and age-specific population estimates of risk strata distribution in CVD-free, nonpregnant US adults ages 30 to 70 years. Each panel displays the proportion of the specific populations at high risk (red bars) for sudden cardiac death. (Color version of figure is available online.)

than a high school education were more frequently classified as high risk than were participants with a college degree (19.0% vs 11.3%). Finally, 18.8% of the US adults with household income <$45,000 were designated as high risk, but only 14.1% of those with income ≥$45,000 were predicted to be at high risk of SCD.

Discussion

In this study, we describe the distribution of predicted SCD risk in a multiracial representative sample of the US population. The average predicted 10-year risk of SCD was 3.6% in predicted high-risk participants, and 0.37% in lower risk participants, a 10-fold difference in risk. Importantly, predicted SCD risk rose in an exponential fashion across increasing deciles of risk, with the majority of predicted SCD risk concentrated in the top 2 deciles. High risk participants were older, had higher blood pressure, total cholesterol and BMI, lower high-density lipoprotein, were more likely to be men, black, smokers, and diabetic, and were poorer and less educated. In aggregate, our findings demonstrate a striking gradient in predicted SCD risk in NHANES participants, supporting the utility of our previously derived and validated 10-year risk score as the first step in a sequential screening strategy for SCD.

A feature that is advantageous when taking a population approach to risk reduction is that much of the risk for the outcome in question is concentrated in relatively few subjects. If those subjects are easily identifiable, potential exists to affect a large reduction in the population burden of a disease.[8] If SCD risk increased steadily by decile, or was relatively flat across deciles, we would have no identifiable subpopulation on whom to focus our SCD-reduction efforts. In this case, we observe an exponential increase in the risk estimates, such that the predicted risk in the top decile is approximately 100 times greater than the risk in the lowest decile. Using the current risk score, the top quintile of the SCD risk distribution has a 10-year predicted SCD risk of approximately 3.6%%; the top decile has a 10-year SCD risk of approximately 5.8%.

This risk distribution information aids in determining whether SCD risk stratification would be amenable to a sequential screening strategy in which we can identify and target a high-risk segment of the population. This analysis

Table 3
Relation between Sociodemographics and predicted sudden cardiac death risk status in the US population

Characteristic	n	Weighted, n	High risk % (SE)	Low risk % (SE)	p value*
Overall	10,811	119,596,283			
Age (years)					
30-40	3265	36,010,754	1.1(0.18)	98.9(0.18)	
41-50	2963	36,412,947	6.1(0.50)	93.9(0.50)	<.001
51-60	2556	30,489,703	24.3(1.10)	75.7(1.10)	
61-70	2027	16,682,879	52.9(1.41)	47.1(1.41)	
Race/ethnicity					
Non-Hispanic white	4706	84,457,346	16.4(0.67)	83.6(0.67)	
Non-Hispanic black	2250	11,960,189	18.0(0.85)	82.0(0.85)	<.001
Hispanic	3009	15,529,551	12.4(0.66)	87.6(0.66)	
Other	846	7,649,197	12.4(1.60)	87.6(1.60)	
Sex					
Female	5,369	60,183,213	7.4(0.36)	92.6(0.36)	<.001
Male	5,442	59,413,070	24.3(0.89)	75.7(0.89)	
Education					
Less than high school	2765	19150927	19.0(0.84)	81.0(0.84)	
Completed high school	2382	26093270	18.5(1.14)	81.5(1.14)	<.001
Some college	2992	35751232	16.9(0.95)	83.1(0.95)	
College Degree	2662	38515512	11.3(0.82)	88.7(0.82)	
Annual Household Income					<.001
<$45,000	4847	39428059	18.8(0.74)	81.2(0.74)	
≥$45,000	5187	73750926	14.1(0.71)	85.9(0.71)	

* Significance tests for the comparison of risk distributions across demographic categories are based on the Rao-Scott chi-square test.

illustrates 2 points: (1) the preponderance of SCD risk is concentrated in a relatively small percentage of the population; (2) those who are at elevated risk are identifiable based on readily available health information.

Bayesian sequential testing maximizes positive predictive value in identifying high-risk subjects while sparing the cost and inconvenience of in-depth parallel testing in the general population. This score could initially be applied to an electronic health record to yield a list of subjects at increased risk. In a second screening step, those who screened as high risk in step one would be candidates for more in-depth evaluation and testing to further delineate risk (e.g., echocardiography, signal-averaged electrocardiography). This implementation of Bayesian sequential testing identifies an enriched subpopulation of higher risk subjects based on the initial round of testing. The predicted 10-year SCD risk is approximately 5.8% in the top decile of the NHANES study. These subjects have a notably higher pretest probability of SCD than does the general population. The second round of more in-depth testing is then focused on this group and results in the identification of an even smaller group of very high-risk subjects who can then be assessed for candidacy for interventions to reduce risk of SCD.

A paradigm shift toward a focus on screening in the general population may brighten our prospects for combating SCD. For a score to be feasibly applied on a population level as the first step in screening, it should be simple and use readily available data. Our score incorporates widely available metrics that are obtained at a routine primary care visit and can be automatically calculated in the electronic health record. Therefore, it may hold advantages over other scores that have recently been published.[9,10] The inclusion of additional laboratory and electrocardiography parameters in other risk scores may limit their feasibility in screening the general population. Indeed, the United States Preventive Services Task Force recently noted insufficient evidence to recommend screening electrocardiography even in patients at intermediate or high risk of cardiovascular events.[11] Bayesian theory illustrates that the goal of the first step in a sequential screening strategy should not be to implement a complex or costly test with perfect test characteristics, but instead to employ a simple tool that identifies with reasonable accuracy those who should be assessed in more detail.

This study has several limitations. Our risk scores were validated only in black and white populations, and further assessment of their applicability to other races/ethnicities is needed. Additionally, SCD outcome data is not available in NHANES, and therefore we are not able to compare predicted versus observed risk in this study. The focus of the manuscript is on illustrating the distribution of predicted SCD risk in the general US population, a task for which NHANES is better suited than is any single cohort study, which tend to be more limited in their representativeness of the US population.

In a multiracial representative sample of the US population, a simple, inexpensive risk score for SCD identifies a quintile of the population at substantial predicted 10-year risk of SCD. These data further elucidate the distribution of predicted SCD risk across the diverse adult US population. This risk score can identify a subgroup of individuals in the US community who are at an appreciably increased risk of SCD, and in so doing provide an enriched pool of subjects who are candidates for additional screenings.

Disclosures

The investigators have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.01.020.

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