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# **BMJ Open**

### Socioeconomic Status and Modification of Atherosclerotic Cardiovascular Disease Risk Prediction: The Atherosclerosis Risk in Communities Study

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Prediction: The Atherosclerosis Risk in Communities Study

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## Socioeconomic Status and Modification of Atherosclerotic Cardiovascular Disease Risk First Author: Henderson Short Title: Socioeconomic Status and Cardiovascular Disease Risk Prediction Authors: Kamal H. Henderson, MD MSc<sup>1,2</sup>; Brystana G. Kaufman, Ph.D. MSPH<sup>3</sup>; Jason S. Rotter, Ph.D. MHS<sup>4</sup>; Sally C. Stearns, Ph.D.<sup>5</sup>; Carla A. Sueta, MD, Ph.D.<sup>6</sup>; Randi E. Foraker, Ph.D.<sup>7,8</sup>; Michael Ho, MD, Ph.D.<sup>1,2</sup>; Patricia P. Chang, MD, MHS<sup>9</sup> Author Affiliations: Rocky Mountain Regional Veteran Affairs Medical Center<sup>1</sup>; University of Colorado School of Medicine<sup>2</sup>; Department of Population Health Sciences, Duke University<sup>3</sup>; Mathematica Policy Research, Washington D.C.4; Department of Health Policy and Management, University of North Carolina (UNC) Gillings School of Global Public Health<sup>5</sup>; UNC School of Medicine<sup>7</sup>; Division of General Medical Sciences, Washington University School of Medicine<sup>7</sup>; Brown School of Public Health<sup>8</sup>; UNC School of Medicine<sup>9</sup>. **Corresponding Author:** Kamal H Henderson

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**Objective:** Examine whether the relationship between the Pooled Cohort Equations (PCE) predicted 10-year risk for atherosclerotic cardiovascular disease (ASCVD) and absolute risk for ASCVD is modified by socioeconomic status (SES).

**Design:** Population-based longitudinal cohort study –Atherosclerosis Risk in Communities (ARIC) – investigating the development of cardiovascular disease across demographic subgroups.

Setting: Four communities in the United States– Forsyth County, North Carolina, Jackson, Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland.
Participants: We identified 9,782 ARIC men and women age 54-73 without ASCVD at study visit 4 (1996-1998).

**Primary outcome measures:** Risk ratio (RR) differences in 10-year incident hospitalizations or death for ASCVD by SES and PCE predicted 10-year ASCVD risk categories to assess for risk modification. SES measures included educational attainment and census-tract neighborhood deprivation using the Area Deprivation Index. PCE risk categories were 0%-5%, >5%-10%, >10%-15%, and >15%. SES as a prognostic factor to estimate ASCVD absolute risk categories was further investigated as an interaction term with the PCE.

**Results:** ASCVD risk ratios for participants without a high school education (referent collegeeducated) increased at higher PCE estimated risk categories and was consistently >1. Results indicate education is both a risk modifier and delineates populations at higher ASCVD risk independent of PCE. Neighborhood deprivation did modify association but was less consistent in direction of effect. However, for participants residing in the most deprived neighborhoods (referent least deprived neighborhoods) with a PCE estimated risk >10%-15%, risk was significantly elevated (RR 1.65 [95% CI; 1.05-2.59]). Education and neighborhood deprivation inclusion as an interaction term on the PCE risk score was statistically significant (Likelihood ratio  $P \le 0.0001$ ).

**Conclusions:** SES modifies the association between PCE estimated risk and absolute risk of ASCVD. SES added into ASCVD risk prediction models as an interaction term may improve our ability to predict absolute ASCVD risk among socially disadvantaged populations.

### Strengths and limitations of the study:

- Population-based prospective cohort with over three decades of follow-up data to investigate the development of cardiovascular disease across demographic subgroups are major strengths of this study.
- Hospitalizations for coronary heart disease and stroke hospitalizations an outcome measured – was based on the Atherosclerosis Risk in Communities abstraction of hospital data, and some hospitalizations may be missing.
- A potential misclassification bias of area-level deprivation exposure possibly exists due to not accounting for Atherosclerosis Risk in Communities participants moving to different neighborhoods with a different degree of area-level deprivation exposure.

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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and morbidity in the United States (US) and globally.<sup>1-4</sup> A substantially higher burden of ASCVD is experienced among those with lower socioeconomic status (SES).<sup>5-14</sup> The Pooled Cohort Equations (PCE) are currently recommended in the US to estimate the 10-year risk of ASCVD and guide primary prevention treatment decisions.<sup>15-18</sup> The PCE does not currently account for SES factors such as educational attainment or neighborhood deprivation. However, SES measures may have prognostic value in predicting ASCVD outcomes and identifying populations in greatest need of primary ASCVD prevention. Existing evidence regarding the prognostic value of controlling for SES in ASCVD prediction models is mixed. A recent analysis showed that PCE overestimated ASCVD risk among low SES populations, but including SES measures such as household income or educational attainment in the PCE model did not improve model calibration.<sup>19</sup> Conversely, prior research evaluating the use of SES measures, such as household income or neighborhood deprivation, with the Framingham Risk Score that estimates coronary heart disease risk only, showed that such measures improved model fit statistics.<sup>20-22</sup> The latter findings eventually led to ASCVD risk models, such as QRISK2, primarily used in the United Kingdom that incorporate the Townsend deprivation score, a neighborhood measure of deprivation.<sup>23-25</sup> Such discrepancies have important implications globally and for the US, creating uncertainty regarding the importance of incorporating SES into ASCVD risk prediction models and the value of SES as a marker to identify individuals in need of additional ASCVD primary prevention interventions and services.

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1	How prior ASCVD prediction models incorporated SES into the model is a potential
2	reason for the discrepancies in understanding the prognostic value and use of SES in ASCVD
3	prediction models. SES traditionally is modeled as an independent risk factor or confounder. <sup>19-</sup>
4	<sup>22,24</sup> However, SES's prognostic value in predicting ASCVD risk is likely identifying
5	populations most impacted by proximate causes of ASCVD. If true, SES incorporated into risk
6	prediction models as a risk modifier is more appropriate in determining ASCVD risk than an
7	independent risk factor. For example, the health impact of hypertension over 10-years is
8	different for an individual living in abject poverty versus an individual residing in an affluent
9	neighborhood. SES likely modifies the association between risk estimated from algorithms that
10	use proximate causes of ASCVD (i.e., hypertension and smoking) and actual ASCVD incidence.
11	This study explored whether SES modifies the association of PCE 10-year estimated risk
12	with actual ASCVD 10-year incidence using data from the Atherosclerosis Risk in Communities
13	(ARIC) study. That is, actual observed ASCVD 10-year incidence will vary depending on the
14	PCE estimated risk and the individual's SES. We defined SES along two dimensions typically
15	utilized in social epidemiology research: educational attainment and neighborhood deprivation. <sup>26</sup>
16	Educational attainment as a measure of individual SES was selected over other measures - e.g.,
17	income level – due to being a stable measure of SES that remain relatively stable over an adult
18	life course when compared to other measures. We hypothesize that the long-term effects of
19	proximate causes of ASCVD measured in the PCE (e.g., hypertension and smoking) impact on
20	actual ASCVD incidence are dependent on SES (i.e., risk modification).
21	Methods
22	Data Source

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Data obtained for our analyses came from the Atherosclerosis Risk in Communities (ARIC) study. In brief, the ARIC study is an ongoing prospective observational cohort study of 15,792 men and women age 45-64 years, recruited from population-based sampling from four communities in the United States-Forsyth County, North Carolina, Jackson, Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland.<sup>27</sup> The study was designed to investigate the development of cardiovascular disease across demographic subgroups. Follow-up has included seven in-person study visits to-date from the baseline visit in 1987-1989; surveillance of the cohort continues with annual telephone interviews and active surveillance of discharges from local hospitals. Institutional review boards at all ARIC centers approved study procedures, and participants give written informed consent at each visit.

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### 11 Study Population

We restricted our analysis to 11,374 ARIC participants who attended Visit 4 (1996-1998) to maintain an observational cohort that reflected similar temporal trends in ASCVD outcomes as the cohorts used to derive the PCE. We excluded Visit 4 participants with prevalent coronary heart disease (CHD) (N=1210), prior stroke (N=231), participants missing clinical variables for ASCVD risk assessment (N=155), and participants missing educational attainment information collected at study Visit 1 (N=12). Prevalent CHD was defined as self-reported or physician diagnoses of myocardial infarction at baseline and incident CHD occurring between baseline and Visit 4. We defined prevalent stroke as self-reported or physician diagnoses of stroke, transient ischemic attack, and stroke-like symptoms at baseline or hospitalization for a definite or probable stroke between baseline and Visit 4. Due to small numbers, we excluded Blacks in Minneapolis and Washington County (N=35). Three participants were excluded due to unclear incident ASCVD dates for a final sample of 9,728.

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### Individual-Level Covariate Measures

Trained staff administered in-home interviews that collected information on demographics, socioeconomic factors, lifestyle, and medical co-morbidities. Race, gender, and educational attainment were self-reported. We used the information on race, gender, and educational attainment collected at ARIC Visit 1; we used data on age and medical comorbidities collected during Visit 4 for our analyses.

We categorized smoking status as current or not current smokers. Hypertension was defined as having a systolic blood pressure of 140 mmHg or greater (mean of two measurements recorded at study visit), diastolic blood pressure 90 mmHg or greater (mean of two measurements recorded at study visit) or were taking antihypertensive medications. We classified diabetes as having a fasting blood glucose level ≥126 mg/dL, non-fasting blood glucose ≥200 mg/dL, use of anti-diabetic medications, or self-reported history of physician-diagnosed diabetes. We used total cholesterol and high-density lipoprotein (HDL) levels collected at Visit 4 to assess ASCVD risk. Pill bottle review, when available, was performed at every ARIC Visit to confirm medication use. Statin medication use at Visit 4 was self-reported or based on medications brought to the visit.

### 17 Socioeconomic Status Measures

18 We examined one individual and one neighborhood exposure of SES. We classified 19 educational level attainment into three categories: no high school degree, high school/some 20 college, or college graduate and above. The Area Deprivation Index (ADI) was used to analyze 21 neighborhood deprivation.<sup>28-30</sup> The ADI is a validated measure of neighborhood deprivation that 22 utilizes 17 different markers to measure area-level deprivation from 2000 census block group-

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level data. We used the participants' census tract according to the 9-digit zip code to assign ADI.
The ADI measures neighborhood deprivation along a continuum; higher values represent higher
levels of neighborhood deprivation. We stratified ADI into three categories according to
interquartile range. Levels chosen represent lowest (residing in the least deprived
neighborhoods), top (residing in the most deprived neighborhoods), and middle two ADI
quartiles.

7 Estimation of ASCVD Risk

8 We estimated individual ASCVD risk using the published PCE covariate parameters.<sup>15</sup> 9 The following factors were used to estimate ASCVD risk according to the PCE: age, gender, 10 race (Black or other), levels of total cholesterol, levels of high-density lipoprotein cholesterol 11 (HDL-C), systolic blood pressure, evidence of treatment for high blood pressure, diabetes status, 12 and current smoker status. We used laboratory measures collected at Visit 4 to estimate risk 13 using the PCE. We partitioned the ARIC study population into four categories of 10-year PCE 14 predicted ASCVD risk: 0%-5%, >5%-10%, >10%-15%, and >15%. BMJ Open: first published as 10.1136/bmjopen-2021-058777 on 7 November 2022. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES).

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### 15 Ascertainment of Myocardial Infarction and Stroke Outcomes

Hospital records were abstracted to identify hospitalizations for myocardial infarction and
stroke. CHD and stroke events were classified algorithmically and following physician review
and adjudication, as previously published.<sup>27,31</sup> Criteria for the incidence of definite or probable
myocardial infarction for the ARIC cohort were based on combinations of chest pain,
electrocardiographic changes, and cardiac enzyme levels during hospitalization. Classification
of events as fatal myocardial infarction was based on the following factors: cause of death on the
death certificate for both hospitalized or out of hospital deaths; and diagnoses at the time of

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hospitalization from medical records before death. The minimum criterion for definite or
probable stroke was evidence of sudden or rapid onset of neurological symptoms lasting >24
hours or leading to death, in the absence of a non-stroke etiology.<sup>27,32</sup> We included adjudicated
events that occurred within ten years of participants' Visit 4 date (from January 1, 1996, through
December 31, 2008) in our analysis.

### Statistical Analysis

7 Univariate descriptive statistics examined baseline participant-level characteristics. We 8 calculated the mean and standard deviation (SD) for continuous variables, percentages for 9 dichotomous variables, and median with interquartile range (IQR) for ordinal or nominal 10 variables. We performed bivariate analysis using Pearson's  $\chi^2$  test or Kruskal-Wallis test for 11 categorical data and a two-sample *t*-test for continuous variables.

The 10-year incidence rate for hospitalizations or death for coronary heart disease or stroke were estimated in subgroups defined by education attainment, ADI categories (interquartile range), and PCE risk categories (0%-5%, >5%-10%, >10%-15%, >15%).
Incidence rates are presented as per 1,000 person-years. Individual time at risk was measured from Visit 4 until an ASCVD event occurred or one of the censoring events (whichever came

17 first): death, loss to follow-up, or end of the observation period.

The absolute risk (AR) was calculated as crude cumulative incidence using the pseudovalues methodology, which accounted for competing risk of death for reasons other than death due to ASCVD.<sup>33</sup> We estimated absolute risk according to participant educational attainment and ADI, stratified by the PCE 10-year estimated risk category. We calculated risk ratios (RR) within each PCE predicted risk category comparing absolute risk across educational attainment Page 11 of 38

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1	levels and ADI categories. Absolute risk differences between SES measures were estimated for
2	each PCE 10-year estimated risk category (0%-5%, >5%-10%, >10%-15%, >15%). The
3	referent group for educational attainment level is a college degree or above, and the referent
0 4 1	group for ADI is residing in the least deprived neighborhoods (lowest ADI quartile). Point
2 3 4 5 6 6 7 8 7 9 0 8	estimates are reported with 95% confidence intervals (CI).
5 6 6	Generalized linear estimation models with a log-link function were used to predict the
7 87 9	probability of ASCVD events. The naïve model included only the PCE predicted risk score
	category as the predictor. To evaluate the effect of socioeconomic status on model fit statistics,
2 3 9	additional models included: 1) education category added as a predictor and interacted with the
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	PCE score, 2) ADI category added as a predictor and interacted with the PCE category, and 3)
7 11 8	both education and ADI categories as predictors and interacted with the PCE category.
	Generalized linear models compared took the following form:
1 2 13	(1) Prob(ASCVD) = $\beta_0 + \beta_1$ (i.Score)
1 13 2 13 3 4 14 6 14	(2) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_3(i.Education) + \beta_4(i.Score x i.Education)$
7 15	(3) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_2(i.ADI) + \beta_3(i.Score \ x \ i.ADI)$
8 9 16 0	(4) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_2(i.Education) + \beta_3(i.ADI) + \beta_4(i.Score x)$
1	i.Education) + $\beta_5$ (i.Score x i.ADI)
2 17 3 4 5 18 6 7 19 8	The likelihood ratio test, Akaike Information Criterion, and Bayesian Information Criterion
7 8 19	evaluations were performed to compare model fit statistics of the different models. All analyses
9 0 20	were performed using STATA, version 13.
1 2 3 21 4 5	Patient and Public Involvement

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1 Patients or the public were not involved in this specific research project.

### **Results**

Of 9,728 ARIC study participants, 1,764 (18%) did not have a high school education (Table 1). Participants with a 10-year predicted risk of ASCVD >15% were older, less likely to be male, and had more comorbid conditions such as diabetes or hypertension, and more likely to smoke. Increases in PCE estimated risk categories corresponded to a higher proportion of igh sen. participants without a high school degree or residing in the most deprived neighborhoods.

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Table 1. Participant Characteristics by 10-year	ASCVD Predicted Risk C	ategory*		21-0587 ght, inc		
Variable	$\frac{\text{All}}{(n = 9728)}$	0%-5% (n = 2383)	>5%-10% (n = 2652)	>108%-15% (n=1880)	>15% (n= 2813)	P-value
		Demogr	· · · ·	t z	,	
Age, mean (SD)	62.61 (5.65)	58.09 (3.29)	61.44 (4.76)	64.41 (\$19) 880749	66.61 (5.10)	< 0.00
Male, No. (%)	5728 (59)	2203 (92)	1656 (62)	8 <b>90 - 4 - - - - - - - - - -</b>	999 (36)	< 0.00
Race, No. (%)				- 0 ¥		
White	7528 (77)	2097 (76)	2027 (76)	14000000000000000000000000000000000000	2004 (71)	< 0.00
Black	2200 (23)	286 (12)	625 (24)	480323	809 (29)	0.00
Dinok		Clinical Co-			(-))	
Hypertension, No. (%)	3875 (40)	460 (19)	865 (33)	7 <b>8</b> 0 <b>24</b>	1770 (63)	< 0.001
Diabetes, No. (%)	1495 (15)	400 (19) 47 (2)	143 (5)		1077 (38)	< 0.00
Total Cholesterol, mean (SD), mg/dL	201.81 (36.48)	201.22 (35.14)	200.63 (36.17)	201. <b>52</b> 7( <b>3</b> ).91)	203.4 (37.56)	0.00
				48.5 <b>37 (18.</b> 73)		
HDL Cholesterol, mean (SD), mg/dL	50.84 (16.69)	60.11 (16.59)	50.88 (15.56)		44.48 (14.83)	< 0.00
Current Smoker, No. (%)	1431 (15)	147 (6)	332 (13)	3 3 MBES MININI	622 (22)	< 0.00
	0.17 (0)	Medicat			200 (11)	
Statin Use, No. (%)	845 (9)	138 (6)	232 (9)		298 (11)	< 0.00
		ARIC Fiel		- <u>-</u>		
Forsyth, NC, No. (%)	2343 (24)	603 (25)	642 (24)	AGR (25) 4AR (25) 4AR (25)	637 (23)	< 0.00
Jackson, MS, No. (%)	1955 (20)	256 (11)	570 (22)	4월4 (🔯)	705 (25)	
Minneapolis, MN, No. (%)	2902 (30)	892 (37)	777 (29)	551 (2)	722 (26)	
Washington County, MD, No. (%)	2529 (26)	632 (27)	663 (25)	484 (25)	749 (27)	
	( )		Risk Factors	4 4 5 4 7 4 7 4 7 4 7 4 7 7 9 7 9 7 9 7 9 7 9		
Educational Attainment				s. <mark>c</mark>		
College or Above, No. (%)	3843 (40)	1063 (45)	1097 (41)	707 (38)	976 (35)	< 0.00
High School/Some College, No. (%)	4110 (42)	1120 (47)	1132 (43)	7988 (48)	1080 (39)	
No High School, No. (%)	1764 (18)	199 (8)	419 (16)	395 (2)	751 (27)	
ADI, median (IQR) $^{\dagger}$	102 (96.3-108.8)	100 (93.8-104.9)	101.9 (96.1-108.9)	102.5 (6.9, 109.6)	103.2 (97.6-111.5)	< 0.00
Abbreviations: ADI, Area Deprivation In					() () () () () () () () () () () () () (	0.00
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2 *Risk categories estimated using the Pool				2025 gies		
3 <sup>†</sup> Area Deprivation Index measures area-le	evel social deprivation a	and estimated using	the census-tract of part	ticipants' 5- <b>d</b> igit zip c	ode; higher values	
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1	Incidence rates stratified by education level, ADI category and 10-year PCE estimated
2	risk category are shown in Table 2. A total of 751 incident ASCVD events occurred over ten
3	years of follow up. Mean follow-up was 9.28 years. As expected, 10-year ASCVD incidence
4	rates increased with increases in 10-year PCE estimated risk categories. Conditional on PCE
5	estimated risk category, incidence rates were higher for participants without a high school
6	education than participants with a high school education. Conditional on PCE estimated risk
7	category, incidence rates were higher for participants residing in the most deprived
8	neighborhoods than less deprived neighborhoods, except for participants with PCE estimated risk
9	of >5%-10%. Among participants without a high school degree, incidence rates for ASCVD
10	correlated with the 10-year PCE estimated risk categories. The relationship between 10-year
11	estimated ASCVD risk and observed incidence rates of ASCVD varied for all ADI categories
12	with <15% PCE estimated risk, with less variation for the degree of neighborhood deprivation
13	for participants at the highest PCE estimated risk category of $>15\%$ .
14 15 16 17 18 19 20 21 22	for participants at the highest PCE estimated risk category of >15%.

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Table 2. Event Co	ounts and In	cidence Rates Str	ratified by Predicted A	ASCVD, Ed	lucation, and Area	a Deprivation Index.		n-2021- ppyrigh	
ASCVD Predicted Risk*	Events	1,000 Person Years	Rate <sup>†</sup> Per 1,000 Person Years	Events	1,000 Person Years	Rate <sup>†</sup> Per 1,000 Person Years	Events	E000 Person E000 Person La Years Ngo High Schoo	Rate <sup>†</sup> Per 1,0 Person Year
Treater Hisk		College or A	Above		High School/Sor	ne College		Bo High Schoo	ol Degree
0%-5%	28	10.39	2.70	25	10.87	2.30	6	5° 🛓 94	3.09
>5%-10%	45	10.41	4.32	62	10.66	5.72	32	ஜ நத்91	8.19
>10%-15%	35	6.58	5.32	50	7.23	6.91	41	n be ss re	11.79
>15%	145	8.33	17.40	147	9.30	15.81	135	r uses related t	21.38
		Lowest ADI (			Middle Two AD				ıartile
0%-5%	19	9.68	1.96	24	8.29	2.89	16	to text and data mining, Al t	3.06
>5%-10%	56	8.52	6.57	33	8.27	3.99	49	a up e 23	5.96
>10%-15%	30	5.45	5.51	37	5.45	6.78	59	nd and a second se	9.24
>15%	119	6.62	17.96	127	7.80	16.29	181		18.92
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### Risk Modification Analysis

2	Within each PCE predicted risk category, we evaluated if SES modified the relationship
3	between PCE estimated risk and actual ASCVD 10-year observed incidence for each educational
4	attainment level and neighborhood deprivation (college-educated and least deprived
5	neighborhood as the referent) (Table 3). Large risk ratio differences (i.e., more than 10%) within
6	stratum-specific PCE estimated risk categories by SES indicates risk modification. We found
7	that the risk ratio was greater than 1 among those not having a high school degree for all PCE
8	estimated risk categories. This result indicated a heavier burden of ASCVD than in college-
9	educated participants independent of PCE estimated risk. This relative increase in ASCVD risk
10	was statistically significant for groups with >5%-10% and >10%-15% PCE estimated risk; risk
11	ratio 1.78 (95% CI; 1.16-2.76) and 2.15 (95% CI; 1.39-3.34) respectively. The risk of ASCVD
12	in the most deprived neighborhoods (referent least deprived neighborhoods) was significantly
13	higher only for the 10-year PCE estimated risk category >10%-15%, risk ratio 1.65 (95% CI;
14	1.05-2.59).
15	
16	1.05-2.39).
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		Education			لي تلفي المحمد المحم Area Deperivation Index			
10-Year ASCVD Predicted Risk <sup>‡</sup>	No High School RR (95% CI)	High School/Some College RR (95% CI)	College <sup>*</sup> or Above RR (95% CI)	Top ADI Quartile RR (95% CI)	or ح Middle Two ADI Quartin RR (95% 21)	Lowest <sup>†</sup> AD Quartile RR (95% Cl		
0%-5%	1.16 (0.48-1.53)	0.84 (0.46-1.53)	1.00	1.61 (0.76-3.38)	1.51 60 1.51	1.00		
>5%-10%	1.78 (1.16-2.76)	1.29 (0.86-1.93)	1.00	0.92 (0.65-1.32)	0.61 and c	1.00		
>10%-15%	2.15 (1.39-3.34)	1.30 (0.82-2.05)	1.00	1.65 (1.05-2.59)	data (ABEES) 1.22400 1.22400 1.224000 1.224000 1.22400000000000000000000000000000000000	1.00		
<ul> <li>2 *College or Ab</li> <li>3 *Lowest ADI as</li> </ul>	ove as referent. s the referent.	n Index; ASCVD, athero			0.93 (0.74,1.17) tio. tio. tio.			

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1	In analyses stratified by educational attainment and neighborhood deprivation,
2	participants without a high school degree who resided in the most deprived neighborhoods had a
3	higher risk of ASCVD for all 10-year PCE estimated risk categories than other SES groups
4	(Supplement Table 1). At 10-year PCE estimated risk categories of 0%-5% and >10%-15%,
5	having both individual and neighborhood measures of low-SES (without high school education
6	and residing in the most deprived neighborhood) meant a substantially higher risk of ASCVD
7	than either measure alone; risk ratio 3.64 (95% CI, 1.46-9.07) and 4.78 (95% CI, 1.62-14.09)
8	respectively.
9	Observed 10-year absolute risk is presented for each education category, and ADI
10	category across PCE estimated risk categories (Figure 1). We found heterogeneous differences
11	in absolute risk (i.e., risk modification) by SES within stratum-specific PCE estimated risk
12	categories. For example, the difference in absolute risk for participants without a high school
13	degree (referent college-educated) rose by 6 percentage points for PCE estimated risk of >10%-
14	15%; absolute risk difference decreased to 3.4 percentage points for PCE estimated risk >15%
15	(Supplement Figure 1). Heterogenous differences in absolute risk for ADI categories were also
16	noted, albeit smaller differences than educational attainment categories. Differences in absolute
17	risk for participants living in the most deprived neighborhoods (referent least deprived
18	neighborhoods) were 1.2 percentage points higher for PCE estimated risk of >5%-15%, and 1.6
19	percentage points higher for PCE estimated risk 10%-15%.
20	Socioeconomic Status Interaction with PCE Model Analysis

The coefficient for each SES risk factor's interactions with estimated risk categories was statistically significant, and model fit measures to estimate ASCVD risk improved (Table 4). For 

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1	example, the likelihood ratio test comparing models 1 and 4, which included education and ADI
2	categories, and their interaction with the PCE 10-year predicted ASCVD risk categories [Model
3	4: Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_2(i.Education) + \beta_3(i.ADI) + \beta_4(i.Score \ x \ i.Education) + \beta_4(i.Score \ x \ i.Educati$
4	$\beta_5(i.Score \ x \ i.ADI)$ ] demonstrated a statistically significant model improvement when measures
<u>s</u> 5	of SES was added as an interaction term with PCE estimated risk category ( <i>p</i> -value <0.0001).
6	Additionally, the Akaike information criterion was smaller, suggesting that educational
, 3 7	attainment measures and area deprivation improved model fit for predicting 10-year ASCVD
8	outcomes compared to the PCE predicted risk category alone.
2 3 9 4	
5 2 10	
3 9 11	outcomes compared to the PCE predicted risk category alone.
2 3 12	
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	Table 4. Comparison of models prediction	1094-05-87777 Om					
	Model	Number	Akaike <sup>*</sup> Information Criterion	Bayesian <sup>†</sup> Information Criterion	P-Value		
	PCE‡	9728	2371				
	i.PCE + i.Education <sup>§</sup>	9717	2366	2395 <b>tem</b>	0.004		
	(i.PCE)x(i.Education)	9717	2331	23/4 <del>c</del> 😐 :			
	i.PCE + i.ADI <sup>II</sup>	9728	2371	2400 <b>e</b> s	0.14		
	(i.PCE) x (i.ADI)	9728	2346	2389 and ie 2400 d	< 0.0001		
	i.PCE + i.Education + i.ADI	9717	2366	2400the superior238924092409da	0.002		
	(i.PCE) x (i.Education)x(i.ADI) Abbreviations: ADI, Area Deprivation	9717	2328	2458 🖬 🏹 =	<b>s</b> <0.0001		
5 7 3 9 9 1 2 3	model indicate an improvement in prediction. <sup>‡</sup> Pooled Cohort Equations predicted risk was stratified into 4 categories of risk: 0-5%; >5-10%; >10-15%; >15%. <sup>§</sup> Education was stratified into three categories: no high school; high school/some college; college or above (reference) <sup>§</sup> Higher Area Deprivation Index indicates higher neighborhood deprivation and was stratified into three categories are interquartile range: top ADI quartile; middle two ADI; lowest ADI quartile (referent) <sup>#</sup> All models that added in the social deprivation factor as a risk factor was compared to the Pooled Cohort Equations of the social deprivation as an interaction term was compared to the Pooled Cohort Equations of with social deprivation as an interaction term was compared to the Pooled Cohort Equations of with social deprivation added as a risk factor.						
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2	In the current study, we investigated whether SES's individual and neighborhood
3	measures modify the association between the PCE risk score and actual 10-year ASCVD
4	observed outcomes. We also described the excess burden of ASCVD events among low-SES
5	populations relative to high-SES populations conditional on PCE estimated risk. The PCE
6	estimated risk underestimated incidence of ASCVD events experienced among low-SES groups,
7	and absolute differences in risk among SES measures became most pronounced at higher PCE
8	predicted risk categories, indicating risk modification by measures of SES. Our results also
9	suggest that SES factors' value in predicting incident ASCVD events may vary by PCE predicted
10	risk levels.

A potential reason for the inconsistent evidence for SES's prognostic value to predict 10-year ASCVD outcomes could be the different outcome modeling strategies used in prior studies. Prior studies have historically modeled SES as an independent risk factor or confounder.<sup>19-22,24</sup> Classical social epidemiological frameworks such as the "fundamentals causes of health inequalities theory" suggest that despite any 10-year estimated risk of ASCVD for an individual at a given time, the clinical trajectory and outcomes are both influenced and dependent on the individual's SES.<sup>26,34-37</sup> According to the fundamental cause theory, high-SES individuals, possess a variety of flexible resources (i.e., knowledge, money, prestige, and power) to protect their health in a way that low-SES individuals cannot. As such, the effects of the non-SES traditional ASCVD risk factors used in the PCE (i.e., hypertension and total cholesterol) on ASCVD incidence will likely be modified by whether the individual is of lower or higher SES. Our results show that having at least a college-education was protective against ASCVD relative to not having a high school degree across all risk levels, with greater protective effects at higher

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PCE estimated risk levels. Living in the least deprived neighborhood was also protective, but
likely less consistently than an individual SES exposure measure due to the potential for the
ecological fallacy that can occur when making inferences about individuals based on group-level factors.

5 The substantial model fit improvement by interacting SES factors with the PCE risk score 6 suggests that this modeling strategy will significantly improve ASCVD outcome prediction 7 accuracy, but further analysis is required. Any 10-year ASCVD model that does not account for 8 SES as a risk modifier may lead to measurement error. Prior modeling studies and current 9 ASCVD risk models that incorporate SES into predicting risk do not incorporate SES as an 10 interaction term into the model.

The current PCE model estimates a graded ASCVD risk irrespective of SES status. Our results show that the PCE placed disadvantaged individuals with an inherently higher risk of ASCVD into the corresponding 10-year estimated ASCVD risk categories at the expense of over-estimating risk for higher SES individuals. At the very least, the PCE will direct ASCVD preventive care to our most disadvantaged populations. The same population for which research has shown is less likely to receive appropriate preventive measures.<sup>38-41</sup> However, our findings show that the PCE model may inadvertently lead to the inverse care law.<sup>42,43</sup> That is, high-SES individuals, when compared to low-SES individuals, will receive ASCVD prevention measures out of proportion of their actual need.

Additional research is needed to improve ASCVD risk prediction among different SES
 groups and prevent ASCVD among disadvantaged populations. Our data only allow us to
 describe these epidemiologic phenomena of excess ASCVD events experienced among lower

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SES individuals and possible ways to model future risk, but our analysis does not po identify underlying mechanisms. Many unknown factors exist along the socio-ecolo paradigm that works in concert with individual behavioral and physiologic factors to higher burden of ASCVD among low-SES populations. These findings have clinical and policy implications, with current guideline recommendations for using the PCE model to guide primary prevention ASCVD str cholesterol management, hypertension management, and aspirin use.<sup>16,18,44,45</sup> For ex estimated 10-year PCE risk of 7.5%, statin therapy is recommended for primary pre ASCVD.<sup>18</sup> We show that a higher SES is a risk-protecting factor, and the absolute r ASCVD does not cross the 7.5% threshold until a PCE 10-year risk of >15% (Figur of SES in estimating an individual's risk can potentially improve the efficiency of re-and more precisely target interventions to achieve population-level objectives to dec ASCVD burden globally and in the United States. However, without a validated AS prediction model that incorporates SES in the US, we don't advocate for the use of clinical decision of ASCVD preventive therapies for US patients.

16 Limitations

17 The study has several limitations. The ARIC study is restricted to 4 communities in the 18 United States and is not nationally or internationally representative. The measurement of 19 outcomes based on ARIC abstraction of hospitalization data is a strength since it avoids reliance 20 on self-report of events. However, some hospitalizations may be missing since comparing 21 Medicare claims to ARIC records showed that between 10% to 20% of hospitalizations are 22 missed if only one source is used.<sup>46</sup> Internal exploration of this issue suggested that the additiona

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hospitalizations were not correlated with our SES measures and did not substantively affect the
results.

Results from our area-level deprivation analyses must be considered in the context of analytical limitations. For example, the use of the ADI as an aggregate measure of SES can potentially introduce ecological fallacy bias. Furthermore, we did not account for possible movement to other neighborhoods for our sample over 10-years of follow up. A potential misclassification bias of area-level deprivation exposure may exist. We expect that this misclassification bias is likely small and non-differential, and our results are conservative estimates because bias from random measurement error is towards the null. Last, we didn't control for the ARIC study site in our area-level deprivation analyses. Without controlling for the ARIC study site, homogeneity in participant characteristics (i.e., a predominantly African-American/Black population versus a predominantly white population) by ARIC study site may have resulted in the loss of statistical power to detect a meaningful difference in ASCVD outcomes according to ADI.

### 15 Conclusions

16 The current study extends our understanding of the relationship between socioeconomic 17 factors and the risk of heart disease and stroke outcomes. We find that the associations of PCE 18 risk score and incident ASCVD are dependent on education level and area deprivation. Our 19 findings may partially explain the discrepancy in results from earlier studies evaluating the utility 20 of adding SES as a prognostic measure into ASCVD prediction models. Given the potentially 21 important clinical and policy implications of our results, we suggest further refinement of the

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2		
3 4	1	PCE model is needed to improve the estimation of risk among historically vulnerable and less
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39 40	16	Institutional review boards at all ARIC centers in the United States approved study procedures.
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43 44 45	18	study was approved by the University of North Carolina at Chapel Hill Institutional Review
46 47	19	Board (IRB# 18-1187).
48 49 50	20	
50 51 52	21	
53 54 55 56 57 58	22	Contributors

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KH, PC, and SS initiated the project. JR and BK performed all statistical analyses. KH had main responsibility for writing the manuscript. KH, PC, SS, JR, BK, RF, CS and MH all contributed to the statistical analyses, interpretation of outcomes, and provided comments on the manuscript. KH, PC, SS, JR, BK, RF, CS and MH all read and approved the final manuscript. PC is the senior author. Data Sharing Statement No additional data are available References 1. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sexspecific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736-1788. 2. Heron M. Deaths: Leading Causes for 2015. Natl Vital Stat Rep. 2017;66(5):1-76. Heron M. Deaths: Leading Causes for 2016. Natl Vital Stat Rep. 2018;67(6):1-77. 3. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 4. Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56e528. Diez Roux AV, Merkin SS, Arnett D, et al. Neighborhood of residence and incidence of 5. coronary heart disease. The New England journal of medicine. 2001;345(2):99-106. Brown AF, Liang LJ, Vassar SD, et al. Neighborhood disadvantage and ischemic stroke: 6. the Cardiovascular Health Study (CHS). Stroke. 2011;42(12):3363-3368. Addo J, Averbe L, Mohan KM, et al. Socioeconomic status and stroke: an updated 7. review. Stroke. 2012;43(4):1186-1191. Grimaud O, Bejot Y, Heritage Z, et al. Incidence of stroke and socioeconomic 8. neighborhood characteristics: an ecological analysis of Dijon stroke registry. Stroke. 2011:42(5):1201-1206. Rao SV, Kaul P, Newby LK, et al. Poverty, process of care, and outcome in acute 9. coronary syndromes. Journal of the American College of Cardiology. 2003;41(11):1948-1954. 10. Spatz ES, Beckman AL, Wang Y, Desai NR, Krumholz HM. Geographic Variation in Trends and Disparities in Acute Myocardial Infarction Hospitalization and Mortality by Income Levels, 1999-2013. JAMA Cardiol. 2016;1(3):255-265. Kucharska-Newton AM, Harald K, Rosamond WD, Rose KM, Rea TD, Salomaa V. 11. Socioeconomic indicators and the risk of acute coronary heart disease events: comparison of population-based data from the United States and Finland. Annals of epidemiology. 2011;21(8):572-579.

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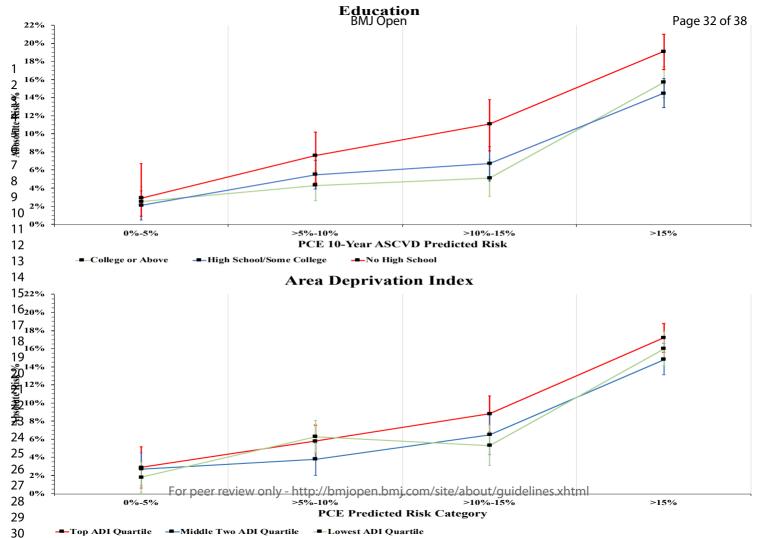
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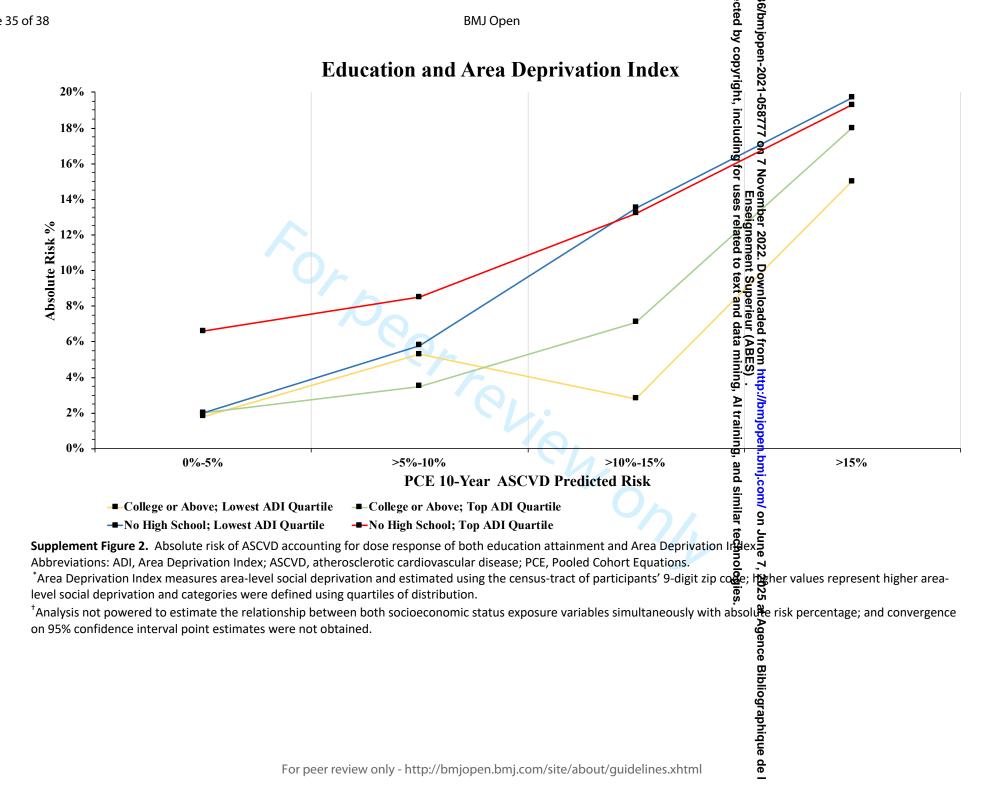
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	PCE Risk Category	Absolute Risk % (95% Cl)	Absolute Risk % Difference (College or Above Refe
No High School	0%-5%	2.9% (0.9%-6.7%)	<b>•</b> • • •
	>5%-10%	7.6% (5.0%-10.2%)	0.4%
	>10%-15%	11.1% (8.4%-13.8%)	6.0%
	>15%	19.1% (17.1%-21.0%)	3.4%
			Г
High School/Some Colleg	9 <b>e</b> 0%-5%	2.1% (0.5%-3.7%)	-0.4%
	>5%-10%	5.5% (3.9%-7.1%)	1.2%
	>10%-15%	6.7% (4.8%-8.6%)	1.6%
	>15%	14.5% (12.9%-16.1%)	-1.2%
College or Above	0%-5%	2.5% (0.9%-4.2%)	
	>5%-10%	4.3% (2.6%-5.9%)	Referent
	>10%-15%	5.1% (3.1%-7.2%)	
	>15%	15.7% (14.0%-17.4%)	
	Are	a Deprivation Inc	
	PCE Risk Category	Absolute Risk % (95% Cl)	Absolute Risk % Difference (Lowest ADI Quartile as Referent)
Top ADI Quartile	0%-5%	2.9% (0.6%-5.2%)	1.1%
	>5%-10%	5.8% (4.0%-7.6%)	-0.5%
	>10%-15%	8.8% (6.8%-10.8%)	3.5%
	>15%	17.2% (15.6%-18.8%)	1.2%
Median ADI Quartile	0%-5%	2.7% (0.9%-4.5%)	0.9%
	>5%-10%	3.8% (2.0%-5.6%)	-2.5%
	>10%-15%	6.5% (4.3%-8.7%)	1.2
	>15%	14.8% (13.1%-16.6%)	-1.2%
Lowest ADI Quartile	0%-5%	1.8% (0.1%-3.5%)	
	>5%-10%	6.3% (4.5%-8.1%)	Referent
	>10%-15%	5.3% (3.1%-7.6%)	
	>15%	16.0% (14.1%-17.9%)	
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						10-Year ASCV	D Predicted	Risk		, including	1	
		0%-5%			0%-5%		. <u> </u>	>10%-15%	6		×15%	
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No High School*	3.64 (1.46- 9.07)			1.59 (0.92- 2.76)	1.18 (0.51- 2.72)	1.10 (0.35- 3.48)	4.78 (1.62- 14.09)	1.88 (0.69- 5.15)	4.93 (1.94- 12.50)	Superieur (ABES) . 1.2%Gatamining, Alga 0.94(0.177) 0.94(0.177) 0.94(0.177)	1.22 (0.84- 1.77)	1.31 (0.85- 2.02)
High School/Some College	1.23 (0.43- 3.54)	1.23 (0.49- 3.09)	1.07 (0.39- 2.92)	1.04 (0.58- 1.88)	0.69 (0.36- 1.32)	1.48 (0.87- 2.53)	2.28 (0.89- 5.82)	2.48 (0.95- 6.47)	2.52 (0.97- 6.52)	S) . ning, Alg- 0.9 Alg- 1.3 Aning, and 1.2 Conv 1.2 Conv 1.3 Aning, and 1.2 Conv 1.4 Conv 1.4 Conv 1.6 March 1.2 Conv	0.90 (0.65- 1.26)	1.08 (0.75- 1.54)
College or Above	1.08 (0.30- 3.87)	2.33 (0.94- 5.75)	1.00	0.66 (0.28- 1.53)	0.62 (0.28- 1.36)	1.00	2.59 (1.00- 6.70)	2.48 (0.97- 6.36)	1.00	ເຊິ່, a 1.280 (0.85 1.690 1.690 1.690	- /	1.00

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		STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cont studies 은 것	
Section/Topic	ltem #	Recommendation	Reported on page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was done and what	2-3
Introduction		aneme ated	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods		all	
Study design	4	Present key elements of study design early in the paper	5-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure file w-up, and data collection	5-9
Participants	6	( <i>a</i> ) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifies. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	11-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-11
		(b) Describe any methods used to examine subgroups and interactions	9-11
		(c) Explain how missing data were addressed	9-11
		(d) If applicable, explain how loss to follow-up was addressed	Na (only used participants witho missing).

ResultsParticipants13*	(e) Describe any sensitivity analyses       5         (e) Describe any sensitivity analyses       5         (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	11-12
Participants 13*		11-12
	eligible, included in the study, completing follow-up, and analysed	
	(b) Give reasons for non-participation at each stage	11-12
	(c) Consider use of a flow diagram	No (discussed in
	(c) Consider use of a flow diagram	text)
Descriptive data 14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information $b$	11-12
	(b) Indicate number of participants with missing data for each variable of interest	na
	(b) Indicate number of participants with missing data for each variable of interest       Image: Construction of participants with missing data for each variable of interest         (c) Summarise follow-up time (eg, average and total amount)       Image: Construction of participants with missing data for each variable of interest         Report numbers of outcome events or summary measures over time       Image: Construction of participants with missing data for each variable of interest	8, 25
Outcome data 15*	Report numbers of outcome events or summary measures over time $a > b$	25-26
Main results 16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their preside (eg, 95% confidence	8-10; 22-23
	interval). Make clear which confounders were adjusted for and why they were included	
	(b) Report category boundaries when continuous variables were categorized	8-11
	(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaning fur period	21, 23
Other analyses 17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion	an bi	
Key results 18	Summarise key results with reference to study objectives	11
Limitations		
Interpretation 20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability 21		11-14
Other information	Discuss the generalisability (external validity) of the study results	
Funding 22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on	15
	which the present article is based	

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39 of 38	BMJ Open <b>bte:</b> An Explanation and Elaboration article discusses each checklist item and gives methodological background and published	njopen-2021
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# Socioeconomic Status and Modification of Atherosclerotic Cardiovascular Disease Risk Prediction: epidemiological analysis using data from the Atherosclerosis Risk in Communities Study

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Keywords:	PREVENTIVE MEDICINE, Cardiac Epidemiology < CARDIOLOGY, SOCIAL MEDICINE, Coronary heart disease < CARDIOLOGY, EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES

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# Socioeconomic Status and Modification of Atherosclerotic Cardiovascular Disease Risk Prediction: epidemiological analysis using data from the Atherosclerosis Risk in **Communities Study** First Author: Henderson Short Title: Socioeconomic Status and Cardiovascular Disease Risk Prediction Authors: Kamal H. Henderson, MD MSc<sup>1,2</sup>; Brystana G. Kaufman, Ph.D. MSPH<sup>3</sup>; Jason S. Rotter, Ph.D. MHS<sup>4</sup>; Sally C. Stearns, Ph.D.<sup>5</sup>; Carla A. Sueta, MD, Ph.D.<sup>6</sup>; Randi E. Foraker, Ph.D.<sup>7,8</sup>; Michael Ho, MD, Ph.D.<sup>1,2</sup>; Patricia P. Chang, MD, MHS<sup>9</sup> Author Affiliations: Rocky Mountain Regional Veteran Affairs Medical Center<sup>1</sup>; University of Colorado School of Medicine<sup>2</sup>; Department of Population Health Sciences, Duke University<sup>3</sup>; Mathematica Policy Research, Washington D.C.4; Department of Health Policy and Management, University of North Carolina at Chapel Hill (UNC-CH) Gillings School of Global Public Health<sup>5</sup>; UNC School of Medicine<sup>7</sup>; Division of General Medical Sciences, Washington University School of Medicine<sup>7</sup>; Brown School of Public Health<sup>8</sup>; UNC School of Medicine<sup>9</sup>. **Corresponding Author:** Kamal H Henderson Rocky Mountain Regional VA Medical Center 1700 N Wheeling St Aurora, CO 80045 Fax: 303-393-2826 Telephone: 720-723-6072 Email: kamal.henderson@cuanschutz.edu **Total Word Count: 3,882**

# Abstract

**Objective:** Examine whether the relationship between the Pooled Cohort Equations (PCE) predicted 10-year risk for atherosclerotic cardiovascular disease (ASCVD) and absolute risk for ASCVD is modified by socioeconomic status (SES).

**Design:** Population-based longitudinal cohort study –Atherosclerosis Risk in Communities (ARIC) – investigating the development of cardiovascular disease across demographic subgroups.

Setting: Four communities in the United States– Forsyth County, North Carolina, Jackson,
Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland.
Participants: We identified 9,782 ARIC men and women aged 54-73 without ASCVD at study visit 4 (1996-1998).

**Primary outcome measures:** Risk ratio (RR) differences in 10-year incident hospitalizations or death for ASCVD by SES and PCE predicted 10-year ASCVD risk categories to assess for risk modification. SES measures included educational attainment and census-tract neighborhood deprivation using the Area Deprivation Index. PCE risk categories were 0%-5%, >5%-10%, >10%-15%, and >15%. SES as a prognostic factor to estimate ASCVD absolute risk categories was further investigated as an interaction term with the PCE.

**Results:** ASCVD risk ratios for participants without a high school education (referent collegeeducated) increased at higher PCE estimated risk categories and was consistently >1. Results indicate education is both a risk modifier and delineates populations at higher ASCVD risk independent of PCE. Neighborhood deprivation did modify association but was less consistent in direction of effect. However, for participants residing in the most deprived neighborhoods (referent least deprived neighborhoods) with a PCE estimated risk >10%-15%, risk was significantly elevated (RR 1.65 [95% CI; 1.05-2.59]). Education and neighborhood deprivation inclusion as an interaction term on the PCE risk score was statistically significant (Likelihood ratio  $P \le 0.0001$ ).

**Conclusions:** SES modifies the association between PCE estimated risk and absolute risk of ASCVD. SES added into ASCVD risk prediction models as an interaction term may improve our ability to predict absolute ASCVD risk among socially disadvantaged populations.

# Strengths and limitations of the study:

- Population-based prospective cohort with over three decades of follow-up data to investigate the development of cardiovascular disease across demographic subgroups are major strengths of this study.
- Hospitalizations for coronary heart disease and stroke hospitalizations an outcome measured – was based on the Atherosclerosis Risk in Communities abstraction of hospital data, and some hospitalizations may be missing.
- A potential misclassification bias of area-level deprivation exposure possibly exists due to not accounting for Atherosclerosis Risk in Communities participants moving to different neighborhoods with a different degree of area-level deprivation exposure.

#### BMJ Open

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and morbidity in the United States (US) and globally.<sup>[[1], 2-4]</sup> A substantially higher burden of ASCVD is experienced among those with lower socioeconomic status (SES).<sup>[5-14]</sup> The Pooled Cohort Equations (PCE) are currently recommended in the US to estimate the 10-year risk of ASCVD and guide primary prevention treatment decisions.<sup>[15-18]</sup> The PCE does not currently account for SES factors such as educational attainment or neighborhood deprivation. However, SES measures may have prognostic value in predicting ASCVD outcomes and identifying populations in greatest need of primary ASCVD prevention. Existing evidence regarding the prognostic value of controlling for SES in ASCVD prediction models is mixed. A recent analysis showed that PCE overestimated ASCVD risk among low SES populations, but including SES measures such as household income or educational attainment in the PCE model did not improve model calibration.<sup>[19]</sup> Conversely, prior research evaluating the use of SES measures, such as household income or neighborhood deprivation, with the Framingham Risk Score that estimates coronary heart disease risk only, showed that such measures improved model fit statistics.<sup>[20-22]</sup> The latter findings eventually led to ASCVD risk models, such as QRISK2, primarily used in the United Kingdom that incorporate the Townsend deprivation score, a neighborhood measure of deprivation.<sup>[23-25]</sup> Such discrepancies have important implications globally and for the US, creating uncertainty regarding the importance of incorporating SES into ASCVD risk prediction models and the value of SES as a marker to identify individuals in need of additional ASCVD primary prevention interventions and services.

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1	How prior ASCVD prediction models incorporated SES into the model is a potential
2	reason for the discrepancies in understanding the prognostic value and use of SES in ASCVD
3	prediction models. SES traditionally is modeled as an independent risk factor or confounder. <sup>[19-22,</sup>
4	<sup>24]</sup> However, SES's prognostic value in predicting ASCVD risk is likely identifying populations
5	most impacted by proximate causes of ASCVD. If true, SES incorporated into risk prediction
6	models as a risk modifier is more appropriate in determining ASCVD risk than an independent
7	risk factor. For example, the health impact of hypertension over 10-years is different for an
8	individual living in abject poverty versus an individual residing in an affluent neighborhood.
9	SES likely modifies the association between risk estimated from algorithms that use proximate
10	causes of ASCVD (i.e., hypertension and smoking) and actual ASCVD incidence.
11	This study explored whether SES modifies the association of PCE 10-year estimated risk
12	with actual ASCVD 10-year incidence using data from the Atherosclerosis Risk in Communities
13	(ARIC) study. That is, actual observed ASCVD 10-year incidence will vary depending on the
14	PCE estimated risk and the individual's SES. We defined SES along two dimensions typically
15	utilized in social epidemiology research: educational attainment and neighborhood
16	deprivation. <sup>[26]</sup> Educational attainment as a measure of individual SES was selected over other
17	measures – e.g., income level – due to being a stable measure of SES that remain relatively
18	stable over an adult life course when compared to other measures. We hypothesize that the long-
19	term effects of proximate causes of ASCVD measured in the PCE (e.g., hypertension and
20	smoking) impact on actual ASCVD incidence are dependent on SES (i.e., risk modification).
21	Methods
22	Data Source

#### **BMJ** Open

Data obtained for our analyses came from the Atherosclerosis Risk in Communities (ARIC) study. In brief, the ARIC study is an ongoing prospective observational cohort study of 15,792 men and women age 45-64 years, recruited from population-based sampling from four communities in the United States-Forsyth County, North Carolina, Jackson, Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland.<sup>[27]</sup> The study was designed to investigate the development of cardiovascular disease across demographic subgroups. Follow-up has included seven in-person study visits to-date from the baseline visit in 1987-1989; surveillance of the cohort continues with annual telephone interviews and active surveillance of discharges from local hospitals. Institutional review boards at all ARIC centers approved study procedures, and participants give written informed consent at each visit.

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# 11 Study Population

We restricted our analysis to 11,374 ARIC participants who attended Visit 4 (1996-1998) to maintain an observational cohort that reflected similar temporal trends in ASCVD outcomes as the cohorts used to derive the PCE. We excluded Visit 4 participants with prevalent coronary heart disease (CHD) (N=1210), prior stroke (N=231), participants missing clinical variables for ASCVD risk assessment (N=155), and participants missing educational attainment information collected at study Visit 1 (N=12). Prevalent CHD was defined as self-reported or physician diagnoses of myocardial infarction at baseline and incident CHD occurring between baseline and Visit 4. We defined prevalent stroke as self-reported or physician diagnoses of stroke, transient ischemic attack, and stroke-like symptoms at baseline or hospitalization for a definite or probable stroke between baseline and Visit 4. Due to small numbers, we excluded Blacks in Minneapolis and Washington County (N=35). Three participants were excluded due to unclear incident ASCVD dates for a final sample of 9,728.

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Individual-Level Covariate Measures

Trained staff administered in-home interviews that collected information on demographics, socioeconomic factors, lifestyle, and medical co-morbidities. Race, gender, and educational attainment were self-reported. We used the information on race, gender, and educational attainment collected at ARIC Visit 1; we used data on age and medical comorbidities collected during Visit 4 for our analyses.

We categorized smoking status as current or not current smokers. Hypertension was defined as having a systolic blood pressure of 140 mmHg or greater (mean of two measurements recorded at study visit), diastolic blood pressure 90 mmHg or greater (mean of two measurements recorded at study visit) or were taking antihypertensive medications. We classified diabetes as having a fasting blood glucose level ≥126 mg/dL, non-fasting blood glucose ≥200 mg/dL, use of anti-diabetic medications, or self-reported history of physician-diagnosed diabetes. We used total cholesterol and high-density lipoprotein (HDL) levels collected at Visit 4 to assess ASCVD risk. Pill bottle review, when available, was performed at every ARIC Visit to confirm medication use. Statin medication use at Visit 4 was self-reported or based on medications brought to the visit.

17 Socioeconomic Status Measures

18 We examined one individual and one neighborhood exposure of SES. We classified 19 educational level attainment into three categories: no high school degree, high school/some 20 college, or college graduate and above. The Area Deprivation Index (ADI) was used to analyze 21 neighborhood deprivation.<sup>[28-30]</sup> The ADI is a validated measure of neighborhood deprivation that 22 utilizes 17 different markers to measure area-level deprivation from 2000 census block group-

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level data. We used the participants' census tract according to the 9-digit zip code to assign ADI.
The ADI measures neighborhood deprivation along a continuum; higher values represent higher
levels of neighborhood deprivation. We stratified ADI into three categories according to
interquartile range. Levels chosen to represent lowest (residing in the least deprived
neighborhoods), top (residing in the most deprived neighborhoods), and middle two ADI
quartiles.

7 Estimation of ASCVD Risk

8 We estimated individual ASCVD risk using the published PCE covariate parameters.<sup>[15]</sup> 9 The following factors were used to estimate ASCVD risk according to the PCE: age, gender, 10 race (Black or other), levels of total cholesterol, levels of high-density lipoprotein cholesterol 11 (HDL-C), systolic blood pressure, evidence of treatment for high blood pressure, diabetes status, 12 and current smoker status. We used laboratory measures collected at Visit 4 to estimate risk 13 using the PCE. We partitioned the ARIC study population into four categories of 10-year PCE 14 predicted ASCVD risk: 0%-5%, >5%-10%, >10%-15%, and >15%. BMJ Open: first published as 10.1136/bmjopen-2021-058777 on 7 November 2022. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES).

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# 15 Ascertainment of Myocardial Infarction and Stroke Outcomes

Hospital records were abstracted to identify hospitalizations for myocardial infarction and
stroke. CHD and stroke events were classified algorithmically and following physician review
and adjudication, as previously published.<sup>[27, 31]</sup> Criteria for the incidence of definite or probable
myocardial infarction for the ARIC cohort were based on combinations of chest pain,
electrocardiographic changes, and cardiac enzyme levels during hospitalization. Classification
of events as fatal myocardial infarction was based on the following factors: cause of death on the
death certificate for both hospitalized or out of hospital deaths; and diagnoses at the time of

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hospitalization from medical records before death. The minimum criterion for definite or
probable stroke was evidence of sudden or rapid onset of neurological symptoms lasting >24
hours or leading to death, in the absence of a non-stroke etiology.<sup>[27, 32]</sup> We included adjudicated
events that occurred within ten years of participants' Visit 4 date (from January 1, 1996, through
December 31, 2008) in our analysis.

## Statistical Analysis

7 Univariate descriptive statistics examined baseline participant-level characteristics. We 8 calculated the mean and standard deviation (SD) for continuous variables, percentages for 9 dichotomous variables, and median with interquartile range (IQR) for ordinal or nominal 10 variables. We performed bivariate analysis using Pearson's  $\chi^2$  test or Kruskal-Wallis test for 11 categorical data and a two-sample *t*-test for continuous variables.

The 10-year incidence rate for hospitalizations or death for coronary heart disease or
stroke were estimated in subgroups defined by education attainment, ADI categories
(interquartile range), and PCE risk categories (0%-5%, >5%-10%, >10%-15%, >15%).
Incidence rates are presented as per 1,000 person-years. Individual time at risk was measured
from Visit 4 until an ASCVD event occurred or one of the censoring events (whichever came

18 The absolute risk (AR) was calculated as crude cumulative incidence using the pseudo-19 values methodology, which accounted for competing risk of death for reasons other than death 20 due to ASCVD.[33] We estimated absolute risk according to participant educational attainment 21 and ADI, stratified by the PCE 10-year estimated risk category. We calculated risk ratios (RR) 22 within each PCE predicted risk category comparing absolute risk across educational attainment

first): death, loss to follow-up, or end of the observation period.

1	levels and ADI categories. Absolute risk differences between SES measures were estimated for
2	each PCE 10-year estimated risk category (0%-5%, >5%-10%, >10%-15%, >15%). The
3	referent group for educational attainment level is a college degree or above, and the referent
4	group for ADI is residing in the least deprived neighborhoods (lowest ADI quartile). Point
5	estimates are reported with 95% confidence intervals (CI).
6	Generalized linear estimation models with a log-link function were used to predict the
7	probability of ASCVD events. The naïve model included only the PCE predicted risk score
8	category as the predictor. To evaluate the effect of socioeconomic status on model fit statistics,
9	additional models included: 1) education category added as a predictor and interacted with the
10	PCE score, 2) ADI category added as a predictor and interacted with the PCE category, and 3)
11	both education and ADI categories as predictors and interacted with the PCE category.
12	Generalized linear models compared took the following form:
13	(1) Prob(ASCVD) = $\beta_0 + \beta_1$ (i.Score)
14	(2) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_3(i.Education) + \beta_4(i.Score x i.Education)$
15	(3) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_2(i.ADI) + \beta_3(i.Score x i.ADI)$
16	(4) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_2(i.Education) + \beta_3(i.ADI) + \beta_4(i.Score x)$
17	i.Education) + $\beta_5$ (i.Score x i.ADI)
18	The likelihood ratio test, Akaike Information Criterion, and Bayesian Information Criterion
19	evaluations were performed to compare model fit statistics of the different models. All analyses
20	were performed using STATA, version 13.
21	Patient and Public Involvement

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1 Patients or the public were not involved in this specific research project.

# **Results**

Of 9,728 ARIC study participants, 1,764 (18%) did not have a high school education (Table 1). Participants with a 10-year predicted risk of ASCVD >15% were older, less likely to be male, and had more comorbid conditions such as diabetes or hypertension, and more likely to smoke. Increases in PCE estimated risk categories corresponded to a higher proportion of igh sen. participants without a high school degree or residing in the most deprived neighborhoods.

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Table 1. Participant Characteristics by 10-year A	ASCVD Predicted Risk C	ategory*		21-0587 ght, inc		
Variable	$\frac{\text{All}}{(n = 9728)}$	0%-5% (n = 2383)	>5%-10% (n = 2652)	>108%-15% (n= 1880)	>15% (n= 2813)	P-value
	,	Demog	· · · ·	to 7	( )	
Age, mean (SD)	62.61 (5.65)	58.09 (3.29)	61.44 (4.76)	64.41 (\$19) 880745	66.61 (5.10)	< 0.00
Male, No. (%)	5728 (59)	2203 (92)	1656 (62)	8 <b>907</b> ,4 <b>3</b> 5)	999 (36)	< 0.00
Race, No. (%)				- 0 ¥		
White	7528 (77)	2097 (76)	2027 (76)	14200; (255)	2004 (71)	< 0.00
Black	2200 (23)	286 (12)	625 (24)		809 (29)	
	2200 (20)	Clinical Co-		to Pi		
Hypertension, No. (%)	3875 (40)	460 (19)	865 (33)	7 <b>802</b>	1770 (63)	< 0.001
Diabetes, No. (%)	1495 (15)	47 (2)	143 (5)		1077 (38)	< 0.001
Total Cholesterol, mean (SD), mg/dL	201.81 (36.48)	201.22 (35.14)	200.63 (36.17)	201.527 (35.91)	203.4 (37.56)	0.034
HDL Cholesterol, mean (SD), mg/dL	50.84 (16.69)	. ,	· · · · · ·	48.5 <b>3 18</b> 73)	44.48 (14.83)	< 0.032
		60.11 (16.59)	50.88 (15.56)			
Current Smoker, No. (%)	1431 (15)	147 (6)	332 (13)	3 3 MBES MININI	622 (22)	< 0.00
	0.45 (0)	Medicat			209(11)	-0.00
Statin Use, No. (%)	845 (9)	138 (6)	232 (9)	ĮĮ Ž	298 (11)	< 0.00
		ARIC Fie				
Forsyth, NC, No. (%)	2343 (24)	603 (25)	642 (24)	AGA (25) 4AAA (25) 4AAA (25)	637 (23)	< 0.00
Jackson, MS, No. (%)	1955 (20)	256 (11)	570 (22)	424 (28)	705 (25)	
Minneapolis, MN, No. (%)	2902 (30)	892 (37)	777 (29)	5,51 (2)	722 (26)	
Washington County, MD, No. (%)	2529 (26)	632 (27)	663 (25)	4 <b>8</b> 4 (25)	749 (27)	
		Social-F	Risk Factors	4 4 5 月 月 3 4 8 4 8 4 8 4 8 1 6 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1 9 1		
Educational Attainment				<u>v</u> . <u>q</u>		
College or Above, No. (%)	3843 (40)	1063 (45)	1097 (41)	7027 (33)	976 (35)	< 0.00
High School/Some College, No. (%)	4110 (42)	1120 (47)	1132 (43)	7 <b>%</b> 8 (4 <b>8</b> )	1080 (39)	
No High School, No. (%)	1764 (18)	199 (8)	419 (16)	3 <b>§</b> 5 (2 <u>4</u> )	751 (27)	
ADI, median $(IQR)^{\dagger}$	102 (96.3-108.8)	100 (93.8-104.9)	101.9 (96.1-108.9)	102.5 <b>@</b> 6.9 <b>6</b> 109.6)	103.2 (97.6-111.5)	< 0.00
Abbreviations: ADI, Area Deprivation Ir	ndex; ASCVD, atherosc	clerotic cardiovascul	lar disease; HDL, high-	-density gipoprotein.		
2 *Risk categories estimated using the Pool				202 Jgie		
		1 1 .	.1		1 1 1 1 1	
3 <sup>†</sup> Area Deprivation Index measures area-le	—	and estimated using	the census-tract of par	ticipants' 5- <b>q</b> igit zip c	ode; higher values	
4 represent higher area-level social deprivation	tion.			Ag		
5				en		
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3 4 5	1
6 7	2
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<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> <li>52</li> <li>53</li> <li>54</li> <li>55</li> <li>56</li> <li>57</li> <li>58</li> <li>59</li> <li>60</li> </ul>	14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29

1	Incidence rates stratified by education level, ADI category and 10-year PCE estimated
2	risk category are shown in Table 2. A total of 751 incident ASCVD events occurred over ten
3	years of follow up. Mean follow-up was 9.28 years. As expected, 10-year ASCVD incidence
4	rates increased with increases in 10-year PCE estimated risk categories. Conditional on PCE
5	estimated risk category, incidence rates were higher for participants without a high school
6	education than participants with a high school education. Conditional on PCE estimated risk
7	category, incidence rates were higher for participants residing in the most deprived
8	neighborhoods than less deprived neighborhoods, except for participants with PCE estimated risk
9	of >5%-10%. Among participants without a high school degree, incidence rates for ASCVD
10	correlated with the 10-year PCE estimated risk categories. The relationship between 10-year
11	estimated ASCVD risk and observed incidence rates of ASCVD varied for all ADI categories
12	with <15% PCE estimated risk, with less variation for the degree of neighborhood deprivation
13	for participants at the highest PCE estimated risk category of $>15\%$ .
14 15 16 17 18 19 20 21 22	for participants at the highest PCE estimated risk category of >15%.

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Table 2. Event Co	ounts and In	cidence Rates Str	atified by Predicted A	ASCVD, Ed	lucation, and Area	a Deprivation Index.		ר-2021- pyrigh	
ASCVD Predicted Risk*	Events	1,000 Person Years	Rate <sup>†</sup> Per 1,000 Person Years	Events	1,000 Person Years	Rate <sup>†</sup> Per 1,000 Person Years	Events	5006 Person	Rate <sup>†</sup> Per 1,0 Person Year
TT curcicu Tuşk		College or A	Above		High School/Son	ne College		E Years So High Schoo	ol Degree
0%-5%	28	10.39	2.70	25	10.87	2.30	6	5 <del>2</del> 94	3.09
>5%-10%	45	10.41	4.32	62	10.66	5.72	32	<b>б ш б</b> 91	8.19
>10%-15%	35	6.58	5.32	50	7.23	6.91	41	n <b>be</b> srei srei	11.79
>15%	145	8.33	17.40	147	9.30	15.81	135	r uses related to	21.38
		Lowest ADI (			Middle Two AD				uartile
0%-5%	19	9.68	1.96	24	8.29	2.89	16		3.06
>5%-10%	56	8.52	6.57	33	8.27	3.99	49	st and cat and	5.96
>10%-15%	30	5.45	5.51	37	5.45	6.78	59	nd arieu	9.24
>15%	119	6.62	17.96	127	7.80	16.29	181	data mir	18.92
4 <sup>†</sup> Incidence 1 5 <sup>‡</sup> Area Depr	ories were rate of com ivation Ind	estimated using bined stroke an ex measures are	the Pooled Cohort d coronary heart di a-level social depri	Equations sease was o vation and	estimated over t estimated using	en years. g the census-tract o		<b>=.</b> ¥	code; higher va
<ul> <li>3 *Risk categ</li> <li>4 †Incidence</li> <li>5 *Area Depr</li> </ul>	ories were rate of com ivation Ind	estimated using bined stroke an ex measures are	the Pooled Cohort d coronary heart di	Equations sease was o vation and	estimated over t estimated using	en years. g the census-tract o		nts 9- gigit zip c	code; higher va
<ul> <li>3 *Risk categ</li> <li>4 †Incidence n</li> <li>5 *Area Deprin</li> <li>6 represent his</li> <li>7</li> </ul>	ories were rate of com ivation Ind	estimated using bined stroke an ex measures are	the Pooled Cohort d coronary heart di a-level social depri	Equations sease was o vation and	estimated over t estimated using	en years. g the census-tract o		m <mark>j</mark> igit zip c m <mark>9</mark> pen.bmj.com/ on June 7, 2025 training, and similar technologies	code; higher va
<ul> <li>3 *Risk categ</li> <li>4 †Incidence n</li> <li>5 *Area Depr</li> <li>6 represent hi</li> <li>7</li> <li>8</li> </ul>	ories were rate of com ivation Ind	estimated using bined stroke an ex measures are	the Pooled Cohort d coronary heart di a-level social depri	Equations sease was o vation and	estimated over t estimated using	en years. g the census-tract o		m <mark>j</mark> igit zip c m <mark>9</mark> pen.bmj.com/ on June 7, 2025 training, and similar technologies	code; higher val
<ul> <li>3 *Risk categ</li> <li>4 †Incidence n</li> <li>5 *Area Depr</li> <li>6 represent hi</li> <li>7</li> <li>8</li> </ul>	ories were rate of com ivation Ind	estimated using bined stroke an ex measures are	the Pooled Cohort d coronary heart di a-level social depri	Equations sease was o vation and	estimated over t estimated using	en years. g the census-tract o		nts 9- gigit zip c	ode; higher va

# Risk Modification Analysis

2	Within each PCE predicted risk category, we evaluated if SES modified the relationship
3	between PCE estimated risk and actual ASCVD 10-year observed incidence for each educational
4	attainment level and neighborhood deprivation (college-educated and least deprived
5	neighborhood as the referent) (Table 3). Large risk ratio differences (i.e., more than 10%) within
6	stratum-specific PCE estimated risk categories by SES indicates risk modification. We found
7	that the risk ratio was greater than 1 among those not having a high school degree for all PCE
8	estimated risk categories. This result indicated a heavier burden of ASCVD than in college-
9	educated participants independent of PCE estimated risk. This relative increase in ASCVD risk
10	was statistically significant for groups with >5%-10% and >10%-15% PCE estimated risk; risk
11	ratio 1.78 (95% CI; 1.16-2.76) and 2.15 (95% CI; 1.39-3.34) respectively. The risk of ASCVD
12	in the most deprived neighborhoods (referent least deprived neighborhoods) was significantly
13	higher only for the 10-year PCE estimated risk category >10%-15%, risk ratio 1.65 (95% CI;
14	1.05-2.59).
15	
16	1.05-2.39).
17	
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			Education		egories within each predi	Area Deprivation Index	
	-Year ASCVD edicted Risk <sup>‡</sup>	No High School RR (95% CI)	High School/Some College RR (95% CI)	College <sup>*</sup> or Above RR (95% CI)	Top ADI Quartile RR (95% CI)	ත් වී වී Middæ Two ADI Quarale RR (ඉදියු දිවි)	Lowest <sup>†</sup> AD Quartile RR (95% Cl
	0%-5%	1.16 (0.48-1.53)	0.84 (0.46-1.53)	1.00	1.61 (0.76-3.38)	1.51 #0975-3.04)	1.00
	>5%-10%	1.78 (1.16-2.76)	1.29 (0.86-1.93)	1.00	0.92 (0.65-1.32)	0.61 Hole 0.61 Hole 0.61 Hole 0.61 Hole 0.61 Hole 0.61 Hole 0.61 Hole 0.61 Hole 0.97)	1.00
	>10%-15%	2.15 (1.39-3.34)	1.30 (0.82-2.05)	1.00	1.65 (1.05-2.59)	1.22 min. 1.22 min. 1.23 m	1.00
1 2 3 4 5 6 7	*College or Abo †Lowest ADI as	the referent.	n Index; ASCVD, athero		ilar disease; RR, risk ra	tio. I training, and similar technologies.	

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1	In analyses stratified by educational attainment and neighborhood deprivation,
2	participants without a high school degree who resided in the most deprived neighborhoods had a
3	higher risk of ASCVD for all 10-year PCE estimated risk categories than other SES groups
4	(Supplement Table 1). At 10-year PCE estimated risk categories of 0%-5% and >10%-15%,
5	having both individual and neighborhood measures of low-SES (without high school education
6	and residing in the most deprived neighborhood) meant a substantially higher risk of ASCVD
7	than either measure alone; risk ratio 3.64 (95% CI, 1.46-9.07) and 4.78 (95% CI, 1.62-14.09)
8	respectively.
9	Observed 10-year absolute risk is presented for each education category, and ADI
10	category across PCE estimated risk categories (Figure 1). We found heterogeneous differences
11	in absolute risk (i.e., risk modification) by SES within stratum-specific PCE estimated risk
12	categories. For example, the difference in absolute risk for participants without a high school
13	degree (referent college-educated) rose by 6 percentage points for PCE estimated risk of >10%-
14	15%; absolute risk difference decreased to 3.4 percentage points for PCE estimated risk >15%
15	(Supplement Figure 1). Heterogenous differences in absolute risk for ADI categories were also
16	noted, albeit smaller differences than educational attainment categories. Differences in absolute
17	risk for participants living in the most deprived neighborhoods (referent least deprived
18	neighborhoods) were 1.2 percentage points higher for PCE estimated risk of >5%-15%, and 1.6
19	percentage points higher for PCE estimated risk 10%-15%.
20	Socioeconomic Status Interaction with PCE Model Analysis

The coefficient for each SES risk factor's interactions with estimated risk categories was statistically significant, and model fit measures to estimate ASCVD risk improved (Table 4). For 

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1		
2 3 4	1	example, the likelihood ratio test comparing models 1 and 4, which included education and ADI
5 6	2	categories, and their interaction with the PCE 10-year predicted ASCVD risk categories [Model
7 8 9	3	4: Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_2(i.Education) + \beta_3(i.ADI) + \beta_4(i.Score x i.Education) + \beta_$
10 11	4	$\beta_5(i.Score \ x \ i.ADI)]$ demonstrated a statistically significant model improvement when measures
12 13	5	of SES was added as an interaction term with PCE estimated risk category ( <i>p</i> -value <0.0001).
14 15 16	6	Additionally, the Akaike information criterion was smaller, suggesting that educational
17 18	7	attainment measures and area deprivation improved model fit for predicting 10-year ASCVD
19 20 21	8	outcomes compared to the PCE predicted risk category alone.
22 23	9	outcomes compared to the PCE predicted risk category alone.
24 25 26	10	
27 28	10	
29 30 21	11	
31 32 33	12	
34 35		
36 37 38	13	
39 40	14	
41 42 43	15	
43 44 45	15	
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50		

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	Table 4. Comparison of models prediction	ng ASCVD 10-year Incident	events with and without meas		4 4 4
	Model	Number	Akaike <sup>*</sup> Information Criterion	Bayesian <sup>†</sup> Information	J
	PCE <sup>‡</sup>	9728	2371	2386 s reig	
	i.PCE + i.Education <sup>§</sup>	9717	2366	2395 2374 <b>Haneme</b>	0.004
	(i.PCE)x(i.Education)	9717	2331	2386 relation 2395 relation 2374 to the	< 0.0001
	i.PCE + i.ADI <sup>11</sup>	9728	2371	2400 te sup	0.14
	(i.PCE) x (i.ADI)	9728	2346	2389 tand 2400 diamond	< 0.0001
	i.PCE + i.Education + i.ADI	9717	2366	2374 to the superior control of the superior control o	0.002
	(i.PCE) x (i.Education)x(i.ADI) Abbreviations: ADI, Area Deprivation	9717	2328	בענים <sup>24</sup> 38	<0.0001
4 5 6 7 8 9 10 11 12 13	<sup>†</sup> Bayesian Information Criterion measu model indicate an improvement in pred <sup>‡</sup> Pooled Cohort Equations predicted ris <sup>§</sup> Education was stratified into three cat <sup>II</sup> Higher Area Deprivation Index indica range: top ADI quartile; middle two AI <sup>#</sup> All models that added in the social depriv- factor. <sup>**</sup> All models that added in social depriv- added as a risk factor.	liction. k was stratified into 4 cat egories: no high school; h tes higher neighborhood o DI; lowest ADI quartile (n privation factor as a risk f	egories of risk: 0-5%; >5-10 igh school/some college; co deprivation and was stratifie referent) factor was compared to the I	20%; >10-15%; >15%. و ollege or above (referently) ed into three categories Pooled Cohort Equation	ding to the interquartile hout a social deprivation with social deprivation
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2	In the current study, we investigated whether SES's individual and neighborhood
3	measures modify the association between the PCE risk score and actual 10-year ASCVD
4	observed outcomes. We also described the excess burden of ASCVD events among low-SES
5	populations relative to high-SES populations conditional on PCE estimated risk. The PCE
6	estimated risk underestimated incidence of ASCVD events experienced among low-SES groups,
7	and absolute differences in risk among SES measures became most pronounced at higher PCE
8	predicted risk categories, indicating risk modification by measures of SES. Our results also
9	suggest that SES factors' value in predicting incident ASCVD events may vary by PCE predicted
10	risk levels.

A potential reason for the inconsistent evidence for SES's prognostic value to predict 10-year ASCVD outcomes could be the different outcome modeling strategies used in prior studies. Prior studies have historically modeled SES as an independent risk factor or confounder.<sup>[19-22, 24]</sup> Classical social epidemiological frameworks such as the "fundamentals causes of health inequalities theory" suggest that despite any 10-year estimated risk of ASCVD for an individual at a given time, the clinical trajectory and outcomes are both influenced and dependent on the individual's SES.<sup>[26, 34-37]</sup> According to the fundamental cause theory, high-SES individuals, possess a variety of flexible resources (i.e., knowledge, money, prestige, and power) to protect their health in a way that low-SES individuals cannot. As such, the effects of the non-SES traditional ASCVD risk factors used in the PCE (i.e., hypertension and total cholesterol) on ASCVD incidence will likely be modified by whether the individual is of lower or higher SES. Our results show that having at least a college-education was protective against ASCVD relative to not having a high school degree across all risk levels, with greater protective effects at higher

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PCE estimated risk levels. Living in the least deprived neighborhood was also protective, but
likely less consistently than an individual SES exposure measure due to the potential for the
ecological fallacy that can occur when making inferences about individuals based on group-level factors.

5 The substantial model fit improvement by interacting SES factors with the PCE risk score 6 suggests that this modeling strategy will significantly improve ASCVD outcome prediction 7 accuracy, but further analysis is required. Any 10-year ASCVD model that does not account for 8 SES as a risk modifier may lead to measurement error. Prior modeling studies and current 9 ASCVD risk models that incorporate SES into predicting risk do not incorporate SES as an 10 interaction term into the model.

The current PCE model estimates a graded ASCVD risk irrespective of SES status. Our results show that the PCE placed disadvantaged individuals with an inherently higher risk of ASCVD into the corresponding 10-year estimated ASCVD risk categories at the expense of over-estimating risk for higher SES individuals. At the very least, the PCE will direct ASCVD preventive care to our most disadvantaged populations. The same population which research shows are less likely to receive appropriate preventive measures are just as likely to receive needed ASCVD risk management as their higher SES counterparts when the PCE is used to guide ASCVD prevention.[38-41] 

Additional research is needed to improve ASCVD risk prediction among different SES groups and prevent ASCVD among disadvantaged populations. Our data only allow us to describe these epidemiologic phenomena of excess ASCVD events experienced among lower SES individuals and possible ways to model future risk, but our analysis does not permit us to

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1	identify underlying mechanisms. Many unknown factors exist along the socio-ecological
2	paradigm that works in concert with individual behavioral and physiologic factors to lead to a
3	higher burden of ASCVD among low-SES populations.
4	These findings have clinical and policy implications, with current guideline
5	recommendations for using the PCE model to guide primary prevention ASCVD strategies in
6	cholesterol management, hypertension management, and aspirin use. <sup>[16, 18, 42, 43]</sup> For example, at
7	an estimated 10-year PCE risk of 7.5%, statin therapy is recommended for primary prevention of
8	ASCVD.[18] We show that a higher SES is a risk-protecting factor, and the absolute risk of
9	ASCVD does not cross the 7.5% threshold until a PCE 10-year risk of >15% (Figure 1). The use
10	of SES in estimating an individual's risk can potentially improve the efficiency of resource use
11	and more precisely target interventions to achieve population-level objectives to decrease the
12	ASCVD burden globally and in the United States. However, without a validated ASCVD
13	prediction model that incorporates SES in the US, we don't advocate for the use of SES in the
14	clinical decision of ASCVD preventive therapies for US patients. Our findings do suggest
15	validation of an ASCVD prediction model that appropriately incorporates SES is warranted.
16	Model validation comparison measures such as net risk reclassification -similar to Mosley et al.
17	evaluation of PCE risk prediction improvement with adding a polygenic risk score – can help
18	guide decisions on the utility of incorporating SES to guide clinical decision making. <sup>[44, 45]</sup>
19	Limitations
20	The study has several limitations. The ARIC study is restricted to four communities in
21	the United States and is not nationally or internationally representative. Furthermore, some

22 communities have limited diversity with respect to race or SES measures. The measurement of

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outcomes based on ARIC abstraction of hospitalization data is a strength since it avoids reliance
on self-report of events. However, some hospitalizations may be missing since comparing
Medicare claims to ARIC records showed that between 10% to 20% of hospitalizations are
missed if only one source is used.<sup>[46]</sup> Internal exploration of this issue suggested that the
additional hospitalizations were not correlated with our SES measures and did not substantively
affect the results.

Results from our area-level deprivation analyses must be considered in the context of analytical limitations. For example, the use of the ADI as an aggregate measure of SES can potentially introduce ecological fallacy bias. Furthermore, we did not account for possible movement to other neighborhoods for our sample over 10-years of follow up. A potential misclassification bias of area-level deprivation exposure may exist over time. We expect that this misclassification bias is likely small. Our results are conservative estimates because bias from random measurement error is towards the null. Also, we did not adjust for ASCVD preventive medication use -e.g., statin therapy -as a time-varying covariate in our models. Whilemedication use could influence ASCVD outcome differences by SES, our focus was on the overall differences in prediction and outcome by SES rather than on causal pathways of the differences. Last, we didn't control for the ARIC study site in our area-level deprivation analyses. Without controlling for the ARIC study site, homogeneity in participant characteristics (i.e., a predominantly African-American/Black population versus a predominantly white population) by ARIC study site may have resulted in the loss of statistical power to detect a meaningful difference in ASCVD outcomes according to ADI.

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The current study extends our understanding of the relationship between socioeconomic factors and the risk of heart disease and stroke outcomes. We find that the associations of PCE risk score and incident ASCVD are dependent on education level and area deprivation. Our findings may partially explain the discrepancy in results from earlier studies evaluating the utility of adding SES as a prognostic measure into ASCVD prediction models. Given the potentially important clinical and policy implications of our results, we suggest further refinement of the PCE model is needed to improve the estimation of risk for all populations, both historically vulnerable and less vulnerable populations. We believe the development of a new ASCVD risk prediction model should apply appropriate validation methods and use a more racially and ethnically diverse observational cohort for validation. Acknowledgements The authors thank the staff and participants of the ARIC study for their important contributions. Sources of Funding This work was supported in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I). **Competing Interests** None declared. Ethics Approval

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3	1	Institutional review boards at all ARIC centers in the United States approved study procedures.
4		
5 6 7	2	All participants gave written informed consent for the collection of data used in this study. This
7 8 9	3	study was approved by the University of North Carolina at Chapel Hill Institutional Review
9 10 11	4	Board (IRB# 18-1187).
12 13	5	
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15 16	6	
10 17 18	7	Contributors
19 20	8	KH, PC, and SS initiated the project. JR and BK performed all statistical analyses. KH had
21 22	9	main responsibility for writing the manuscript. KH, PC, SS, JR, BK, RF, CS and MH all
23 24 25	10	contributed to the statistical analyses, interpretation of outcomes, and provided comments on the
26 27	11	manuscript. KH, PC, SS, JR, BK, RF, CS and MH all read and approved the final manuscript.
28 29	12	PC is the senior author.
30 31	13	
32 33 34	14	Data Sharing Statement
35 36	15	No additional data are available
37	1.6	
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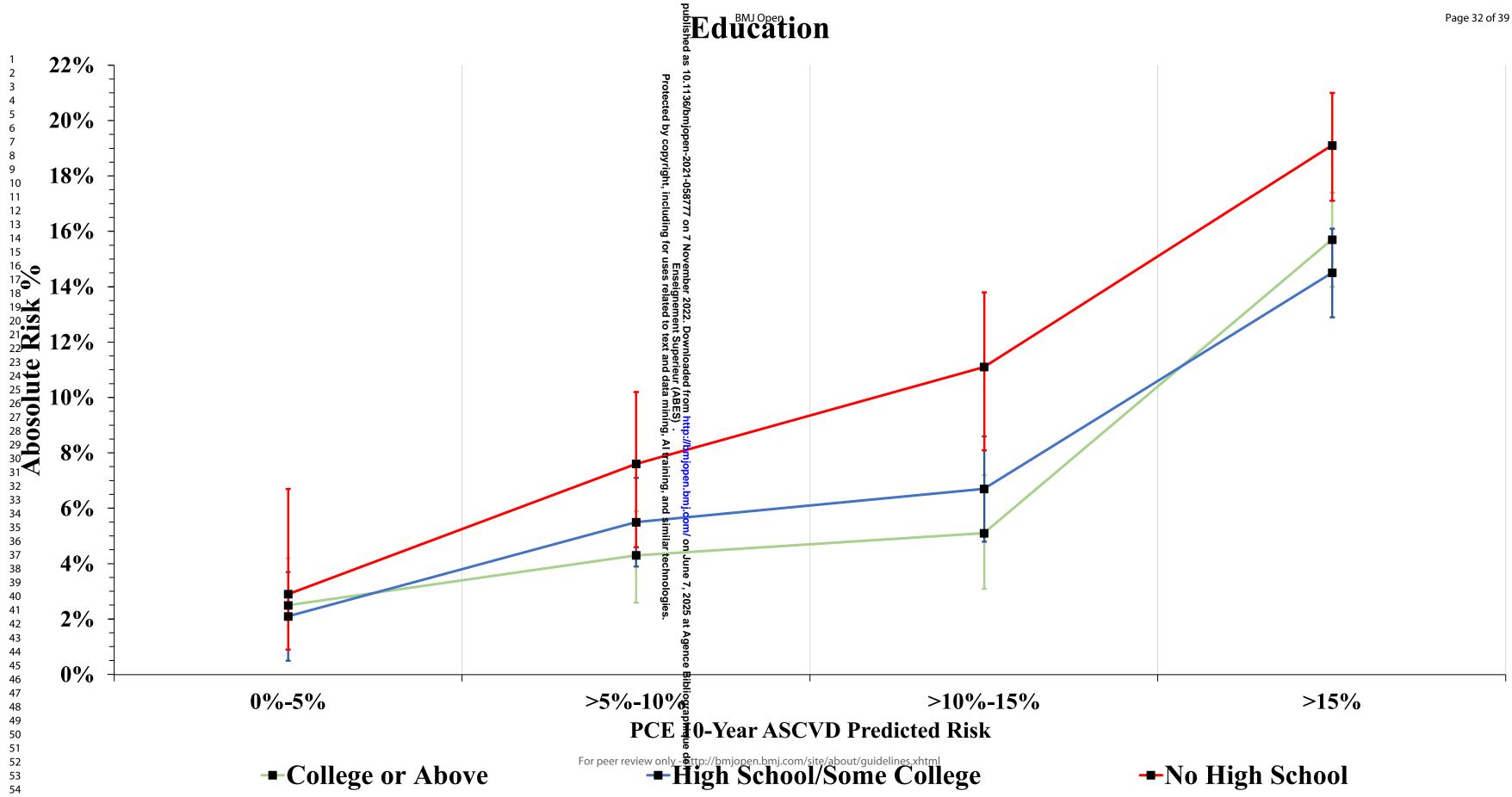
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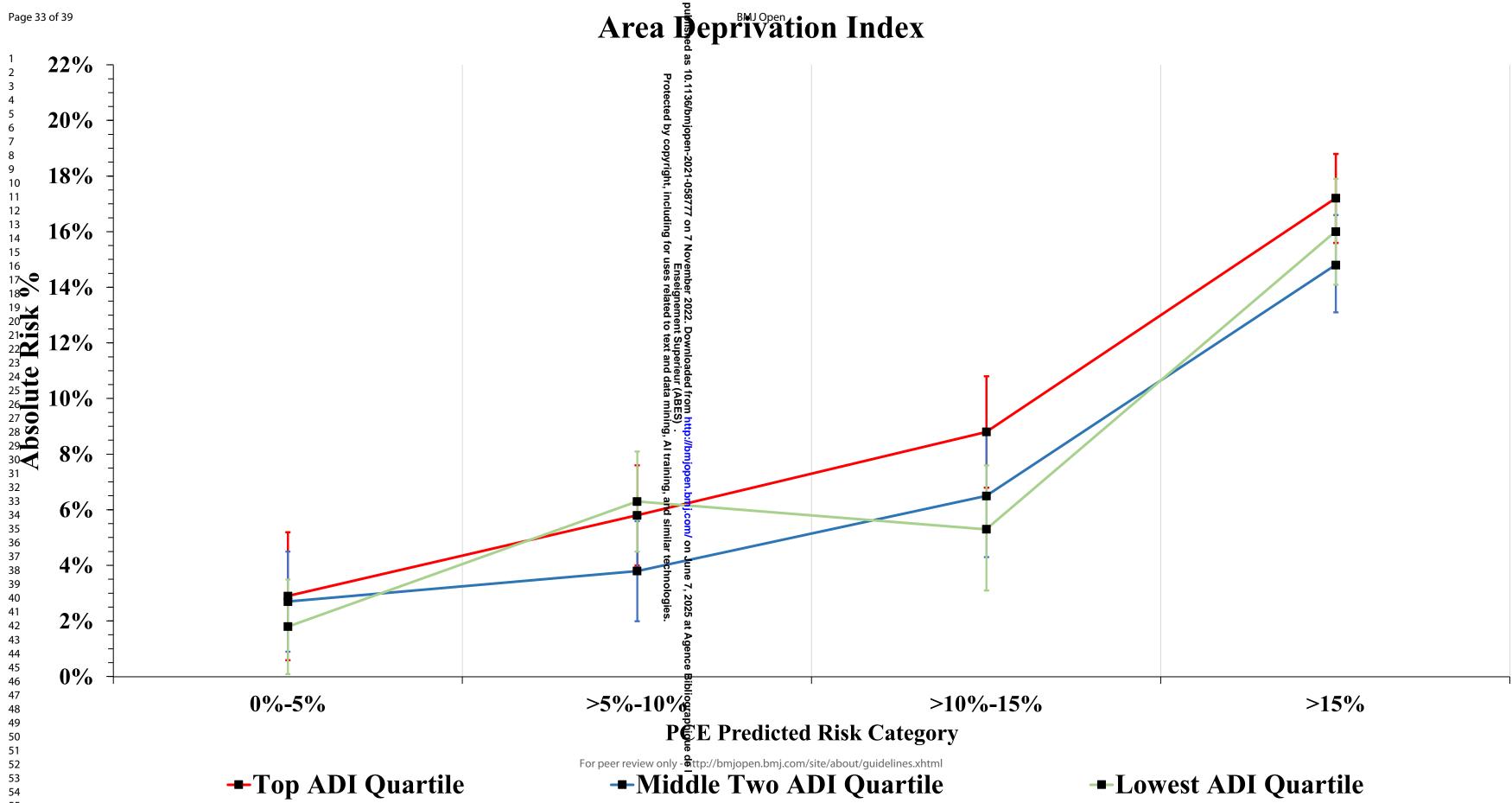
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1	Figure 1. Observed 10-year incidence rate of ASCVD events by socioeconomic status. 10-year incidence rate of ASCVD events by education
2	attainment (A) and Area Deprivation Index (B).
3	Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohog Egations
4	BMJ Open Figure 1. Observed 10-year incidence rate of ASCVD events by socioeconomic status. 10-year incidence rate of ASCVD events by socioeconomic status. 10-year incidence rate of ASCVD events by socioeconomic status. 10-year incidence rate of ASCVD events by education attainment (A) and Area Deprivation Index. (ASCVD, atheroselerotic cardiovascular disease; PCE, Pooled Cover attain the consustance of participant of part
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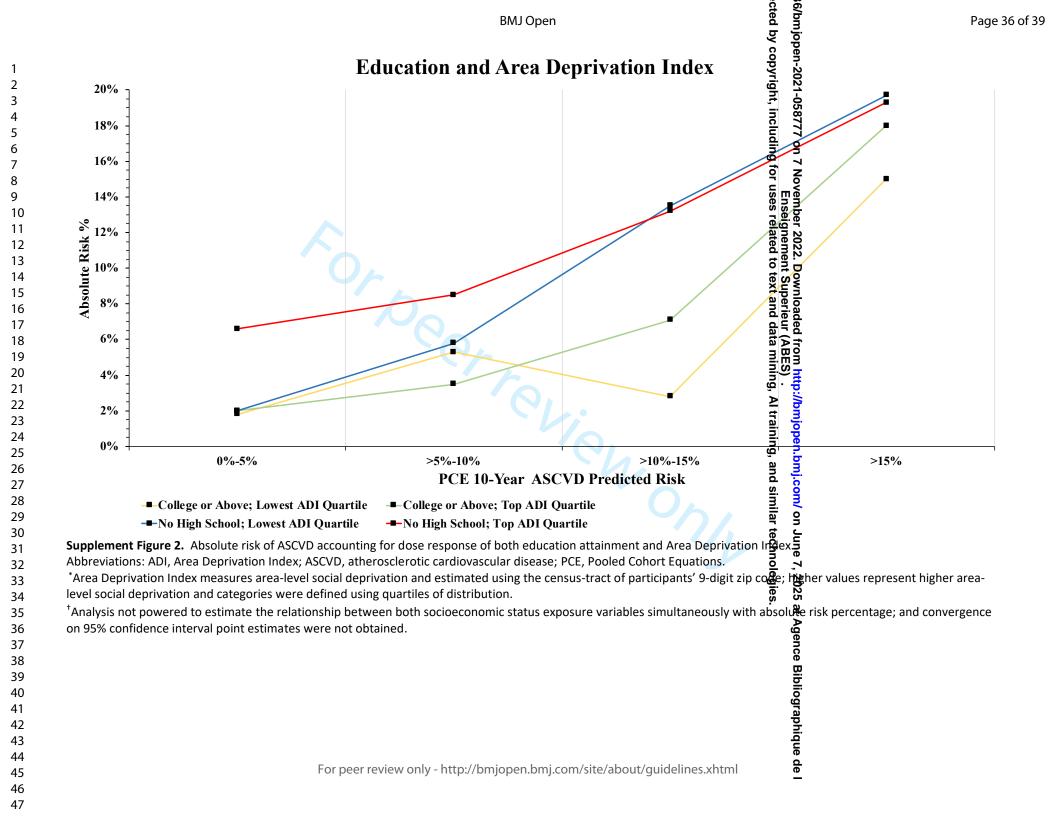


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<section-header>

	PCE Risk Category	Absolute Risk % (95% CI)	Absolute Risk % Difference (Col	lege or Above Refere
No High School	0%-5%	2.9% (0.9%-6.7%)		
	>5%-10%	7.6% (5.0%-10.2%)	0.4%	
	>10%-15%	11.1% (8.4%-13.8%)	3.3	
	>15%	19.1% (17.1%-21.0%)	3.4	6.0%
	120,0	1011/0 (1111/0 1110/0)	5.4	70
– High School/Some College	0%-5%	2.1% (0.5%-3.7%)	-0.4%	
	>5%-10%	5.5% (3.9%-7.1%)	-0.476	1.2%
	>10%-15%	6.7% (4.8%-8.6%)		1.6%
	>15%	14.5% (12.9%-16.1%)	-1.2%	
College or Above	0%-5%	2.5% (0.9%-4.2%)		
	>5%-10%	4.3% (2.6%-5.9%)	Referent	
	>10%-15%	5.1% (3.1%-7.2%)		
	>15%	15.7% (14.0%-17.4%)		
	Are	ea Deprivation Inc		
	PCE Risk Category	Absolute Risk % (95% Cl)	Absolute Risk % Difference (Lov Referent)	vest ADI Quartile as
Top ADI Quartile	0%-5%	2.9% (0.6%-5.2%)		
	>5%-10%	5.8% (4.0%-7.6%)	-0.5%	
	>10%-15%	8.8% (6.8%-10.8%)		3.5%
	>15%	17.2% (15.6%-18.8%)	1.2%	
Median ADI Quartile	0%-5%	2.7% (0.9%-4.5%)	0	
	>5%-10%	3.8% (2.0%-5.6%)	-2.5%	0.9%
	>10%-15%	6.5% (4.3%-8.7%)	-2.370	1.2%
	>15%	14.8% (13.1%-16.6%)	-1.2%	
Lowest ADI Quartile	0%-5%	1.8% (0.1%-3.5%)		1
	>5%-10%	6.3% (4.5%-8.1%)	Referent	
	>10%-15%	5.3% (3.1%-7.6%)		
	>15%	16.0% (14.1%-17.9%)		
Supplement Figure 1. Diff predicted risk category. Abbreviations: ADI, Area D *Predicted risk categories	eprivation Index; AS	SCVD, atherosclerotic car		omic status, conditi



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tion Index Lowest DI ADI e Quartile 6 RR (95%	Area Top ADI Quartile	>10%-15%		07	a Deprivatio	n Index
Lowest DI ADI e Quartile	Top ADI	Middle			a Deprivatio	n Index
01 ADI e Quartile	•		Lowest	nse Ps r	1	
CI)	RR (95% CI)	Quartile RR (95% CI)	ADI Quartile RR (95% CI)	inder 2022. Dom is relatentient So Topten So te RR (I) CI)	Middle Two ADI Quartile RR (95% Cl)	Lowes ADI Quart RR (95 CI)
1.10 (0.35- 3.48)	4.78 (1.62- 14.09)	1.88 (0.69- 5.15)	4.93 (1.94- 12.50)	rnioaded from uperieur (ABES) (t and dataquini 1.2.0.9 1.7 1.7 1.7	1.22 (0.84- 1.77)	1.31 (0.85- 2.02)
1.48 (0.87- 2.53)	2.28 (0.89- 5.82)	2.48 (0.95- 6.47)	2.52 (0.97- 6.52)	ng, 200 0.95 (0.64 1.34 1.34 1.34 1.34 1.34 1.34 1.34 1.3	0.90 (0.65- 1.26)	1.08 (0.75- 1.54)
1.00	2.59 (1.00- 6.70)	2.48 (0.97- 6.36)	1.00	1.200 (0.805- 1.690	0.97 (0.67- 1.40)	1.00
	(0.35- 3.48) 1.48 (0.87- 2.53) 1.00 vascular diseas	(0.35- 3.48) 14.09) 1.48 2.28 (0.87- 2.53) 5.82) 2.59 (1.00- 1.00 6.70) vascular disease; CI, confide	(0.35- 3.48) 14.09) 5.15) 1.48 2.28 2.48 (0.87- 2.53) 5.82) 6.47) 2.59 2.48 (1.00- (0.97- 1.00 6.70) 6.36) vascular disease; CI, confidence interv	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2.59 2.48 1.20 (1.00- (0.97- (0.86- 1.00 6.70) 6.36) 1.00 1.69 vascular disease; CI, confidence interval; RR, relative risk ed risk of 0-5% due to lack of ASCVD incidence for category.	(0.35- 3.48) 14.09) 5.15) 12.50) 1.74 (0.94 1.77) 1.48 2.28 2.48 2.52 0.95 (0.87- 2.53) 5.82) 6.47) 6.52) 1.34 1.26) 2.59 2.48 1.26 (0.65- 1.34) 0.97 (0.65- 1.26) 0.97 (0.67- 1.00 6.70) 6.36) 1.00 1.69 1.40) 2.59 2.48 1.26 0.97 (0.67- 1.00 1.69 1.40) 2.59 2.48 1.20 0.97 (0.67- 1.00 1.69 1.40)

		BMJ Open BMJ Open	Page
		STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of comort studies	
Section/Topic	ltem #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		لا ي تحقق المحقق (b) Provide in the abstract an informative and balanced summary of what was done and	2-3
Introduction		Events in the exist if is beckere und and actionals for the investigation being reported to the investigation being reported.	
Background/rationale	2	$\sim$ Explain the scientific background and rationale for the investigation being reported $\sim$ $\sim$ $\sim$	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods		and in a set of the se	
Study design	4	Present key elements of study design early in the paper	5-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure the setting, locations, and data collection	5-9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed 🚊 🕃	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modified. Gove diagnostic criteria, if	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	11-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(a) Describe all statistical methods including those used to control for confounding	9-11
		(b) Describe any methods used to examine subgroups and interactions	9-11
		(c) Explain how missing data were addressed	9-11
		(d) If applicable, explain how loss to follow-up was addressed	Na (only used participants without missing).

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		BMJ Open by copyright (e) Describe any sensitivity analyses in 58	11
Results	-		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed 약 공	11-12
		(b) Give reasons for non-participation at each stage	11-12
		(c) Consider use of a flow diagram	No (discussed in text)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information တို့ရှိ မိုစုosures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	na
		(c) Summarise follow-up time (eg, average and total amount)	8, 25
Outcome data	15*	Report numbers of outcome events or summary measures over time 🛛 🖬 🏹 🚌	25-26
Main results	16	( <i>a</i> ) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their practing (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10; 22-23
		(b) Report category boundaries when continuous variables were categorized	8-11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaning fur time period	21, 23
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-14
Other information		gies gies	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15
Give information separ	rately for	cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in controls in case-control studies and, if applicable, for exposed and unexposed groups in controls in case-control studies and, if applicable, for exposed and unexposed groups in controls in case-control studies and cross-sectional studies	udies.

BMJ Open BMJ Open **V** checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmed inc., Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at we obe-statement.org.

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#### Socioeconomic Status and Modification of Atherosclerotic Cardiovascular Disease Risk Prediction: epidemiological analysis using data from the Atherosclerosis Risk in Communities Study

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## Socioeconomic Status and Modification of Atherosclerotic Cardiovascular Disease Risk Prediction: epidemiological analysis using data from the Atherosclerosis Risk in **Communities Study** First Author: Henderson Short Title: Socioeconomic Status and Cardiovascular Disease Risk Prediction Authors: Kamal H. Henderson, MD MSc<sup>1,2</sup>; Brystana G. Kaufman, Ph.D. MSPH<sup>3</sup>; Jason S. Rotter, Ph.D. MHS<sup>4</sup>; Sally C. Stearns, Ph.D.<sup>5</sup>; Carla A. Sueta, MD, Ph.D.<sup>6</sup>; Randi E. Foraker, Ph.D.<sup>7,8</sup>; Michael Ho, MD, Ph.D.<sup>1,2</sup>; Patricia P. Chang, MD, MHS<sup>9</sup> Author Affiliations: Rocky Mountain Regional Veteran Affairs Medical Center<sup>1</sup>; University of Colorado School of Medicine<sup>2</sup>; Department of Population Health Sciences, Duke University<sup>3</sup>; Mathematica Policy Research, Washington D.C.4; Department of Health Policy and Management, University of North Carolina at Chapel Hill (UNC-CH) Gillings School of Global Public Health<sup>5</sup>; UNC School of Medicine<sup>7</sup>; Division of General Medical Sciences, Washington University School of Medicine<sup>7</sup>; Brown School of Public Health<sup>8</sup>; UNC School of Medicine<sup>9</sup>. **Corresponding Author:** Kamal H Henderson Rocky Mountain Regional VA Medical Center 1700 N Wheeling St Aurora, CO 80045 Fax: 303-393-2826 Telephone: 720-723-6072 Email: kamal.henderson@cuanschutz.edu **Total Word Count: 3,882** Por peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

#### Abstract

**Objective:** Examine whether the relationship between the Pooled Cohort Equations (PCE) predicted 10-year risk for atherosclerotic cardiovascular disease (ASCVD) and absolute risk for ASCVD is modified by socioeconomic status (SES).

**Design:** Population-based longitudinal cohort study –Atherosclerosis Risk in Communities (ARIC) – investigating the development of cardiovascular disease across demographic subgroups.

Setting: Four communities in the United States– Forsyth County, North Carolina, Jackson,
Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland.
Participants: We identified 9,782 ARIC men and women aged 54-73 without ASCVD at study visit 4 (1996-1998).

**Primary outcome measures:** Risk ratio (RR) differences in 10-year incident hospitalizations or death for ASCVD by SES and PCE predicted 10-year ASCVD risk categories to assess for risk modification. SES measures included educational attainment and census-tract neighborhood deprivation using the Area Deprivation Index. PCE risk categories were 0%-5%, >5%-10%, >10%-15%, and >15%. SES as a prognostic factor to estimate ASCVD absolute risk categories was further investigated as an interaction term with the PCE.

**Results:** ASCVD risk ratios for participants without a high school education (referent collegeeducated) increased at higher PCE estimated risk categories and was consistently >1. Results indicate education is both a risk modifier and delineates populations at higher ASCVD risk independent of PCE. Neighborhood deprivation did modify association but was less consistent in direction of effect. However, for participants residing in the most deprived neighborhoods (referent least deprived neighborhoods) with a PCE estimated risk >10%-15%, risk was significantly elevated (RR 1.65 [95% CI; 1.05-2.59]). Education and neighborhood deprivation inclusion as an interaction term on the PCE risk score was statistically significant (Likelihood

ratio P≤0.0001).

 **Conclusions:** SES modifies the association between PCE estimated risk and absolute risk of ASCVD. SES added into ASCVD risk prediction models as an interaction term may improve our ability to predict absolute ASCVD risk among socially disadvantaged populations.

### Strengths and limitations of the study:

- Population-based prospective cohort with over three decades of follow-up data to investigate the development of cardiovascular disease across demographic subgroups are major strengths of this study.
- Hospitalizations for coronary heart disease and stroke hospitalizations an outcome measured – was based on the Atherosclerosis Risk in Communities abstraction of hospital data, and some hospitalizations may be missing.
- A potential misclassification bias of area-level deprivation exposure possibly exists due to not accounting for Atherosclerosis Risk in Communities participants moving to different neighborhoods with a different degree of area-level deprivation exposure.

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Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and morbidity in the United States (US) and globally.<sup>[1-4]</sup> A substantially higher burden of ASCVD is experienced among those with lower socioeconomic status (SES).<sup>[5-14]</sup> The Pooled Cohort Equations (PCE) are currently recommended in the US to estimate the 10-year risk of ASCVD and guide primary prevention treatment decisions.<sup>[15-18]</sup> The PCE does not currently account for SES factors such as educational attainment or neighborhood deprivation. However, SES measures may have prognostic value in predicting ASCVD outcomes and identifying populations in greatest need of primary ASCVD prevention. Existing evidence regarding the prognostic value of controlling for SES in ASCVD prediction models is mixed. A recent analysis showed that PCE overestimated ASCVD risk among low SES populations, but including SES measures such as household income or educational attainment in the PCE model did not improve model calibration.<sup>[19]</sup> Conversely, prior research evaluating the use of SES measures, such as household income or neighborhood deprivation, with the Framingham Risk Score that estimates coronary heart disease risk only, showed that such measures improved model fit statistics.<sup>[20-22]</sup> The latter findings eventually led to ASCVD risk models, such as QRISK2, primarily used in the United Kingdom that incorporate the Townsend deprivation score, a neighborhood measure of deprivation.<sup>[23-25]</sup> Such discrepancies have important implications globally and for the US, creating uncertainty regarding the importance of incorporating SES into ASCVD risk prediction models and the value of SES as a marker to identify individuals in need of additional ASCVD primary prevention interventions and services.

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1	How prior ASCVD prediction models incorporated SES into the model is a potential
2	reason for the discrepancies in understanding the prognostic value and use of SES in ASCVD
3	prediction models. SES traditionally is modeled as an independent risk factor or confounder. <sup>[19-22,</sup>
4	<sup>24]</sup> However, SES's prognostic value in predicting ASCVD risk is likely identifying populations
5	most impacted by proximate causes of ASCVD. If true, SES incorporated into risk prediction
6	models as a risk modifier is more appropriate in determining ASCVD risk than an independent
7	risk factor. For example, the health impact of hypertension over 10-years is different for an
8	individual living in abject poverty versus an individual residing in an affluent neighborhood.
9	SES likely modifies the association between risk estimated from algorithms that use proximate
10	causes of ASCVD (i.e., hypertension and smoking) and actual ASCVD incidence.
11	This study explored whether SES modifies the association of PCE 10-year estimated risk
12	with actual ASCVD 10-year incidence using data from the Atherosclerosis Risk in Communities
13	(ARIC) study. That is, actual observed ASCVD 10-year incidence will vary depending on the
14	PCE estimated risk and the individual's SES. We defined SES along two dimensions typically
15	utilized in social epidemiology research: educational attainment and neighborhood
16	deprivation. <sup>[26]</sup> Educational attainment as a measure of individual SES was selected over other
17	measures – e.g., income level – due to being a stable measure of SES that remain relatively
18	stable over an adult life course when compared to other measures. We hypothesize that the long-
19	term effects of proximate causes of ASCVD measured in the PCE (e.g., hypertension and
20	smoking) impact on actual ASCVD incidence are dependent on SES (i.e., risk modification).
21	Methods
-	
22	Data Source

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Data obtained for our analyses came from the Atherosclerosis Risk in Communities (ARIC) study. In brief, the ARIC study is an ongoing prospective observational cohort study of 15,792 men and women age 45-64 years, recruited from population-based sampling from four communities in the United States-Forsyth County, North Carolina, Jackson, Mississippi, suburbs of Minneapolis, Minnesota, and Washington County, Maryland.<sup>[27]</sup> The study was designed to investigate the development of cardiovascular disease across demographic subgroups. Follow-up has included seven in-person study visits to-date from the baseline visit in 1987-1989; surveillance of the cohort continues with annual telephone interviews and active surveillance of discharges from local hospitals. Institutional review boards at all ARIC centers approved study procedures, and participants give written informed consent at each visit.

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#### 11 Study Population

We restricted our analysis to 11,374 ARIC participants who attended Visit 4 (1996-1998) to maintain an observational cohort that reflected similar temporal trends in ASCVD outcomes as the cohorts used to derive the PCE. We excluded Visit 4 participants with prevalent coronary heart disease (CHD) (N=1210), prior stroke (N=231), participants missing clinical variables for ASCVD risk assessment (N=155), and participants missing educational attainment information collected at study Visit 1 (N=12). Prevalent CHD was defined as self-reported or physician diagnoses of myocardial infarction at baseline and incident CHD occurring between baseline and Visit 4. We defined prevalent stroke as self-reported or physician diagnoses of stroke, transient ischemic attack, and stroke-like symptoms at baseline or hospitalization for a definite or probable stroke between baseline and Visit 4. Due to small numbers, we excluded Blacks in Minneapolis and Washington County (N=35). Three participants were excluded due to unclear incident ASCVD dates for a final sample of 9,728.

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#### 

Individual-Level Covariate Measures

Trained staff administered in-home interviews that collected information on demographics, socioeconomic factors, lifestyle, and medical co-morbidities. Race, gender, and educational attainment were self-reported. We used the information on race, gender, and educational attainment collected at ARIC Visit 1; we used data on age and medical comorbidities collected during Visit 4 for our analyses.

We categorized smoking status as current or not current smokers. Hypertension was defined as having a systolic blood pressure of 140 mmHg or greater (mean of two measurements recorded at study visit), diastolic blood pressure 90 mmHg or greater (mean of two measurements recorded at study visit) or were taking antihypertensive medications. We classified diabetes as having a fasting blood glucose level ≥126 mg/dL, non-fasting blood glucose ≥200 mg/dL, use of anti-diabetic medications, or self-reported history of physician-diagnosed diabetes. We used total cholesterol and high-density lipoprotein (HDL) levels collected at Visit 4 to assess ASCVD risk. Pill bottle review, when available, was performed at every ARIC Visit to confirm medication use. Statin medication use at Visit 4 was self-reported or based on medications brought to the visit.

17 Socioeconomic Status Measures

18 We examined one individual and one neighborhood exposure of SES. We classified 19 educational level attainment into three categories: no high school degree, high school/some 20 college, or college graduate and above. The Area Deprivation Index (ADI) was used to analyze 21 neighborhood deprivation.<sup>[28-30]</sup> The ADI is a validated measure of neighborhood deprivation that 22 utilizes 17 different markers to measure area-level deprivation from 2000 census block group-

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level data. We used the participants' census tract according to the 9-digit zip code to assign ADI.
The ADI measures neighborhood deprivation along a continuum; higher values represent higher
levels of neighborhood deprivation. We stratified ADI into three categories according to
interquartile range. Levels chosen to represent lowest (residing in the least deprived
neighborhoods), top (residing in the most deprived neighborhoods), and middle two ADI
quartiles.

7 Estimation of ASCVD Risk

8 We estimated individual ASCVD risk using the published PCE covariate parameters.<sup>[15]</sup> 9 The following factors were used to estimate ASCVD risk according to the PCE: age, gender, 10 race (Black or other), levels of total cholesterol, levels of high-density lipoprotein cholesterol 11 (HDL-C), systolic blood pressure, evidence of treatment for high blood pressure, diabetes status, 12 and current smoker status. We used laboratory measures collected at Visit 4 to estimate risk 13 using the PCE. We partitioned the ARIC study population into four categories of 10-year PCE 14 predicted ASCVD risk: 0%-5%, >5%-10%, >10%-15%, and >15%. BMJ Open: first published as 10.1136/bmjopen-2021-058777 on 7 November 2022. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES).

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#### 15 Ascertainment of Myocardial Infarction and Stroke Outcomes

Hospital records were abstracted to identify hospitalizations for myocardial infarction and
stroke. CHD and stroke events were classified algorithmically and following physician review
and adjudication, as previously published.<sup>[27, 31]</sup> Criteria for the incidence of definite or probable
myocardial infarction for the ARIC cohort were based on combinations of chest pain,
electrocardiographic changes, and cardiac enzyme levels during hospitalization. Classification
of events as fatal myocardial infarction was based on the following factors: cause of death on the
death certificate for both hospitalized or out of hospital deaths; and diagnoses at the time of

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hospitalization from medical records before death. The minimum criterion for definite or
probable stroke was evidence of sudden or rapid onset of neurological symptoms lasting >24
hours or leading to death, in the absence of a non-stroke etiology.<sup>[27, 32]</sup> We included adjudicated
events that occurred within ten years of participants' Visit 4 date (from January 1, 1996, through
December 31, 2008) in our analysis.

#### Statistical Analysis

7 Univariate descriptive statistics examined baseline participant-level characteristics. We 8 calculated the mean and standard deviation (SD) for continuous variables, percentages for 9 dichotomous variables, and median with interquartile range (IQR) for ordinal or nominal 10 variables. We performed bivariate analysis using Pearson's  $\chi^2$  test or Kruskal-Wallis test for 11 categorical data and a two-sample *t*-test for continuous variables.

The 10-year incidence rate for hospitalizations or death for coronary heart disease or
stroke were estimated in subgroups defined by education attainment, ADI categories
(interquartile range), and PCE risk categories (0%-5%, >5%-10%, >10%-15%, >15%).
Incidence rates are presented as per 1,000 person-years. Individual time at risk was measured
from Visit 4 until an ASCVD event occurred or one of the censoring events (whichever came
first): death, loss to follow-up, or end of the observation period.

The absolute risk (AR) was calculated as crude cumulative incidence using the pseudovalues methodology, which accounted for competing risk of death for reasons other than death due to ASCVD.[33] We estimated absolute risk according to participant educational attainment and ADI, stratified by the PCE 10-year estimated risk category. We calculated risk ratios (RR) within each PCE predicted risk category comparing absolute risk across educational attainment

1	levels and ADI categories. Absolute risk differences between SES measures were estimated for
2	each PCE 10-year estimated risk category (0%-5%, >5%-10%, >10%-15%, >15%). The
3	referent group for educational attainment level is a college degree or above, and the referent
4	group for ADI is residing in the least deprived neighborhoods (lowest ADI quartile). Point
5	estimates are reported with 95% confidence intervals (CI).
6	Generalized linear estimation models with a log-link function were used to predict the
7	probability of ASCVD events. The naïve model included only the PCE predicted risk score
8	category as the predictor. To evaluate the effect of socioeconomic status on model fit statistics,
9	additional models included: 1) education category added as a predictor and interacted with the
10	PCE score, 2) ADI category added as a predictor and interacted with the PCE category, and 3)
11	both education and ADI categories as predictors and interacted with the PCE category.
12	Generalized linear models compared took the following form:
13	(1) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score)$
14	(2) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_3(i.Education) + \beta_4(i.Score x i.Education)$
15	(3) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_2(i.ADI) + \beta_3(i.Score \ x \ i.ADI)$
16	(4) Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_2(i.Education) + \beta_3(i.ADI) + \beta_4(i.Score x)$
17	i.Education) + $\beta_5$ (i.Score x i.ADI)
18	The likelihood ratio test, Akaike Information Criterion, and Bayesian Information Criterion
19	evaluations were performed to compare model fit statistics of the different models. All analyses
20	were performed using STATA, version 13.
21	Patient and Public Involvement

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Patients or the public were not involved in this specific research project.

#### **Results**

Of 9,728 ARIC study participants, 1,764 (18%) did not have a high school education (Table 1). Participants with a 10-year predicted risk of ASCVD >15% were older, less likely to be male, and had more comorbid conditions such as diabetes or hypertension, and more likely to smoke. Increases in PCE estimated risk categories corresponded to a higher proportion of igh sur. participants without a high school degree or residing in the most deprived neighborhoods.

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Table 1 Desticinent Characteristics by 10 years	A SCVD Dradicted Disle C	*		copyright, inc		
Table 1. Participant Characteristics by 10-year           Variable	$\frac{ASCVD Predicted Kisk C}{All}$ $(n = 9728)$	0%-5% (n = 2383)	>5%-10% (n = 2652)	>108%-15% (n <u>a</u> 1880)	>15% (n= 2813)	P-valu
	(1 ) / 20)	Demogr	· · · ·		(11 2013)	
Age, mean (SD)	62.61 (5.65)	58.09 (3.29)	61.44 (4.76)	64.43(0) 8860 8860 8860 8860 8860 8860 8860 88	66.61 (5.10)	< 0.00
Male, No. (%)	5728 (59)	2203 (92)	1656 (62)	800=4450	999 (36)	< 0.00
Race, No. (%)	5720 (57)	2203 (92)	1050 (02)	S S S S S S S S S S S S S S S S S S S	<i>))))</i> (30)	-0.0
White	7528 (77)	2097 (76)	2027 (76)	1420 (RS5)	2004 (71)	< 0.0
Black	2200 (23)	286 (12)	625 (24)	480326	809 (29)	<0.00
DIACK	2200 (23)	Clinical Co-	· · · ·		809 (29)	
Hypertension No. $(9/)$	2975 (40)			780848)	1770 (63)	< 0.00
Hypertension, No. (%)	3875 (40)	460 (19)	865 (33)			
Diabetes, No. (%)	1495 (15)	47 (2)	143 (5)		1077 (38)	< 0.0
Total Cholesterol, mean (SD), mg/dL	201.81 (36.48)	201.22 (35.14)	200.63 (36.17)	201. <b>52</b> 735.91)	203.4 (37.56)	0.03
HDL Cholesterol, mean (SD), mg/dL	50.84 (16.69)	60.11 (16.59)	50.88 (15.56)	48.5 18.73)	44.48 (14.83)	< 0.0
Current Smoker, No. (%)	1431 (15)	147 (6)	332 (13)	3 3 MBES Minini	622 (22)	< 0.0
		Medicat				
Statin Use, No. (%)	845 (9)	138 (6)	232 (9)		298 (11)	<0.0
		ARIC Fiel	ld Center	- <u>p</u>		
Forsyth, NC, No. (%)	2343 (24)	603 (25)	642 (24)	4 <b>6</b> 1 (25)	637 (23)	< 0.0
Jackson, MS, No. (%)	1955 (20)	256 (11)	570 (22)	4 🗳 4 (💆 )	705 (25)	
Minneapolis, MN, No. (%)	2902 (30)	892 (37)	777 (29)	A 대 (25) 4대 (25) 4왕4 (25) 5월] (27)	722 (26)	
Washington County, MD, No. (%)	2529 (26)	632 (27)	663 (25)	484 (25)	749 (27)	
			lisk Factors	AG (20) 4Gr (20) 55HP (20) 4Gr (20) 55HP (20) 4Gr (20) 55HP (20) 4Gr (20) 55HP (20) 55		
Educational Attainment				s <u>c</u>		
College or Above, No. (%)	3843 (40)	1063 (45)	1097 (41)	sing (38) 7827 (38)	976 (35)	< 0.0
High School/Some College, No. (%)	4110 (42)	1120 (47)	1132 (43)	7988 (48)	1080 (39)	
No High School, No. (%)	1764 (18)	199 (8)	419 (16)	3 第5 (2 )	751 (27)	
ADI, median (IQR) <sup>†</sup>	102 (96.3-108.8)	100 (93.8-104.9)	101.9 (96.1-108.9)	102.5 86.9 109.6)	103.2 (97.6-111.5)	<0.0
Abbreviations: ADI, Area Deprivation Ir					(**********)	
			ar alsease, fibb, high			
2 Risk categories estimated using the 1001						
3 <sup>†</sup> Area Deprivation Index measures area-le	evel social deprivation a	and estimated using	the census-tract of par	ticipants' 5- <b>d</b> igit zip c	ode; higher values	
4 represent higher area-level social depriva	tion.			β		
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1	Incidence rates stratified by education level, ADI category and 10-year PCE estimated
2	risk category are shown in Table 2. A total of 751 incident ASCVD events occurred over ten
3	years of follow up. Mean follow-up was 9.28 years. As expected, 10-year ASCVD incidence
4	rates increased with increases in 10-year PCE estimated risk categories. Conditional on PCE
5	estimated risk category, incidence rates were higher for participants without a high school
6	education than participants with a high school education. Conditional on PCE estimated risk
7	category, incidence rates were higher for participants residing in the most deprived
8	neighborhoods than less deprived neighborhoods, except for participants with PCE estimated risk
9	of >5%-10%. Among participants without a high school degree, incidence rates for ASCVD
10	correlated with the 10-year PCE estimated risk categories. The relationship between 10-year
11	estimated ASCVD risk and observed incidence rates of ASCVD varied for all ADI categories
12	with <15% PCE estimated risk, with less variation for the degree of neighborhood deprivation
13	for participants at the highest PCE estimated risk category of $>15\%$ .
14 15 16 17 18 19 20 21 22	for participants at the highest PCE estimated risk category of >15%.

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Table 2. Event Co	ounts and In	cidence Rates Str	ratified by Predicted A	ASCVD, Ed	lucation, and Area	a Deprivation Index.		n-2021- opyrigh	
ASCVD Predicted Risk*	Events	1,000 Person Years	Rate <sup>†</sup> Per 1,000 Person Years	Events	1,000 Person Years	Rate <sup>†</sup> Per 1,000 Person Years	Events	5006 Person	Rate <sup>†</sup> Per 1,0 Person Year
Treater Hisk		College or A	Above		High School/Son	ne College		Tears So High Schoo	l Degree
0%-5%	28	10.39	2.70	25	10.87	2.30	6	5 <b>2</b> 94	3.09
>5%-10%	45	10.41	4.32	62	10.66	5.72	32	<b>х пх</b> 91	8.19
>10%-15%	35	6.58	5.32	50	7.23	6.91	41	nbe ssrei ssrei	11.79
>15%	145	8.33	17.40	147	9.30	15.81	135	r uses related t	21.38
		Lowest ADI (			Middle Two AD				ıartile
0%-5%	19	9.68	1.96	24	8.29	2.89	16	te sy by	3.06
>5%-10%	56	8.52	6.57	33	8.27	3.99	49	strand dat 57	5.96
>10%-15% >15%	30 119	5.45 6.62	5.51 17.96	37 127	5.45 7.80	6.78 16.29	59 181	nd c	9.24 18.92
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### Risk Modification Analysis

2	Within each PCE predicted risk category, we evaluated if SES modified the relationship
3	between PCE estimated risk and actual ASCVD 10-year observed incidence for each educational
4	attainment level and neighborhood deprivation (college-educated and least deprived
5	neighborhood as the referent) (Table 3). Large risk ratio differences (i.e., more than 10%) within
6	stratum-specific PCE estimated risk categories by SES indicates risk modification. We found
7	that the risk ratio was greater than 1 among those not having a high school degree for all PCE
8	estimated risk categories. This result indicated a heavier burden of ASCVD than in college-
9	educated participants independent of PCE estimated risk. This relative increase in ASCVD risk
10	was statistically significant for groups with >5%-10% and >10%-15% PCE estimated risk; risk
11	ratio 1.78 (95% CI; 1.16-2.76) and 2.15 (95% CI; 1.39-3.34) respectively. The risk of ASCVD
12	in the most deprived neighborhoods (referent least deprived neighborhoods) was significantly
13	higher only for the 10-year PCE estimated risk category >10%-15%, risk ratio 1.65 (95% CI;
14	1.05-2.59).
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16	1.05-2.59).
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		Education			Area Deprivation Index	
10-Year ASCVD Predicted Risk <sup>‡</sup>	No High School RR (95% CI)	High School/Some College RR (95% CI)	College <sup>*</sup> or Above RR (95% CI)	Top ADI Quartile RR (95% CI)	or Niddle Two ADI Quarti B RR (%5% & 1)	Lowest <sup>†</sup> AD Quartile RR (95% Cl
0%-5%	1.16 (0.48-1.53)	0.84 (0.46-1.53)	1.00	1.61 (0.76-3.38)	1.51 <b>6</b> 022 1.51	1.00
070-370	1.10 (0.46-1.55)	0.04 (0.40-1.33)	1.00	1.01 (0.70-3.38)		1.00
>5%-10%	1.78 (1.16-2.76)	1.29 (0.86-1.93)	1.00	0.92 (0.65-1.32)	0.61 and dat	1.00
>10%-15%	2.15 (1.39-3.34)	1.30 (0.82-2.05)	1.00	1.65 (1.05-2.59)	ata 0 1.22 miles 1.22 miles 1.23	1.00
>15%	1.22 (0.99-1.49)	0.92 (0.99-1.49) 1 Index; ASCVD, athero	1.00	1.07 (0.87-1.32)	0.93 (0.74 1.17)	1.00
<ul> <li><sup>*</sup>College or Abo</li> <li><sup>†</sup>Lowest ADI as</li> <li><sup>‡</sup>Risk categorie</li> </ul>	s the referent. s were estimated using	the Pooled Cohort Equa	1	/site/about/guidelines.xh	tio. tio.	

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1	In analyses stratified by educational attainment and neighborhood deprivation,
2	participants without a high school degree who resided in the most deprived neighborhoods had a
3	higher risk of ASCVD for all 10-year PCE estimated risk categories than other SES groups
4	(Supplement Table 1 and Supplement Figure 1). At 10-year PCE estimated risk categories of
5	0%-5% and >10%-15%, having both individual and neighborhood measures of low-SES
6	(without high school education and residing in the most deprived neighborhood) meant a
7	substantially higher risk of ASCVD than either measure alone; risk ratio 3.64 (95% CI, 1.46-
8	9.07) and 4.78 (95% CI, 1.62-14.09) respectively.
9	Observed 10-year absolute risk is presented for each education category, and ADI
10	category across PCE estimated risk categories (Figure 1). We found heterogeneous differences
11	in absolute risk (i.e., risk modification) by SES within stratum-specific PCE estimated risk
12	categories. For example, the difference in absolute risk for participants without a high school
13	degree (referent college-educated) rose by 6 percentage points for PCE estimated risk of >10%-
14	15%; absolute risk difference decreased to 3.4 percentage points for PCE estimated risk >15%
15	(Supplement Figure 2). Heterogenous differences in absolute risk for ADI categories were also
16	noted, albeit smaller differences than educational attainment categories. Differences in absolute
17	risk for participants living in the most deprived neighborhoods (referent least deprived
18	neighborhoods) were 1.2 percentage points higher for PCE estimated risk of >5%-15%, and 1.6
19	percentage points higher for PCE estimated risk 10%-15%.
20	Socioeconomic Status Interaction with PCE Model Analysis
21	The coefficient for each SES risk factor's interactions with estimated risk categories was

statistically significant, and model fit measures to estimate ASCVD risk improved (Table 4). For

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2 3 4	1	example, the likelihood ratio test comparing models 1 and 4, which included education and ADI
4 5 6	2	categories, and their interaction with the PCE 10-year predicted ASCVD risk categories [Model
7 8 9	3	4: Prob(ASCVD) = $\beta_0 + \beta_1(i.Score) + \beta_2(i.Education) + \beta_3(i.ADI) + \beta_4(i.Score \ x \ i.Education) + \beta_4(i.Score \ x \ i.Educati$
9 10 11	4	$\beta_5$ (i.Score x i.ADI)] demonstrated a statistically significant model improvement when measures
12 13	5	of SES was added as an interaction term with PCE estimated risk category ( <i>p</i> -value <0.0001).
14 15 16	6	Additionally, the Akaike information criterion was smaller, suggesting that educational
17 18	7	attainment measures and area deprivation improved model fit for predicting 10-year ASCVD
19 20	8	outcomes compared to the PCE predicted risk category alone.
21 22 23 24	9	outcomes compared to the PCE predicted risk category alone.
25 26 27	10	
28 29 30 31	11	
32 33 34	12	
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	Table 4. Comparison of models predicting	ng ASCVD 10-year Incident	t events with and without meas		
	Model	Number	Akaike <sup>*</sup> Information Criterion	Bayesian <sup>†</sup> Information	
	PCE‡	9728	2371	2386 related 2395 related for the test of test	
	i.PCE + i.Education <sup>§</sup>	9717	2366	2395 ate	0.004
	(i.PCE)x(i.Education)	9717	2331	2395 2374	<0.0001
	i.PCE + i.ADI <sup>II</sup>	9728	2371	2400 te sup	0.14
	(i.PCE) x (i.ADI)	9728	2346	2374 to the composition of the c	< 0.0001
	i.PCE + i.Education + i.ADI	9717	2366	2389 and c 2409 d c	0.002
	(i.PCE) x (i.Education)x(i.ADI)	9717	2328	2458 da <b>(A</b> )	< 0.0001
5 6 7 8 9 0 1 2 3	model indicate an improvement in prec <sup>‡</sup> Pooled Cohort Equations predicted ris <sup>§</sup> Education was stratified into three cat <sup>II</sup> Higher Area Deprivation Index indicat range: top ADI quartile; middle two AI <sup>#</sup> All models that added in the social depriv- factor. <sup>**</sup> All models that added in social depriv- added as a risk factor.	k was stratified into 4 cat egories: no high school; h tes higher neighborhood o DI; lowest ADI quartile (n privation factor as a risk f	high school/some college; co deprivation and was stratifie referent) actor was compared to the l	Pooled Cohort Equation	hout a social deprivation with social deprivation
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2	In the current study, we investigated whether SES's individual and neighborhood
3	measures modify the association between the PCE risk score and actual 10-year ASCVD
4	observed outcomes. We also described the excess burden of ASCVD events among low-SES
5	populations relative to high-SES populations conditional on PCE estimated risk. The PCE
6	estimated risk underestimated incidence of ASCVD events experienced among low-SES groups,
7	and absolute differences in risk among SES measures became most pronounced at higher PCE
8	predicted risk categories, indicating risk modification by measures of SES. Our results also
9	suggest that SES factors' value in predicting incident ASCVD events may vary by PCE predicted
10	risk levels.

A potential reason for the inconsistent evidence for SES's prognostic value to predict 10-year ASCVD outcomes could be the different outcome modeling strategies used in prior studies. Prior studies have historically modeled SES as an independent risk factor or confounder.<sup>[19-22, 24]</sup> Classical social epidemiological frameworks such as the "fundamentals causes of health inequalities theory" suggest that despite any 10-year estimated risk of ASCVD for an individual at a given time, the clinical trajectory and outcomes are both influenced and dependent on the individual's SES.<sup>[26, 34-37]</sup> According to the fundamental cause theory, high-SES individuals, possess a variety of flexible resources (i.e., knowledge, money, prestige, and power) to protect their health in a way that low-SES individuals cannot. As such, the effects of the non-SES traditional ASCVD risk factors used in the PCE (i.e., hypertension and total cholesterol) on ASCVD incidence will likely be modified by whether the individual is of lower or higher SES. Our results show that having at least a college-education was protective against ASCVD relative to not having a high school degree across all risk levels, with greater protective effects at higher

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PCE estimated risk levels. Living in the least deprived neighborhood was also protective, but likely less consistently than an individual SES exposure measure due to the potential for the ecological fallacy that can occur when making inferences about individuals based on group-level factors.

5 The substantial model fit improvement by interacting SES factors with the PCE risk score 6 suggests that this modeling strategy will significantly improve ASCVD outcome prediction 7 accuracy, but further analysis is required. Any 10-year ASCVD model that does not account for 8 SES as a risk modifier may lead to measurement error. Prior modeling studies and current 9 ASCVD risk models that incorporate SES into predicting risk do not incorporate SES as an 10 interaction term into the model.

The current PCE model estimates a graded ASCVD risk irrespective of SES status. Our results show that the PCE placed disadvantaged individuals with an inherently higher risk of ASCVD into the corresponding 10-year estimated ASCVD risk categories at the expense of over-estimating risk for higher SES individuals. At the very least, the PCE will direct ASCVD preventive care to our most disadvantaged populations. The same population which research shows are less likely to receive appropriate preventive measures are just as likely to receive needed ASCVD risk management as their higher SES counterparts when the PCE is used to guide ASCVD prevention.[38-41] 

Additional research is needed to improve ASCVD risk prediction among different SES groups and prevent ASCVD among disadvantaged populations. Our data only allow us to describe these epidemiologic phenomena of excess ASCVD events experienced among lower SES individuals and possible ways to model future risk, but our analysis does not permit us to

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1	identify underlying mechanisms. Many unknown factors exist along the socio-ecological
2	paradigm that works in concert with individual behavioral and physiologic factors to lead to a
3	higher burden of ASCVD among low-SES populations.
4	These findings have clinical and policy implications, with current guideline
5	recommendations for using the PCE model to guide primary prevention ASCVD strategies in
6	cholesterol management, hypertension management, and aspirin use. <sup>[16, 18, 42, 43]</sup> For example, at
7	an estimated 10-year PCE risk of 7.5%, statin therapy is recommended for primary prevention of
8	ASCVD. <sup>[18]</sup> We show that a higher SES is a risk-protecting factor, and the absolute risk of
9	ASCVD does not cross the 7.5% threshold until a PCE 10-year risk of >15% (Figure 1). The use
10	of SES in estimating an individual's risk can potentially improve the efficiency of resource use
11	and more precisely target interventions to achieve population-level objectives to decrease the
12	ASCVD burden globally and in the United States. However, drug therapy decisions for primary
13	prevention of ASCVD should incorporate other qualifying factors such as patient preference and
14	not base decisions solely on ASCVD risk estimates.
15	We don't advocate for the use of SES in the clinical decision of ASCVD preventive
16	therapies for US patients without a validated ASCVD prediction model that incorporates SES.
17	Our findings do suggest validation of an ASCVD prediction model that appropriately
18	incorporates SES as an ASCVD risk modifier is warranted. Model validation comparison
19	measures such as net risk reclassification -similar to Mosley et al. evaluation of PCE risk
20	prediction improvement with adding a polygenic risk score – can help guide decisions on the
21	utility of incorporating SES to guide clinical decision making. <sup>[44-45]</sup> In addition, what and how
22	SES measures are incorporated into an ASCVD prediction model – e.g., summation of SES
23	factors versus single SES factors – requires further exploration. <sup>[46-47]</sup>
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#### 1 Limitations

The study has several limitations. The ARIC study is restricted to four communities in the United States and is not nationally or internationally representative. Furthermore, some communities have limited diversity with respect to race or SES measures. The measurement of outcomes based on ARIC abstraction of hospitalization data is a strength since it avoids reliance on self-report of events. However, some hospitalizations may be missing since comparing Medicare claims to ARIC records showed that between 10% to 20% of hospitalizations are missed if only one source is used.<sup>[48]</sup> Internal exploration of this issue suggested that the additional hospitalizations were not correlated with our SES measures and did not substantively affect the results.

Results from our area-level deprivation analyses must be considered in the context of analytical limitations. For example, the use of the ADI as an aggregate measure of SES can potentially introduce ecological fallacy bias. Furthermore, we did not account for possible movement to other neighborhoods for our sample over 10-years of follow up. A potential misclassification bias of area-level deprivation exposure may exist over time. We expect that this misclassification bias is likely small. Our results are conservative estimates because bias from random measurement error is towards the null. Also, we did not adjust for ASCVD preventive medication use -e.g., statin therapy -as a time-varying covariate in our models. Whilemedication use could influence ASCVD outcome differences by SES, our focus was on the overall differences in prediction and outcome by SES rather than on causal pathways of the differences. Last, we didn't control for the ARIC study site in our area-level deprivation analyses. Without controlling for the ARIC study site, homogeneity in participant characteristics (i.e., a predominantly African-American/Black population versus a predominantly white

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population) by ARIC study site may have resulted in the loss of statistical power to detect a
 meaningful difference in ASCVD outcomes according to ADI.

#### Conclusions

4 The current study extends our understanding of the relationship between socioeconomic 5 factors and the risk of heart disease and stroke outcomes. We find that the associations of PCE 6 risk score and incident ASCVD are dependent on education level and area deprivation. Our 7 findings may partially explain the discrepancy in results from earlier studies evaluating the utility 8 of adding SES as a prognostic measure into ASCVD prediction models. Given the potentially 9 important clinical and policy implications of our results, we suggest further refinement of the 10 PCE model is needed to improve the estimation of risk for all populations, both historically 11 vulnerable and less vulnerable populations. We believe the development of a new ASCVD risk 12 prediction model should apply appropriate validation methods and use a more racially and 13 ethnically diverse observational cohort for validation. 14 *Acknowledgements* 15 The authors thank the staff and participants of the ARIC study for their important contributions. 16 Sources of Funding 17 18 This work was supported in whole or in part with Federal funds from the National Heart, Lung, 19 and Blood Institute, National Institutes of Health, Department of Health and Human Services, 20 under Contract nos. (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, 21 HHSN268201700005I, HHSN268201700004I). 22

2		
3 4	1	Competing Interests
5 6	2	None declared.
7 8	3	
9 10	4	Ethics Approval
11 12	5	Institutional review boards at all ARIC centers in the United States approved study procedures.
13 14		
15 16	6	All participants gave written informed consent for the collection of data used in this study. This
17 18	7	study was approved by the University of North Carolina at Chapel Hill Institutional Review
19 20	8	Board (IRB# 18-1187).
21 22	9	
23 24	10	
25 26 27	11	Contributors
27 28 29	12	KH, PC, and SS initiated the project. JR and BK performed all statistical analyses. KH had
30 31	13	main responsibility for writing the manuscript. KH, PC, SS, JR, BK, RF, CS and MH all
32 33	14	contributed to the statistical analyses, interpretation of outcomes, and provided comments on the
34 35	15	manuscript. KH, PC, SS, JR, BK, RF, CS and MH all read and approved the final manuscript.
36 37		
38 39	16	PC is the senior author.
40 41	17	
42 43	18	Data Sharing Statement
44	10	No additional data are evailable. All data relevant to the study are included in the article or
45 46	19	No additional data are available. All data relevant to the study are included in the article or
47 48	20	uploaded as supplementary information.
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4	2		the Prevention, Detection, Evaluation, and Management of High Blood Pressure in
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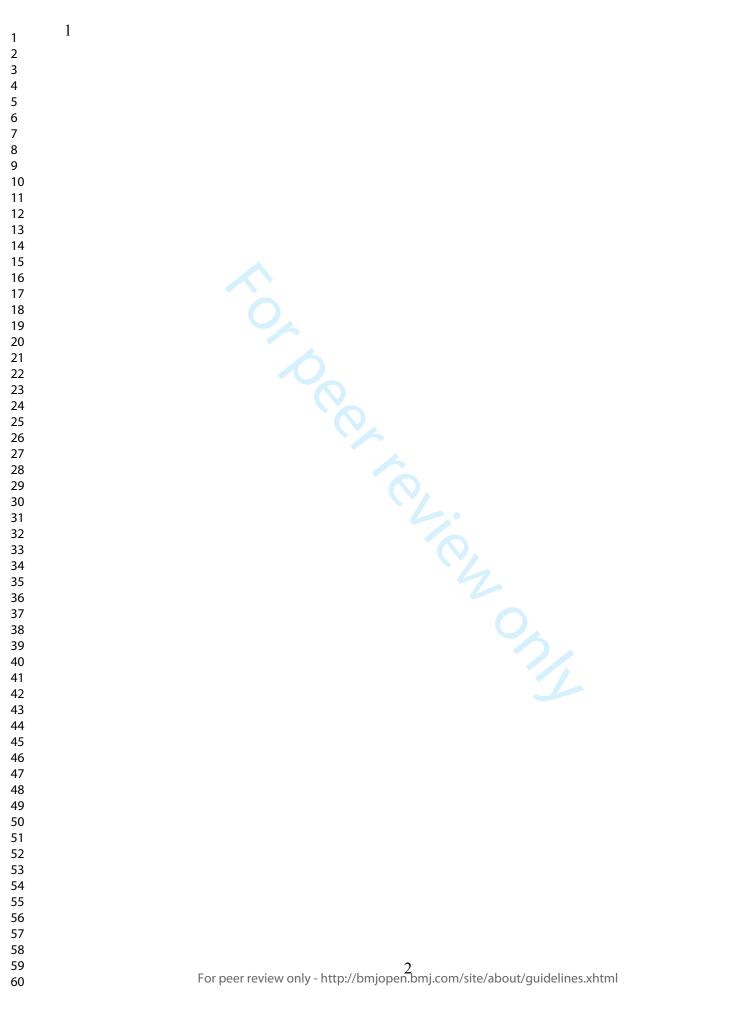
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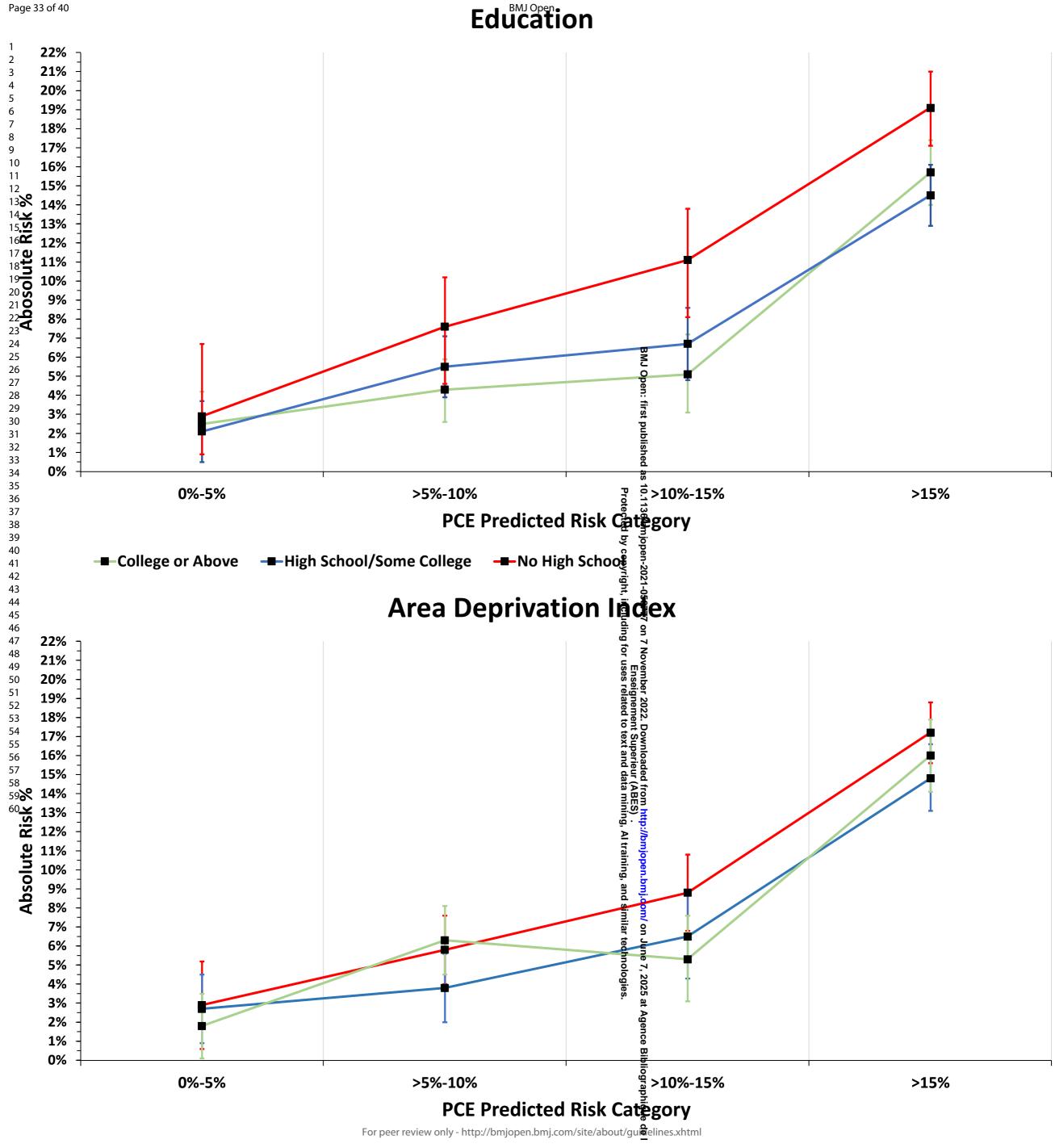
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1 2 3 4	BM Open Figure 1. Observed 10-year incidence rate of ASCVD events by socioeconomic status. 10-year incidence rate atainment (A) and Area Deprivation Index; ASCVD, atheroselerotic cardiovascular disease; PCE, Pooled Cohor 'Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants	Superieur (ABES) text and data mini	mjopen-2021-QSCVD events by education ations to represent the second sec	n
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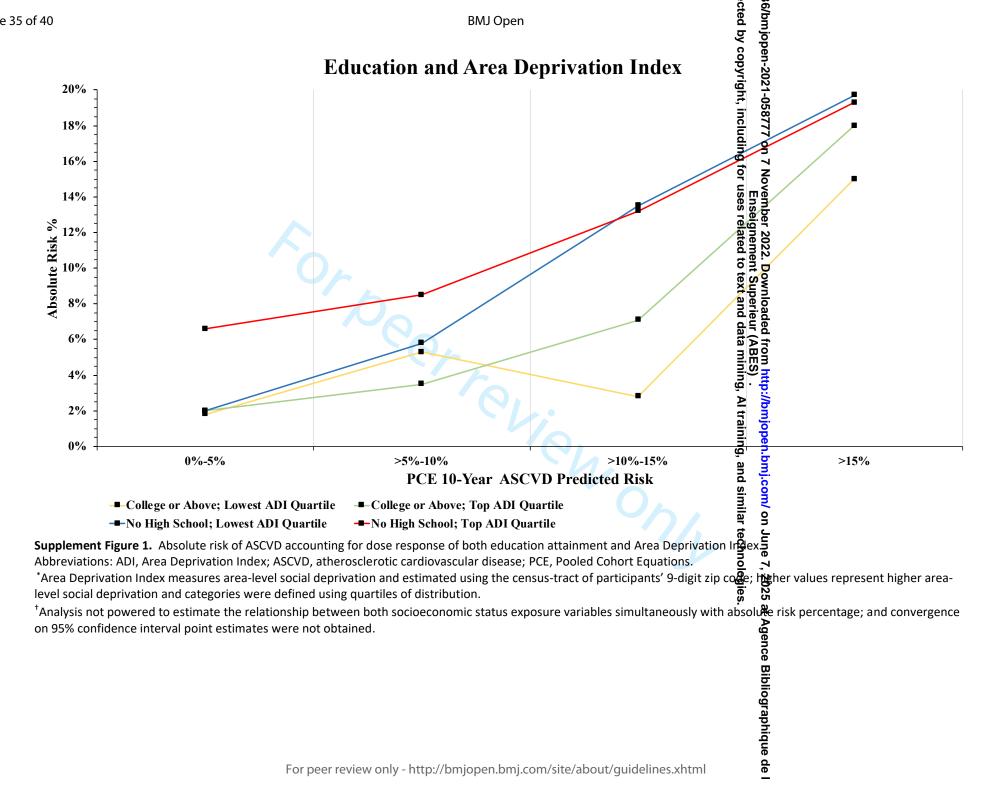


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	Area	0%-5% Deprivation	n Index		>5%-10%			>10%-15%	,	including	ı >15%	
	Area	Deprivation	n Index			>5%-10%			>10%-15%			
				Area Deprivation Index			Area Deprivation Index			⊊ An≩	Z o Maa Deprivation Index	
	Top ADI Quartile RR (95% Cl)	Middle Two ADI Quartile RR (95% CI)	Lowest ADI Quartile RR (95% CI)	Top ADI Quartile RR (95%	Middle Two ADI Quartile RR (95% CI)	Lowest ADI Quartile RR (95% CI)	Top ADI Quartile RR (95% CI)	Middle Two ADI Quartile RR (95% CI)	Lowest ADI Quartile RR (95% CI)	Ses related to contract to con		Lowest ADI Quartile RR (95% CI)
No High School*	3.64 (1.46- 9.07)			1.59 (0.92- 2.76)	1.18 (0.51- 2.72)	1.10 (0.35- 3.48)	4.78 (1.62- 14.09)	1.88 (0.69- 5.15)	4.93 (1.94- 12.50)	Superieur (ABES) . 1.2009 Amining, Alera 0.964 Amining, Alera 0.964 Amining, Alera	1.22 (0.84- 1.77)	1.31 (0.85- 2.02)
High School/Some College	1.23 (0.43- 3.54)	1.23 (0.49- 3.09)	1.07 (0.39- 2.92)	1.04 (0.58- 1.88)	0.69 (0.36- 1.32)	1.48 (0.87- 2.53)	2.28 (0.89- 5.82)	2.48 (0.95- 6.47)	2.52 (0.97- 6.52)	5). S). 0.95Aldraining, apdsign 0.95Aldraining, apdsign 1.2608. 1.6691 1.6691	0.90 (0.65- 1.26)	1.08 (0.75- 1.54)
College or Above	1.08 (0.30- 3.87)	2.33 (0.94- 5.75)	1.00	0.66 (0.28- 1.53)	0.62 (0.28- 1.36)	1.00	2.59 (1.00- 6.70)	2.48 (0.97- 6.36)	1.00	g, apd 1.2 <b>pd</b> (0.8 <b>5</b> 1.6 <b>5</b> 1.6 <b>5</b> 1.6 <b>1</b> 1.6 <b>1</b> 1.6 <b>1</b>		1.00

	PCE Risk Category	Absolute Risk % (95% Cl)	Absolute Risk % Difference (College or Above Referent)
No High School	0%-5%	2.9% (0.9%-6.7%)	0.4%
	>5%-10%	7.6% (5.0%-10.2%)	3.3%
	>10%-15%	11.1% (8.4%-13.8%)	6.0%
	>15%	19.1% (17.1%-21.0%)	3.4%
ligh School/Some College	0%-5%	2.1% (0.5%-3.7%)	-0.4%
	>5%-10%	5.5% (3.9%-7.1%)	1.2%
	>10%-15%	6.7% (4.8%-8.6%)	1.6%
	>15%	14.5% (12.9%-16.1%)	-1.2%
ollege or Above	0%-5%	2.5% (0.9%-4.2%)	
	>5%-10%	4.3% (2.6%-5.9%)	Referent
	>10%-15%	5.1% (3.1%-7.2%)	
	>15%	15.7% (14.0%-17.4%)	
	Δ.	on Deprivation I	nday
	A	rea Deprivation I Absolute Risk %	Absolute Risk % Difference
	PCE Risk Category	(95% CI)	(Lowest ADI Quartile as Referent)
op ADI Quartile	0%-5%	2.9% (0.6%-5.2%)	1.1%
	>5%-10%	5.8% (4.0%-7.6%)	-0.5%
	>10%-15%	8.8% (6.8%-10.8%)	3.5%
	>15%	17.2% (15.6%-18.8%)	1.2%
liddle Two ADI Quartile	0%-5%	2.7% (0.9%-4.5%)	0.9%
	>5%-10%	3.8% (2.0%-5.6%)	-2.5%
	>10%-15%	6.5% (4.3%-8.7%)	1.2%
	>15%	14.8% (13.1%-16.6%)	-1.2%
owest ADI Quartile	0%-5%	1.8% (0.1%-3.5%)	
	>5%-10%	6.3% (4.5%-8.1%)	Referent
	>10%-15%	5.3% (3.1%-7.6%)	
	>15%	16.0% (14.1%-17.9%)	
pplement Figure 2. [ edicted risk category.		bsolute risk of ASCVD ever	its between levels of socioeconomic status, cond

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		STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of <i>count studies</i> 문 ]	
Section/Topic	Item #	Recommendation	Reported on page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract ឆ្លូ ញុត្ត	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what અૹ gound	2-3
Introduction		atem diamente	
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods	1	andre	
Study design	4	Present key elements of study design early in the paper	5-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure by w-up, and data collection	5-9
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifie를. Gove diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	11-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which growpings were chosen and why	9-11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9-11
		(b) Describe any methods used to examine subgroups and interactions	9-11
		(c) Explain how missing data were addressed	9-11
		(d) If applicable, explain how loss to follow-up was addressed	Na (only used participants witho missing).

Results	(e) Describe any sensitivity analyses	11
	(e) Describe any sensitivity analyses	
Participants 13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	11-12
	eligible, included in the study, completing follow-up, and analysed	
	(b) Give reasons for non-participation at each stage	11-12
	(c) Consider use of a flow diagram	No (discussed in
	(c) Consider use of a flow diagram	text)
Descriptive data 14	* (a) Give characteristics of study participants (eg demographic, clinical, social) and information の すい の の の の の の の の の の の の の の の の の	11-12
	(b) Indicate number of participants with missing data for each variable of interest       Image: Constraint of the second s	na
	(c) Summarise follow-up time (eg, average and total amount)	8, 25
Outcome data 15	* Report numbers of outcome events or summary measures over time	25-26
Main results 10		8-10; 22-23
	interval). Make clear which confounders were adjusted for and why they were included	
	(b) Report category boundaries when continuous variables were categorized	8-11
	(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaning fur time period	21, 23
Other analyses 1	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-10
Discussion		
Key results 18	Summarise key results with reference to study objectives	11
Limitations		
Interpretation 20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability 2:		11-14
Other information	Discuss the generalisability (external validity) of the study results	
Funding 22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on	15
	which the present article is based	

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