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

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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 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 college-educated) 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.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and morbidity in the United States (US) and globally.[1-4] A substantially higher burden of ASCVD is experienced among those with lower socioeconomic status (SES).[5-14] 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.[15-18] 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.[19] 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.[20-22] 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.[23-25] 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.

How prior ASCVD prediction models incorporated SES into the model is a potential reason for the discrepancies in understanding the prognostic value and use of SES in ASCVD prediction models. SES traditionally is modeled as an independent risk factor or confounder.[19-22,24] However, SES's prognostic value in predicting ASCVD risk is likely identifying populations most impacted by proximate causes of ASCVD. If true, SES incorporated into risk prediction models as a risk modifier is more appropriate in determining ASCVD risk than an independent risk factor. For example, the health impact of hypertension over 10-years is different for an individual living in abject poverty versus an individual residing in an affluent neighborhood. SES likely modifies the association between risk estimated from algorithms that use proximate causes of ASCVD (i.e., hypertension and smoking) and actual ASCVD incidence.

This study explored whether SES modifies the association of PCE 10-year estimated risk with actual ASCVD 10-year incidence using data from the Atherosclerosis Risk in Communities (ARIC) study. That is, actual observed ASCVD 10-year incidence will vary depending on the PCE estimated risk and the individual's SES. We defined SES along two dimensions typically utilized in social epidemiology research: educational attainment and neighborhood deprivation.[26] Educational attainment as a measure of individual SES was selected over other measures – e.g., income level – due to being a stable measure of SES that remain relatively stable over an adult life course when compared to other measures. We hypothesize that the long-term effects of proximate causes of ASCVD measured in the PCE (e.g., hypertension and smoking) impact on actual ASCVD incidence are dependent on SES (i.e., risk modification).

Methods

Data Source

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.[27] 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.

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.

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 co-morbidities 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.

Socioeconomic Status Measures

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

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.

Estimation of ASCVD Risk

We estimated individual ASCVD risk using the published PCE covariate parameters.[15] The following factors were used to estimate ASCVD risk according to the PCE: age, gender, race (Black or other), levels of total cholesterol, levels of high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, evidence of treatment for high blood pressure, diabetes status, and current smoker status. We used laboratory measures collected at Visit 4 to estimate risk using the PCE. We partitioned the ARIC study population into four categories of 10-year PCE predicted ASCVD risk: 0%-5%, >5%-10%, >10%-15%, and >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.[27,31] 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

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.[27,32] 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

Univariate descriptive statistics examined baseline participant-level characteristics. We calculated the mean and standard deviation (SD) for continuous variables, percentages for dichotomous variables, and median with interquartile range (IQR) for ordinal or nominal variables. We performed bivariate analysis using Pearson's χ^2 test or Kruskal-Wallis test for 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 pseudo-values 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

levels and ADI categories. Absolute risk differences between SES measures were estimated for each PCE 10-year estimated risk category (0%-5%, >5%-10%, >10%-15%, >15%). The referent group for educational attainment level is a college degree or above, and the referent group for ADI is residing in the least deprived neighborhoods (lowest ADI quartile). Point estimates are reported with 95% confidence intervals (CI).

Generalized linear estimation models with a log-link function were used to predict the 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, additional models included: 1) education category added as a predictor and interacted with the PCE score, 2) ADI category added as a predictor and interacted with the PCE category, and 3) both education and ADI categories as predictors and interacted with the PCE category. Generalized linear models compared took the following form:

(1) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score})$

(2) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score}) + \beta_3(\text{i.Education}) + \beta_4(\text{i.Score x i.Education})$

(3) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score}) + \beta_2(\text{i.ADI}) + \beta_3(\text{i.Score x i.ADI})$

(4) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score}) + \beta_2(\text{i.Education}) + \beta_3(\text{i.ADI}) + \beta_4(\text{i.Score x i.Education}) + \beta_5(\text{i.Score x i.ADI})$

The likelihood ratio test, Akaike Information Criterion, and Bayesian Information Criterion evaluations were performed to compare model fit statistics of the different models. All analyses were performed using STATA, version 13.

Patient and Public Involvement

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 participants without a high school degree or residing in the most deprived neighborhoods.

Table 1. Participant Characteristics by 10-year ASCVD Predicted Risk Category*

Variable	All (n = 9728)	0%-5% (n = 2383)	>5%-10% (n = 2652)	>10%-15% (n = 1880)	>15% (n= 2813)	P-value
Demographics						
Age, mean (SD)	62.61 (5.65)	58.09 (3.29)	61.44 (4.76)	64.11 (5.19)	66.61 (5.10)	<0.001
Male, No. (%)	5728 (59)	2203 (92)	1656 (62)	870 (46)	999 (36)	<0.001
Race, No. (%)						
White	7528 (77)	2097 (76)	2027 (76)	1400 (75)	2004 (71)	<0.001
Black	2200 (23)	286 (12)	625 (24)	480 (26)	809 (29)	
Clinical Co-morbidities						
Hypertension, No. (%)	3875 (40)	460 (19)	865 (33)	780 (42)	1770 (63)	<0.001
Diabetes, No. (%)	1495 (15)	47 (2)	143 (5)	228 (12)	1077 (38)	<0.001
Total Cholesterol, mean (SD), mg/dL	201.81 (36.48)	201.22 (35.14)	200.63 (36.17)	201.82 (36.91)	203.4 (37.56)	0.034
HDL Cholesterol, mean (SD), mg/dL	50.84 (16.69)	60.11 (16.59)	50.88 (15.56)	48.53 (15.73)	44.48 (14.83)	<0.001
Current Smoker, No. (%)	1431 (15)	147 (6)	332 (13)	330 (18)	622 (22)	<0.001
Medication Use						
Statin Use, No. (%)	845 (9)	138 (6)	232 (9)	177 (9)	298 (11)	<0.001
ARIC Field Center						
Forsyth, NC, No. (%)	2343 (24)	603 (25)	642 (24)	441 (23)	637 (23)	<0.001
Jackson, MS, No. (%)	1955 (20)	256 (11)	570 (22)	424 (23)	705 (25)	
Minneapolis, MN, No. (%)	2902 (30)	892 (37)	777 (29)	511 (27)	722 (26)	
Washington County, MD, No. (%)	2529 (26)	632 (27)	663 (25)	504 (27)	749 (27)	
Social-Risk Factors						
Educational Attainment						
College or Above, No. (%)	3843 (40)	1063 (45)	1097 (41)	707 (38)	976 (35)	<0.001
High School/Some College, No. (%)	4110 (42)	1120 (47)	1132 (43)	758 (41)	1080 (39)	
No High School, No. (%)	1764 (18)	199 (8)	419 (16)	395 (21)	751 (27)	
ADI, median (IQR)†	102 (96.3-108.8)	100 (93.8-104.9)	101.9 (96.1-108.9)	102.5 (96.9-109.6)	103.2 (97.6-111.5)	<0.001

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein.

*Risk categories estimated using the Pooled Cohort Equations.

†Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants' 5-digit zip code; higher values represent higher area-level social deprivation.

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

Table 2. Event Counts and Incidence Rates Stratified by Predicted ASCVD, Education, and Area Deprivation Index.

ASCVD Predicted Risk*	Events	1,000 Person Years	Rate† Per 1,000 Person Years	Events	1,000 Person Years	Rate† Per 1,000 Person Years	Events	1,000 Person Years	Rate† Per 1,000 Person Years
	College or Above			High School/Some College			No High School Degree		
0%-5%	28	10.39	2.70	25	10.87	2.30	6	1.94	3.09
>5%-10%	45	10.41	4.32	62	10.66	5.72	32	3.91	8.19
>10%-15%	35	6.58	5.32	50	7.23	6.91	41	3.48	11.79
>15%	145	8.33	17.40	147	9.30	15.81	135	6.31	21.38
	Lowest ADI Quartile			Middle Two ADI Quartile			Top ADI Quartile		
0%-5%	19	9.68	1.96	24	8.29	2.89	16	5.23	3.06
>5%-10%	56	8.52	6.57	33	8.27	3.99	49	8.23	5.96
>10%-15%	30	5.45	5.51	37	5.45	6.78	59	6.39	9.24
>15%	119	6.62	17.96	127	7.80	16.29	181	9.57	18.92

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease.

*Risk categories were estimated using the Pooled Cohort Equations.

†Incidence rate of combined stroke and coronary heart disease was estimated over ten years.

‡Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants 9-digit zip code; higher values represent higher area-level social deprivation, and categories were defined using quartiles of distribution.

Risk Modification Analysis

Within each PCE predicted risk category, we evaluated if SES modified the relationship between PCE estimated risk and actual ASCVD 10-year observed incidence for each educational attainment level and neighborhood deprivation (college-educated and least deprived neighborhood as the referent) (Table 3). Large risk ratio differences (i.e., more than 10%) within stratum-specific PCE estimated risk categories by SES indicates risk modification. We found that the risk ratio was greater than 1 among those not having a high school degree for all PCE estimated risk categories. This result indicated a heavier burden of ASCVD than in college-educated participants independent of PCE estimated risk. This relative increase in ASCVD risk was statistically significant for groups with >5%-10% and >10%-15% PCE estimated risk; risk ratio 1.78 (95% CI; 1.16-2.76) and 2.15 (95% CI; 1.39-3.34) respectively. The risk of ASCVD in the most deprived neighborhoods (referent least deprived neighborhoods) was significantly higher only for the 10-year PCE estimated risk category >10%-15%, risk ratio 1.65 (95% CI; 1.05-2.59).

Table 3. Risk ratios comparing observed ASCVD incidence rates across education and ADI categories within each predicted risk category

	Education			Area Deprivation Index		
10-Year ASCVD Predicted Risk‡	**No High School RR (95% CI)**	**High School/Some College RR (95% CI)**	**College* or Above RR (95% CI)**	**Top ADI Quartile RR (95% CI)**	**Middle Two ADI Quartiles RR (95% CI)**	**Lowest† ADI Quartile RR (95% CI)**
0%-5%	1.16 (0.48-1.53)	0.84 (0.46-1.53)	1.00	1.61 (0.76-3.38)	1.51 (0.71-3.04)	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 (0.37-0.97)	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 (0.78-2.03)	1.00
>15%	1.22 (0.99-1.49)	0.92 (0.99-1.49)	1.00	1.07 (0.87-1.32)	0.93 (0.74-1.17)	1.00

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; RR, risk ratio.

*College or Above as referent.

†Lowest ADI as the referent.

‡Risk categories were estimated using the Pooled Cohort Equations.

In analyses stratified by educational attainment and neighborhood deprivation, participants without a high school degree who resided in the most deprived neighborhoods had a higher risk of ASCVD for all 10-year PCE estimated risk categories than other SES groups (Supplement Table 1). At 10-year PCE estimated risk categories of 0%-5% and >10%-15%, having both individual and neighborhood measures of low-SES (without high school education and residing in the most deprived neighborhood) meant a substantially higher risk of ASCVD than either measure alone; risk ratio 3.64 (95% CI, 1.46-9.07) and 4.78 (95% CI, 1.62-14.09) respectively.

Observed 10-year absolute risk is presented for each education category, and ADI category across PCE estimated risk categories (Figure 1). We found heterogeneous differences in absolute risk (i.e., risk modification) by SES within stratum-specific PCE estimated risk categories. For example, the difference in absolute risk for participants without a high school degree (referent college-educated) rose by 6 percentage points for PCE estimated risk of >10%-15%; absolute risk difference decreased to 3.4 percentage points for PCE estimated risk >15% (Supplement Figure 1). Heterogenous differences in absolute risk for ADI categories were also noted, albeit smaller differences than educational attainment categories. Differences in absolute risk for participants living in the most deprived neighborhoods (referent least deprived neighborhoods) were 1.2 percentage points higher for PCE estimated risk of >5%-15%, and 1.6 percentage points higher for PCE estimated risk 10%-15%.

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

example, the likelihood ratio test comparing models 1 and 4, which included education and ADI categories, and their interaction with the PCE 10-year predicted ASCVD risk categories [Model 4: Prob(ASCVD) = β_0 + β_1(i.Score) + β_2(i.Education) + β_3(i.ADI) + β_4(i.Score x i.Education) + β_5(i.Score x i.ADI)] demonstrated a statistically significant model improvement when measures of SES was added as an interaction term with PCE estimated risk category (*p*-value <0.0001). Additionally, the Akaike information criterion was smaller, suggesting that educational attainment measures and area deprivation improved model fit for predicting 10-year ASCVD outcomes compared to the PCE predicted risk category alone.

Table 4. Comparison of models predicting ASCVD 10-year Incident events with and without measures of Socioeconomic Status

Model	Number	Akaike* Information Criterion	Bayesian† Information Criterion	Likelihood Ratio Tests P-Value
PCE‡	9728	2371	2386	--
i.PCE + i.Education§	9717	2366	2395	0.004
(i.PCE)x(i.Education)	9717	2331	2374	<0.0001
i.PCE + i.ADI‖	9728	2371	2400	0.14
(i.PCE) x (i.ADI)	9728	2346	2389	<0.0001
i.PCE + i.Education + i.ADI	9717	2366	2409	0.002
(i.PCE) x (i.Education)x(i.ADI)	9717	2328	2458	<0.0001

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohort Equations.

*Akaike Information Criterion measures goodness-of-fit between observed values and expected values; lower scores compared to referent indicate an improvement in prediction.

†Bayesian Information Criterion measures goodness-of-fit between observed values and expected values; lower scores compared to a referent model indicate an improvement in prediction.

‡Pooled Cohort Equations predicted risk was stratified into 4 categories of risk: 0-5%; >5-10%; >10-15%; >15%.

§Education was stratified into three categories: no high school; high school/some college; college or above (referent)

‖Higher Area Deprivation Index indicates higher neighborhood deprivation and was stratified into three categories according to the interquartile range: top ADI quartile; middle two ADI; lowest ADI quartile (referent)

#All models that added in the social deprivation factor as a risk factor was compared to the Pooled Cohort Equations without a social deprivation factor.

**All models that added in social deprivation as an interaction term was compared to the Pooled Cohort Equations model with social deprivation added as a risk factor.

Discussion

In the current study, we investigated whether SES's individual and neighborhood measures modify the association between the PCE risk score and actual 10-year ASCVD observed outcomes. We also described the excess burden of ASCVD events among low-SES populations relative to high-SES populations conditional on PCE estimated risk. The PCE estimated risk underestimated incidence of ASCVD events experienced among low-SES groups, and absolute differences in risk among SES measures became most pronounced at higher PCE predicted risk categories, indicating risk modification by measures of SES. Our results also suggest that SES factors' value in predicting incident ASCVD events may vary by PCE predicted 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.[19-22,24] 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.[26,34-37] 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

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.

The substantial model fit improvement by interacting SES factors with the PCE risk score suggests that this modeling strategy will significantly improve ASCVD outcome prediction accuracy, but further analysis is required. Any 10-year ASCVD model that does not account for SES as a risk modifier may lead to measurement error. Prior modeling studies and current ASCVD risk models that incorporate SES into predicting risk do not incorporate SES as an 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.[38-41] However, our findings show that the PCE model may inadvertently lead to the inverse care law.[42,43] 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

SES individuals and possible ways to model future risk, but our analysis does not permit us to identify underlying mechanisms. Many unknown factors exist along the socio-ecological paradigm that works in concert with individual behavioral and physiologic factors to lead to a 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 strategies in cholesterol management, hypertension management, and aspirin use.[16,18,44,45] For example, at an estimated 10-year PCE risk of 7.5%, statin therapy is recommended for primary prevention of ASCVD.[18] We show that a higher SES is a risk-protecting factor, and the absolute risk of ASCVD does not cross the 7.5% threshold until a PCE 10-year risk of >15% (Figure 1). The use of SES in estimating an individual's risk can potentially improve the efficiency of resource use and more precisely target interventions to achieve population-level objectives to decrease the ASCVD burden globally and in the United States. However, without a validated ASCVD prediction model that incorporates SES in the US, we don't advocate for the use of SES in the clinical decision of ASCVD preventive therapies for US patients.

Limitations

The study has several limitations. The ARIC study is restricted to 4 communities in the United States and is not nationally or internationally representative. 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.[46] 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. 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.

Conclusions

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 among historically vulnerable and less vulnerable populations.

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Competing Interests

None declared.

Ethics Approval

Institutional review boards at all ARIC centers in the United States approved study procedures. All participants gave written informed consent for the collection of data used in this study. This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board (IRB# 18-1187).

Contributors

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

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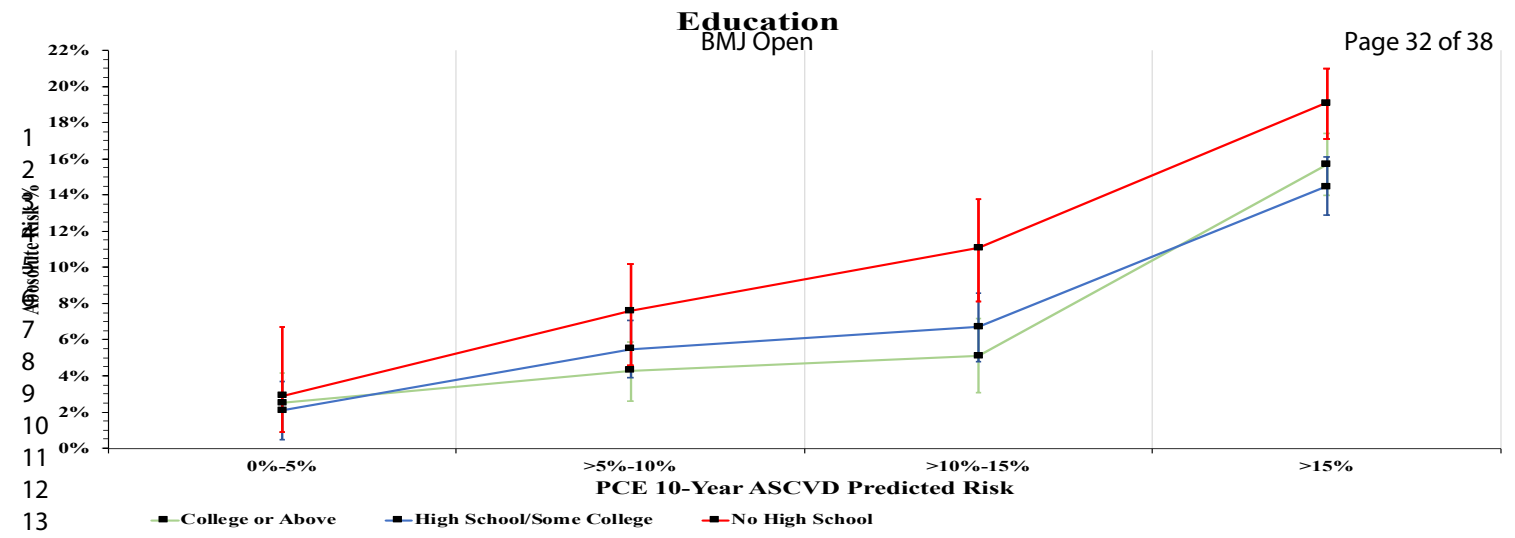
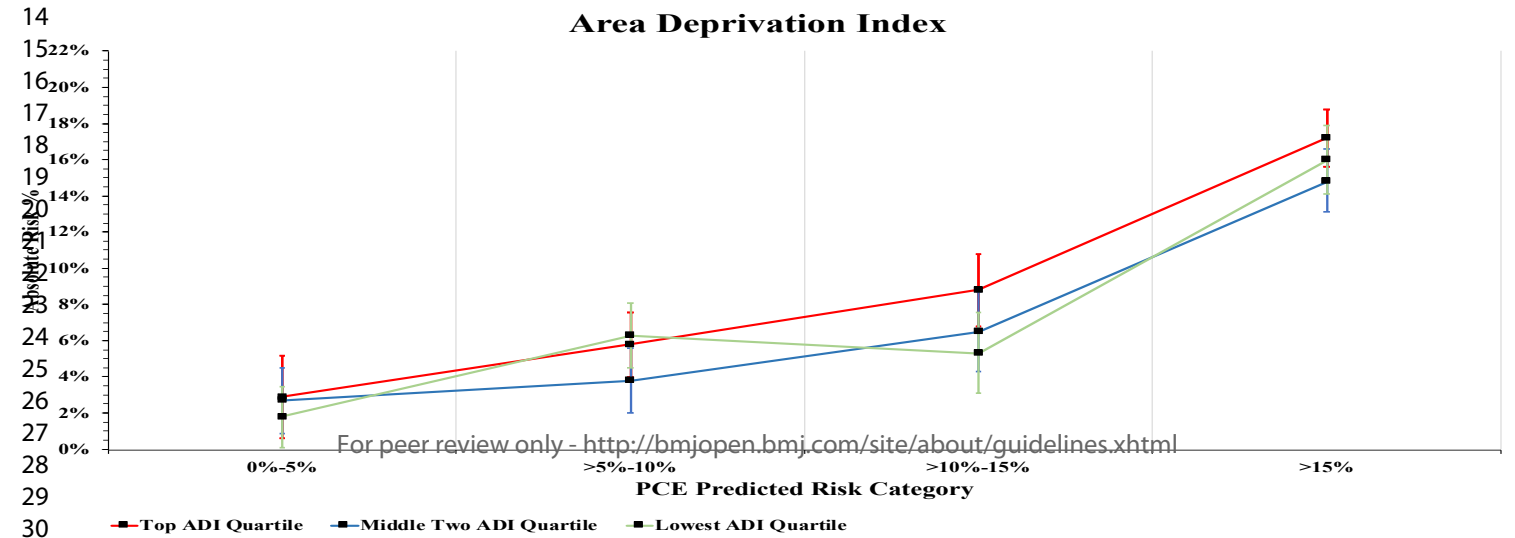
*Figure 1. Observed 10-year incidence rate of ASCVD events by education and Area Deprivation Index.

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohort Equations

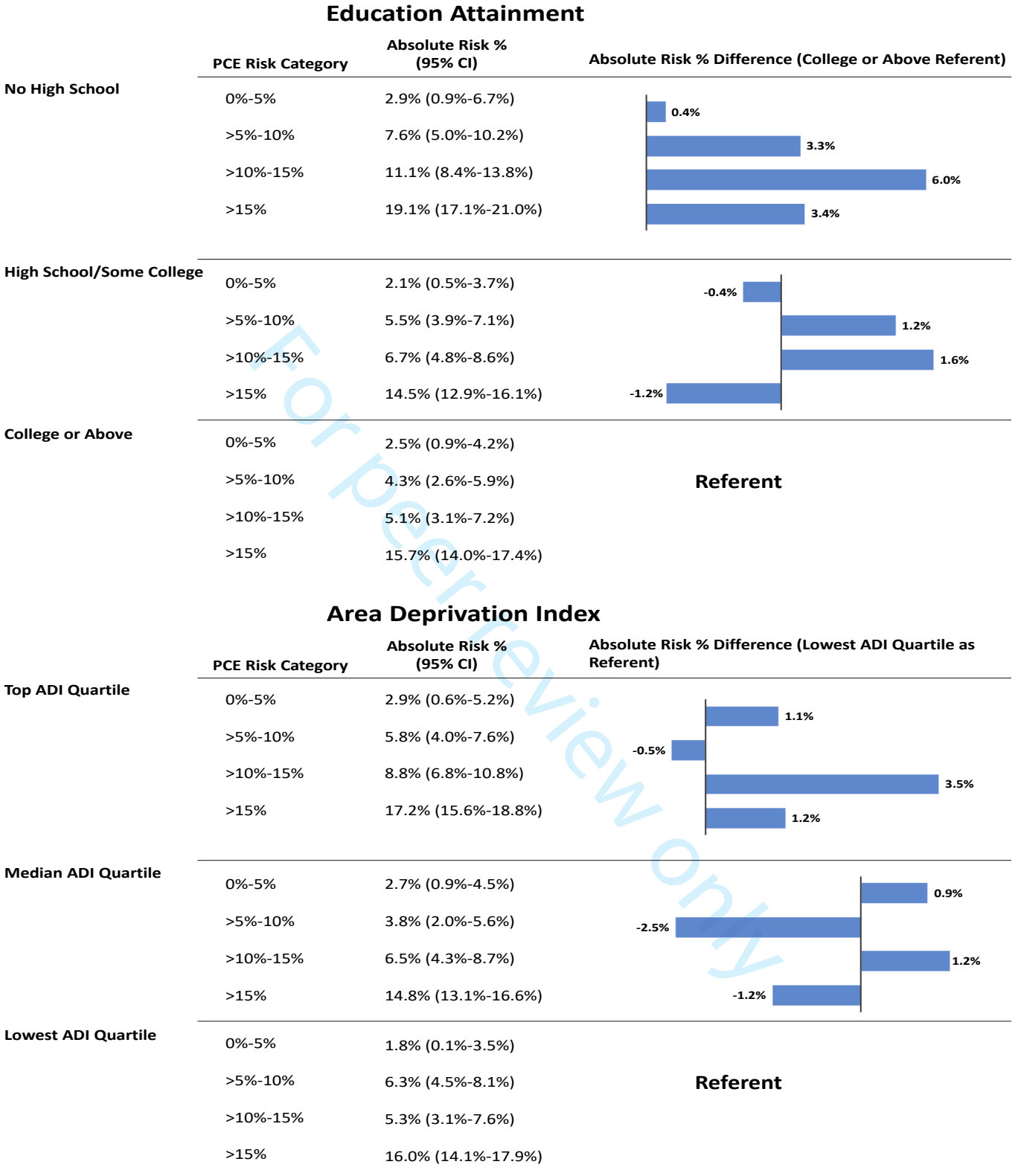
*Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants' 9-digit zip cod

1





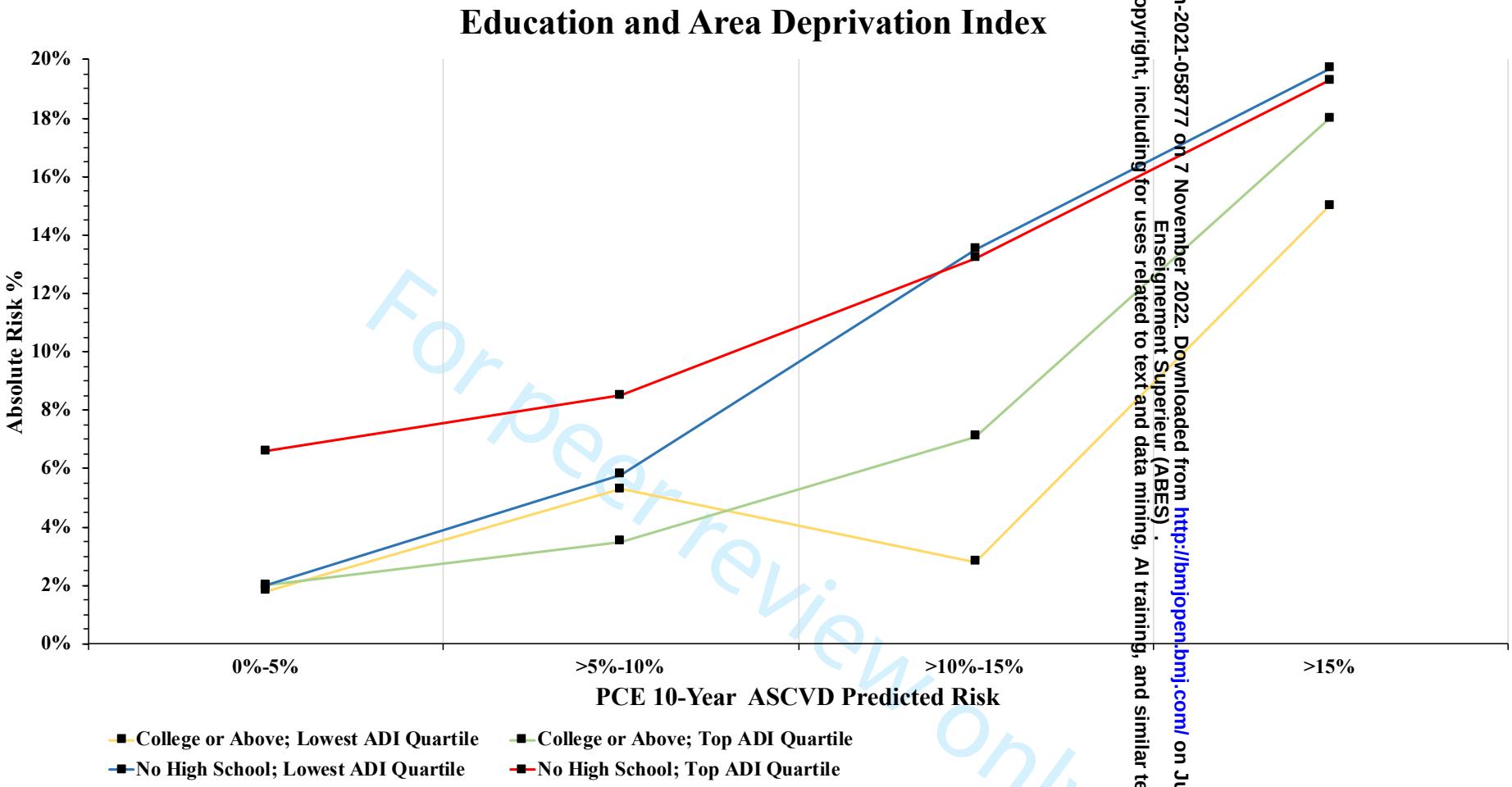
SUPPLEMENTAL MATERIAL



Supplement Figure 1. Difference in 10-year absolute risk of ASCVD events between levels of socioeconomic status, conditional on predicted risk category.

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease

*Predicted risk categories were estimated using the Pooled Cohort Equations.



Supplement Figure 2. Absolute risk of ASCVD accounting for dose response of both education attainment and Area Deprivation Index.
Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohort Equations.
*Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants' 9-digit zip code; higher values represent higher area-level social deprivation and categories were defined using quartiles of distribution.
†Analysis not powered to estimate the relationship between both socioeconomic status exposure variables simultaneously with absolute risk percentage; and convergence on 95% confidence interval point estimates were not obtained.

Supplement Table 1. Risk Ratios comparing 10-year incident ASCVD event rate across Socioeconomic Status (Education and Area Deprivation Index) within category of predicted risk

	10-Year ASCVD Predicted Risk											
	0%-5%			0%-5%			>10%-15%			>15%		
	Area Deprivation Index			Area Deprivation Index			Area Deprivation Index			Area Deprivation Index		
	Top ADI Quartile RR (95% CI)	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)	Top ADI Quartile RR (95% CI)	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)
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)	1.24 (0.91-1.74)	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)	0.93 (0.68-1.34)	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	1.20 (0.81-1.69)	0.97 (0.67-1.40)	1.00

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; RR, relative risk.
*Risk ratio cannot be estimated for social deprivation category at a predicted risk of 0-5% due to lack of ASCVD incidence for category.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
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			
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, follow-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 modifiers. 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 without missing).

		(*e*) Describe any sensitivity analyses	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	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 on exposures 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	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (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 meaningful 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			
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 separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-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

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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 college-educated) 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.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and morbidity in the United States (US) and globally.[[1], 2-4] A substantially higher burden of ASCVD is experienced among those with lower socioeconomic status (SES).[5-14] 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.[15-18] 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.[19] 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.[20-22] 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.[23-25] 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.

How prior ASCVD prediction models incorporated SES into the model is a potential reason for the discrepancies in understanding the prognostic value and use of SES in ASCVD prediction models. SES traditionally is modeled as an independent risk factor or confounder.[19-22, 24] However, SES's prognostic value in predicting ASCVD risk is likely identifying populations most impacted by proximate causes of ASCVD. If true, SES incorporated into risk prediction models as a risk modifier is more appropriate in determining ASCVD risk than an independent risk factor. For example, the health impact of hypertension over 10-years is different for an individual living in abject poverty versus an individual residing in an affluent neighborhood. SES likely modifies the association between risk estimated from algorithms that use proximate causes of ASCVD (i.e., hypertension and smoking) and actual ASCVD incidence.

This study explored whether SES modifies the association of PCE 10-year estimated risk with actual ASCVD 10-year incidence using data from the Atherosclerosis Risk in Communities (ARIC) study. That is, actual observed ASCVD 10-year incidence will vary depending on the PCE estimated risk and the individual's SES. We defined SES along two dimensions typically utilized in social epidemiology research: educational attainment and neighborhood deprivation.[26] Educational attainment as a measure of individual SES was selected over other measures – e.g., income level – due to being a stable measure of SES that remain relatively stable over an adult life course when compared to other measures. We hypothesize that the long-term effects of proximate causes of ASCVD measured in the PCE (e.g., hypertension and smoking) impact on actual ASCVD incidence are dependent on SES (i.e., risk modification).

Methods

Data Source

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.[27] 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.

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.

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 co-morbidities 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.

Socioeconomic Status Measures

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

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.

Estimation of ASCVD Risk

We estimated individual ASCVD risk using the published PCE covariate parameters.[15] The following factors were used to estimate ASCVD risk according to the PCE: age, gender, race (Black or other), levels of total cholesterol, levels of high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, evidence of treatment for high blood pressure, diabetes status, and current smoker status. We used laboratory measures collected at Visit 4 to estimate risk using the PCE. We partitioned the ARIC study population into four categories of 10-year PCE predicted ASCVD risk: 0%-5%, >5%-10%, >10%-15%, and >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.[27, 31] 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

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.[27, 32] 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

Univariate descriptive statistics examined baseline participant-level characteristics. We calculated the mean and standard deviation (SD) for continuous variables, percentages for dichotomous variables, and median with interquartile range (IQR) for ordinal or nominal variables. We performed bivariate analysis using Pearson's χ^2 test or Kruskal-Wallis test for 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 pseudo-values 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

levels and ADI categories. Absolute risk differences between SES measures were estimated for each PCE 10-year estimated risk category (0%-5%, >5%-10%, >10%-15%, >15%). The referent group for educational attainment level is a college degree or above, and the referent group for ADI is residing in the least deprived neighborhoods (lowest ADI quartile). Point estimates are reported with 95% confidence intervals (CI).

Generalized linear estimation models with a log-link function were used to predict the 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, additional models included: 1) education category added as a predictor and interacted with the PCE score, 2) ADI category added as a predictor and interacted with the PCE category, and 3) both education and ADI categories as predictors and interacted with the PCE category. Generalized linear models compared took the following form:

(1) $\text{Prob(ASCVD)} = \beta_{0+}\beta_1(\text{i.Score})$

(2) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score}) + \beta_3(\text{i.Education}) + \beta_4(\text{i.Score x i.Education})$

(3) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score}) + \beta_2(\text{i.ADI}) + \beta_3(\text{i.Score x i.ADI})$

(4) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score}) + \beta_2(\text{i.Education}) + \beta_3(\text{i.ADI}) + \beta_4(\text{i.Score x i.Education}) + \beta_5(\text{i.Score x i.ADI})$

The likelihood ratio test, Akaike Information Criterion, and Bayesian Information Criterion evaluations were performed to compare model fit statistics of the different models. All analyses were performed using STATA, version 13.

Patient and Public Involvement

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 participants without a high school degree or residing in the most deprived neighborhoods.

Table 1. Participant Characteristics by 10-year ASCVD Predicted Risk Category*

Variable	All (n = 9728)	0%-5% (n = 2383)	>5%-10% (n = 2652)	>10%-15% (n = 1880)	>15% (n= 2813)	P-value
Demographics						
Age, mean (SD)	62.61 (5.65)	58.09 (3.29)	61.44 (4.76)	64.11 (4.19)	66.61 (5.10)	<0.001
Male, No. (%)	5728 (59)	2203 (92)	1656 (62)	870 (46)	999 (36)	<0.001
Race, No. (%)						
White	7528 (77)	2097 (76)	2027 (76)	1400 (75)	2004 (71)	<0.001
Black	2200 (23)	286 (12)	625 (24)	480 (26)	809 (29)	
Clinical Co-morbidities						
Hypertension, No. (%)	3875 (40)	460 (19)	865 (33)	780 (42)	1770 (63)	<0.001
Diabetes, No. (%)	1495 (15)	47 (2)	143 (5)	228 (12)	1077 (38)	<0.001
Total Cholesterol, mean (SD), mg/dL	201.81 (36.48)	201.22 (35.14)	200.63 (36.17)	201.82 (36.91)	203.4 (37.56)	0.034
HDL Cholesterol, mean (SD), mg/dL	50.84 (16.69)	60.11 (16.59)	50.88 (15.56)	48.53 (15.73)	44.48 (14.83)	<0.001
Current Smoker, No. (%)	1431 (15)	147 (6)	332 (13)	330 (18)	622 (22)	<0.001
Medication Use						
Statin Use, No. (%)	845 (9)	138 (6)	232 (9)	177 (9)	298 (11)	<0.001
ARIC Field Center						
Forsyth, NC, No. (%)	2343 (24)	603 (25)	642 (24)	441 (23)	637 (23)	<0.001
Jackson, MS, No. (%)	1955 (20)	256 (11)	570 (22)	424 (23)	705 (25)	
Minneapolis, MN, No. (%)	2902 (30)	892 (37)	777 (29)	511 (27)	722 (26)	
Washington County, MD, No. (%)	2529 (26)	632 (27)	663 (25)	504 (27)	749 (27)	
Social-Risk Factors						
Educational Attainment						
College or Above, No. (%)	3843 (40)	1063 (45)	1097 (41)	707 (38)	976 (35)	<0.001
High School/Some College, No. (%)	4110 (42)	1120 (47)	1132 (43)	738 (41)	1080 (39)	
No High School, No. (%)	1764 (18)	199 (8)	419 (16)	365 (19)	751 (27)	
ADI, median (IQR)†	102 (96.3-108.8)	100 (93.8-104.9)	101.9 (96.1-108.9)	102.5 (96.9-109.6)	103.2 (97.6-111.5)	<0.001

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein.

*Risk categories estimated using the Pooled Cohort Equations.

†Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants' 5-digit zip code; higher values represent higher area-level social deprivation.

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

Table 2. Event Counts and Incidence Rates Stratified by Predicted ASCVD, Education, and Area Deprivation Index.

ASCVD Predicted Risk*	Events	1,000 Person Years	Rate† Per 1,000 Person Years	Events	1,000 Person Years	Rate† Per 1,000 Person Years	Events	1,000 Person Years	Rate† Per 1,000 Person Years
	College or Above			High School/Some College			No High School Degree		
0%-5%	28	10.39	2.70	25	10.87	2.30	6	1.94	3.09
>5%-10%	45	10.41	4.32	62	10.66	5.72	32	3.91	8.19
>10%-15%	35	6.58	5.32	50	7.23	6.91	41	3.48	11.79
>15%	145	8.33	17.40	147	9.30	15.81	135	6.31	21.38
	Lowest ADI Quartile			Middle Two ADI Quartile			Top ADI Quartile		
0%-5%	19	9.68	1.96	24	8.29	2.89	16	5.23	3.06
>5%-10%	56	8.52	6.57	33	8.27	3.99	49	8.23	5.96
>10%-15%	30	5.45	5.51	37	5.45	6.78	59	6.39	9.24
>15%	119	6.62	17.96	127	7.80	16.29	181	9.57	18.92

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease.

*Risk categories were estimated using the Pooled Cohort Equations.

†Incidence rate of combined stroke and coronary heart disease was estimated over ten years.

‡Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants 9-digit zip code; higher values represent higher area-level social deprivation, and categories were defined using quartiles of distribution.

Risk Modification Analysis

Within each PCE predicted risk category, we evaluated if SES modified the relationship between PCE estimated risk and actual ASCVD 10-year observed incidence for each educational attainment level and neighborhood deprivation (college-educated and least deprived neighborhood as the referent) (Table 3). Large risk ratio differences (i.e., more than 10%) within stratum-specific PCE estimated risk categories by SES indicates risk modification. We found that the risk ratio was greater than 1 among those not having a high school degree for all PCE estimated risk categories. This result indicated a heavier burden of ASCVD than in college-educated participants independent of PCE estimated risk. This relative increase in ASCVD risk was statistically significant for groups with >5%-10% and >10%-15% PCE estimated risk; risk ratio 1.78 (95% CI; 1.16-2.76) and 2.15 (95% CI; 1.39-3.34) respectively. The risk of ASCVD in the most deprived neighborhoods (referent least deprived neighborhoods) was significantly higher only for the 10-year PCE estimated risk category >10%-15%, risk ratio 1.65 (95% CI; 1.05-2.59).

Table 3. Risk ratios comparing observed ASCVD incidence rates across education and ADI categories within each predicted risk category

	Education			Area Deprivation Index		
10-Year ASCVD Predicted Risk‡	**No High School RR (95% CI)**	**High School/Some College RR (95% CI)**	**College* or Above RR (95% CI)**	**Top ADI Quartile RR (95% CI)**	**Middle Two ADI Quartiles RR (95% CI)**	**Lowest† ADI Quartile RR (95% CI)**
0%-5%	1.16 (0.48-1.53)	0.84 (0.46-1.53)	1.00	1.61 (0.76-3.38)	1.51 (0.73-3.04)	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 (0.39-0.97)	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 (0.81-2.03)	1.00
>15%	1.22 (0.99-1.49)	0.92 (0.99-1.49)	1.00	1.07 (0.87-1.32)	0.93 (0.74-1.17)	1.00

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; RR, risk ratio.

*College or Above as referent.

†Lowest ADI as the referent.

‡Risk categories were estimated using the Pooled Cohort Equations.

In analyses stratified by educational attainment and neighborhood deprivation, participants without a high school degree who resided in the most deprived neighborhoods had a higher risk of ASCVD for all 10-year PCE estimated risk categories than other SES groups (Supplement Table 1). At 10-year PCE estimated risk categories of 0%-5% and >10%-15%, having both individual and neighborhood measures of low-SES (without high school education and residing in the most deprived neighborhood) meant a substantially higher risk of ASCVD than either measure alone; risk ratio 3.64 (95% CI, 1.46-9.07) and 4.78 (95% CI, 1.62-14.09) respectively.

Observed 10-year absolute risk is presented for each education category, and ADI category across PCE estimated risk categories (Figure 1). We found heterogeneous differences in absolute risk (i.e., risk modification) by SES within stratum-specific PCE estimated risk categories. For example, the difference in absolute risk for participants without a high school degree (referent college-educated) rose by 6 percentage points for PCE estimated risk of >10%-15%; absolute risk difference decreased to 3.4 percentage points for PCE estimated risk >15% (Supplement Figure 1). Heterogenous differences in absolute risk for ADI categories were also noted, albeit smaller differences than educational attainment categories. Differences in absolute risk for participants living in the most deprived neighborhoods (referent least deprived neighborhoods) were 1.2 percentage points higher for PCE estimated risk of >5%-15%, and 1.6 percentage points higher for PCE estimated risk 10%-15%.

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

example, the likelihood ratio test comparing models 1 and 4, which included education and ADI categories, and their interaction with the PCE 10-year predicted ASCVD risk categories [Model 4: Prob(ASCVD) = β_0 + β_1(i.Score) + β_2(i.Education) + β_3(i.ADI) + β_4(i.Score x i.Education) + β_5(i.Score x i.ADI)] demonstrated a statistically significant model improvement when measures of SES was added as an interaction term with PCE estimated risk category (*p*-value <0.0001). Additionally, the Akaike information criterion was smaller, suggesting that educational attainment measures and area deprivation improved model fit for predicting 10-year ASCVD outcomes compared to the PCE predicted risk category alone.

Table 4. Comparison of models predicting ASCVD 10-year Incident events with and without measures of Socioeconomic Status

Model	Number	Akaike* Information Criterion	Bayesian† Information Criterion	Likelihood Ratio Tests P-Value
PCE‡	9728	2371	2386	--
i.PCE + i.Education§	9717	2366	2395	0.004
(i.PCE)x(i.Education)	9717	2331	2374	<0.0001
i.PCE + i.ADI‖	9728	2371	2400	0.14
(i.PCE) x (i.ADI)	9728	2346	2389	<0.0001
i.PCE + i.Education + i.ADI	9717	2366	2409	0.002
(i.PCE) x (i.Education)x(i.ADI)	9717	2328	2458	<0.0001

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohort Equations.

*Akaike Information Criterion measures goodness-of-fit between observed values and expected values; lower scores compared to referent indicate an improvement in prediction.

†Bayesian Information Criterion measures goodness-of-fit between observed values and expected values; lower scores compared to a referent model indicate an improvement in prediction.

‡Pooled Cohort Equations predicted risk was stratified into 4 categories of risk: 0-5%; >5-10%; >10-15%; >15%.

§Education was stratified into three categories: no high school; high school/some college; college or above (referent)

‖Higher Area Deprivation Index indicates higher neighborhood deprivation and was stratified into three categories according to the interquartile range: top ADI quartile; middle two ADI; lowest ADI quartile (referent)

#All models that added in the social deprivation factor as a risk factor was compared to the Pooled Cohort Equations without a social deprivation factor.

**All models that added in social deprivation as an interaction term was compared to the Pooled Cohort Equations model with social deprivation added as a risk factor.

Discussion

In the current study, we investigated whether SES's individual and neighborhood measures modify the association between the PCE risk score and actual 10-year ASCVD observed outcomes. We also described the excess burden of ASCVD events among low-SES populations relative to high-SES populations conditional on PCE estimated risk. The PCE estimated risk underestimated incidence of ASCVD events experienced among low-SES groups, and absolute differences in risk among SES measures became most pronounced at higher PCE predicted risk categories, indicating risk modification by measures of SES. Our results also suggest that SES factors' value in predicting incident ASCVD events may vary by PCE predicted 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.[19-22, 24] 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.[26, 34-37] 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

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.

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

identify underlying mechanisms. Many unknown factors exist along the socio-ecological paradigm that works in concert with individual behavioral and physiologic factors to lead to a 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 strategies in cholesterol management, hypertension management, and aspirin use.[16, 18, 42, 43] For example, at an estimated 10-year PCE risk of 7.5%, statin therapy is recommended for primary prevention of ASCVD.[18] We show that a higher SES is a risk-protecting factor, and the absolute risk of ASCVD does not cross the 7.5% threshold until a PCE 10-year risk of >15% (Figure 1). The use of SES in estimating an individual's risk can potentially improve the efficiency of resource use and more precisely target interventions to achieve population-level objectives to decrease the ASCVD burden globally and in the United States. However, without a validated ASCVD prediction model that incorporates SES in the US, we don't advocate for the use of SES in the clinical decision of ASCVD preventive therapies for US patients. Our findings do suggest validation of an ASCVD prediction model that appropriately incorporates SES is warranted. Model validation comparison measures such as net risk reclassification –similar to Mosley et al. evaluation of PCE risk prediction improvement with adding a polygenic risk score – can help guide decisions on the utility of incorporating SES to guide clinical decision making.[44, 45]

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.[46] 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. While medication 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.

Conclusions

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.

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Competing Interests

None declared.

Ethics Approval

Institutional review boards at all ARIC centers in the United States approved study procedures. All participants gave written informed consent for the collection of data used in this study. This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board (IRB# 18-1187).

Contributors

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

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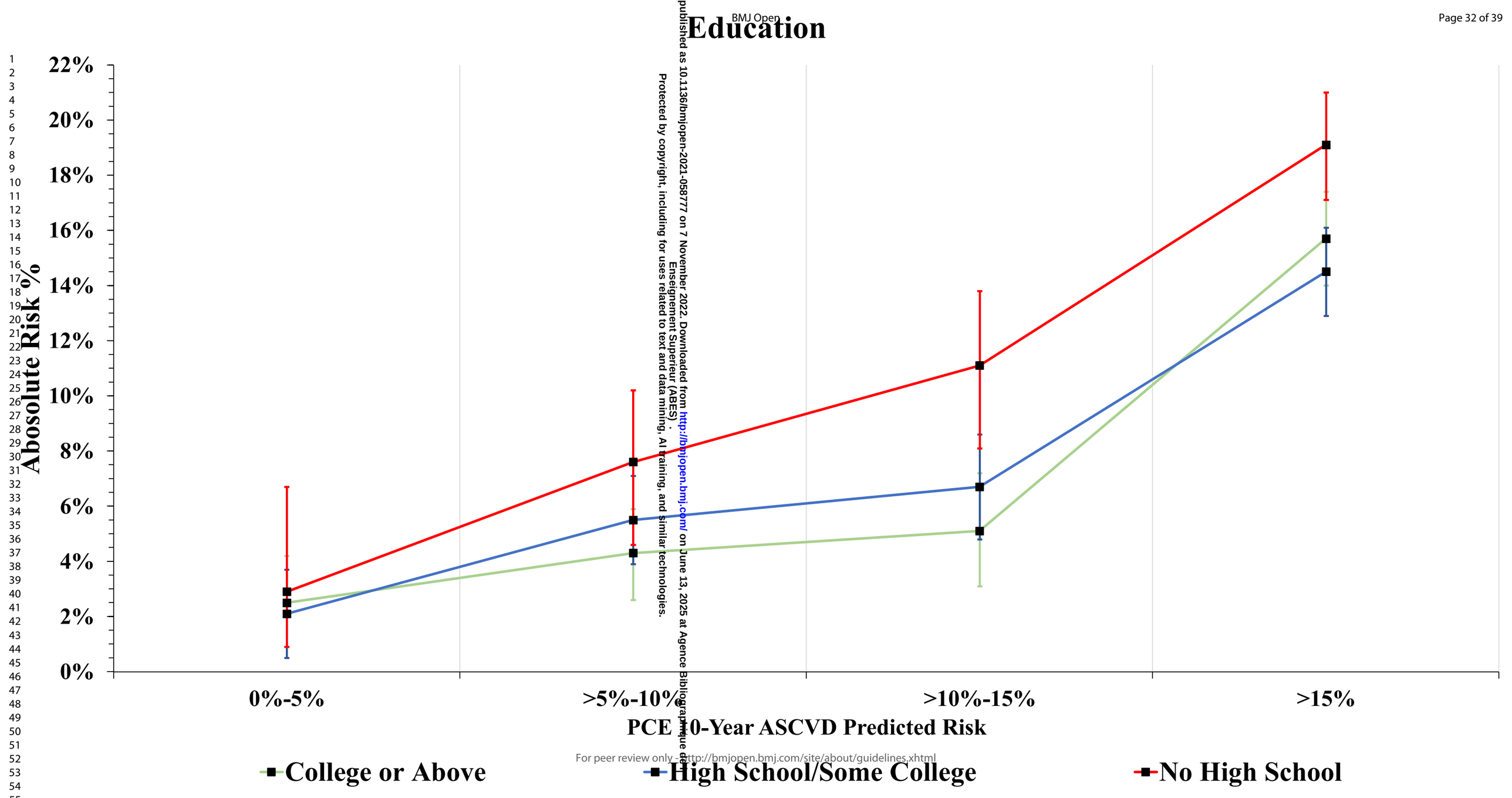
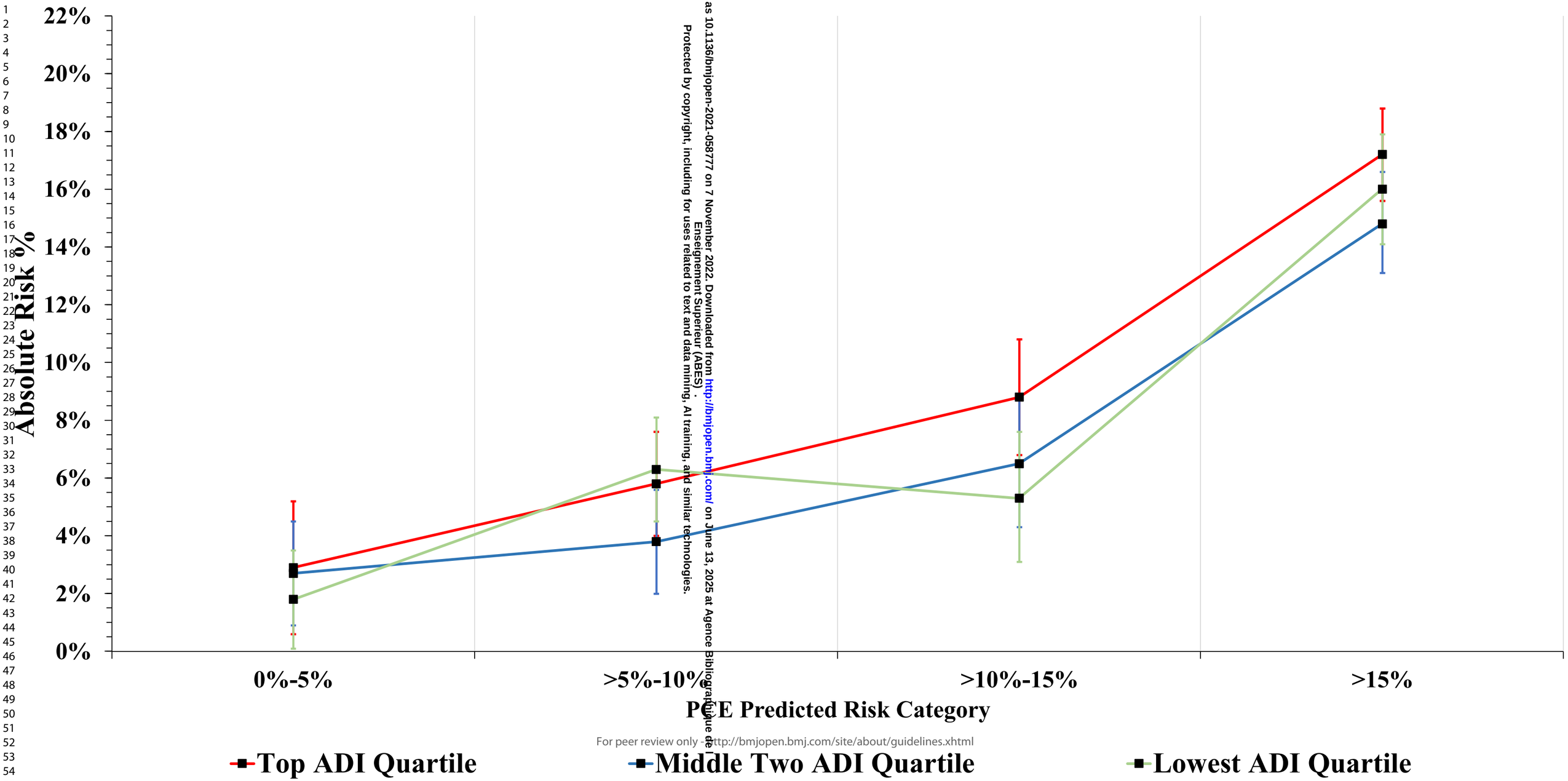
Figure 1. Observed 10-year incidence rate of ASCVD events by socioeconomic status. 10-year incidence rate of ASCVD events by education attainment (A) and Area Deprivation Index (B).

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohort Equations

*Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants 5-digit zip code

1





SUPPLEMENTAL MATERIAL

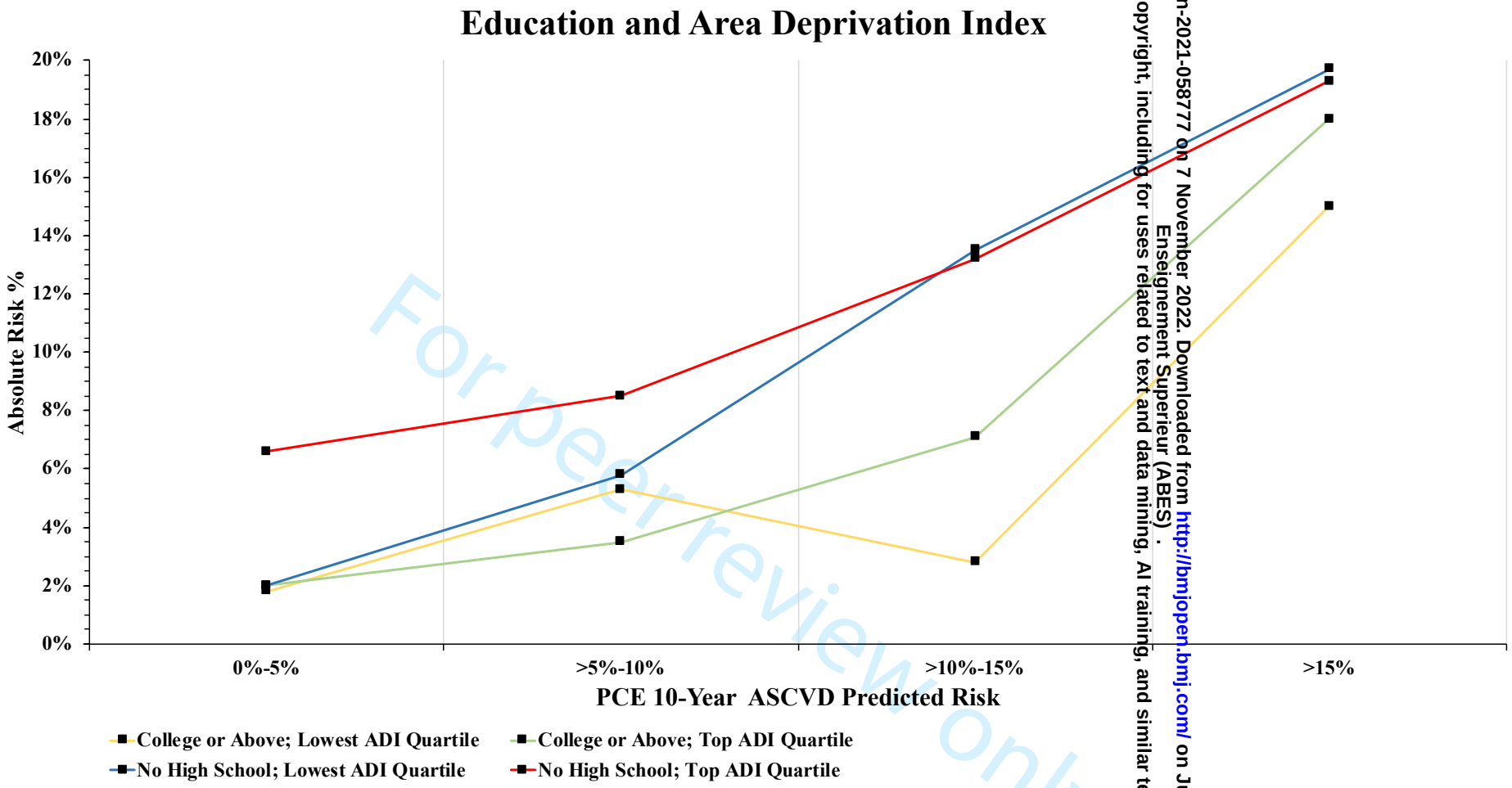
Education Attainment

	PCE Risk Category	Absolute Risk % (95% CI)	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%
High 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%
College or Above	0%-5%	2.5% (0.9%-4.2%)	Referent
	>5%-10%	4.3% (2.6%-5.9%)	
	>10%-15%	5.1% (3.1%-7.2%)	
	>15%	15.7% (14.0%-17.4%)	

Area Deprivation Index

	PCE Risk Category	Absolute Risk % (95% CI)	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%)	Referent
	>5%-10%	6.3% (4.5%-8.1%)	
	>10%-15%	5.3% (3.1%-7.6%)	
	>15%	16.0% (14.1%-17.9%)	

Supplement Figure 1. Difference in 10-year absolute risk of ASCVD events between levels of socioeconomic status, conditional on predicted risk category.
Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease
*Predicted risk categories were estimated using the Pooled Cohort Equations.



Supplement Figure 2. Absolute risk of ASCVD accounting for dose response of both education attainment and Area Deprivation Index.
Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohort Equations.
*Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants' 9-digit zip code; higher values represent higher area-level social deprivation and categories were defined using quartiles of distribution.
†Analysis not powered to estimate the relationship between both socioeconomic status exposure variables simultaneously with absolute risk percentage; and convergence on 95% confidence interval point estimates were not obtained.

Supplement Table 1. Risk Ratios comparing 10-year incident ASCVD event rate across Socioeconomic Status (Education and Area Deprivation Index) within category of predicted risk

	10-Year ASCVD Predicted Risk											
	0%-5%			>5%-10%			>10%-15%			>15%		
	Area Deprivation Index			Area Deprivation Index			Area Deprivation Index			Area Deprivation Index		
	Top ADI Quartile RR (95% CI)	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)	Top ADI Quartile RR (95% CI)	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)
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)	1.28 (0.93-1.74)	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)	0.95 (0.68-1.34)	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	1.20 (0.85-1.69)	0.97 (0.67-1.40)	1.00

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; RR, relative risk.
*Risk ratio cannot be estimated for social deprivation category at a predicted risk of 0-5% due to lack of ASCVD incidence for category.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
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			
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, follow-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 modifiers. 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 without missing).

		(*e*) Describe any sensitivity analyses	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	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 on exposures 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	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (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 meaningful 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			
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 separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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Short Title: Socioeconomic Status and Cardiovascular Disease Risk Prediction

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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 college-educated) 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.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and morbidity in the United States (US) and globally.[1-4] A substantially higher burden of ASCVD is experienced among those with lower socioeconomic status (SES).[5-14] 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.[15-18] 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.[19] 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.[20-22] 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.[23-25] 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.

How prior ASCVD prediction models incorporated SES into the model is a potential reason for the discrepancies in understanding the prognostic value and use of SES in ASCVD prediction models. SES traditionally is modeled as an independent risk factor or confounder.[19-22, 24] However, SES's prognostic value in predicting ASCVD risk is likely identifying populations most impacted by proximate causes of ASCVD. If true, SES incorporated into risk prediction models as a risk modifier is more appropriate in determining ASCVD risk than an independent risk factor. For example, the health impact of hypertension over 10-years is different for an individual living in abject poverty versus an individual residing in an affluent neighborhood. SES likely modifies the association between risk estimated from algorithms that use proximate causes of ASCVD (i.e., hypertension and smoking) and actual ASCVD incidence.

This study explored whether SES modifies the association of PCE 10-year estimated risk with actual ASCVD 10-year incidence using data from the Atherosclerosis Risk in Communities (ARIC) study. That is, actual observed ASCVD 10-year incidence will vary depending on the PCE estimated risk and the individual's SES. We defined SES along two dimensions typically utilized in social epidemiology research: educational attainment and neighborhood deprivation.[26] Educational attainment as a measure of individual SES was selected over other measures – e.g., income level – due to being a stable measure of SES that remain relatively stable over an adult life course when compared to other measures. We hypothesize that the long-term effects of proximate causes of ASCVD measured in the PCE (e.g., hypertension and smoking) impact on actual ASCVD incidence are dependent on SES (i.e., risk modification).

Methods

Data Source

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.[27] 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.

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.

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 co-morbidities 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.

Socioeconomic Status Measures

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

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.

Estimation of ASCVD Risk

We estimated individual ASCVD risk using the published PCE covariate parameters.[15] The following factors were used to estimate ASCVD risk according to the PCE: age, gender, race (Black or other), levels of total cholesterol, levels of high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, evidence of treatment for high blood pressure, diabetes status, and current smoker status. We used laboratory measures collected at Visit 4 to estimate risk using the PCE. We partitioned the ARIC study population into four categories of 10-year PCE predicted ASCVD risk: 0%-5%, >5%-10%, >10%-15%, and >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.[27, 31] 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

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.[27, 32] 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

Univariate descriptive statistics examined baseline participant-level characteristics. We calculated the mean and standard deviation (SD) for continuous variables, percentages for dichotomous variables, and median with interquartile range (IQR) for ordinal or nominal variables. We performed bivariate analysis using Pearson's χ^2 test or Kruskal-Wallis test for 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 pseudo-values 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

levels and ADI categories. Absolute risk differences between SES measures were estimated for each PCE 10-year estimated risk category (0%-5%, >5%-10%, >10%-15%, >15%). The referent group for educational attainment level is a college degree or above, and the referent group for ADI is residing in the least deprived neighborhoods (lowest ADI quartile). Point estimates are reported with 95% confidence intervals (CI).

Generalized linear estimation models with a log-link function were used to predict the 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, additional models included: 1) education category added as a predictor and interacted with the PCE score, 2) ADI category added as a predictor and interacted with the PCE category, and 3) both education and ADI categories as predictors and interacted with the PCE category. Generalized linear models compared took the following form:

(1) $\text{Prob(ASCVD)} = \beta_{0+}\beta_1(\text{i.Score})$

(2) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score}) + \beta_3(\text{i.Education}) + \beta_4(\text{i.Score x i.Education})$

(3) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score}) + \beta_2(\text{i.ADI}) + \beta_3(\text{i.Score x i.ADI})$

(4) $\text{Prob(ASCVD)} = \beta_0 + \beta_1(\text{i.Score}) + \beta_2(\text{i.Education}) + \beta_3(\text{i.ADI}) + \beta_4(\text{i.Score x i.Education}) + \beta_5(\text{i.Score x i.ADI})$

The likelihood ratio test, Akaike Information Criterion, and Bayesian Information Criterion evaluations were performed to compare model fit statistics of the different models. All analyses were performed using STATA, version 13.

Patient and Public Involvement

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 participants without a high school degree or residing in the most deprived neighborhoods.

Table 1. Participant Characteristics by 10-year ASCVD Predicted Risk Category*

Variable	All (n = 9728)	0%-5% (n = 2383)	>5%-10% (n = 2652)	>10%-15% (n = 1880)	>15% (n= 2813)	P-value
Demographics						
Age, mean (SD)	62.61 (5.65)	58.09 (3.29)	61.44 (4.76)	64.11 (4.19)	66.61 (5.10)	<0.001
Male, No. (%)	5728 (59)	2203 (92)	1656 (62)	869 (46)	999 (36)	<0.001
Race, No. (%)						
White	7528 (77)	2097 (76)	2027 (76)	1400 (75)	2004 (71)	<0.001
Black	2200 (23)	286 (12)	625 (24)	480 (26)	809 (29)	
Clinical Co-morbidities						
Hypertension, No. (%)	3875 (40)	460 (19)	865 (33)	780 (42)	1770 (63)	<0.001
Diabetes, No. (%)	1495 (15)	47 (2)	143 (5)	228 (12)	1077 (38)	<0.001
Total Cholesterol, mean (SD), mg/dL	201.81 (36.48)	201.22 (35.14)	200.63 (36.17)	201.82 (36.91)	203.4 (37.56)	0.034
HDL Cholesterol, mean (SD), mg/dL	50.84 (16.69)	60.11 (16.59)	50.88 (15.56)	48.53 (15.73)	44.48 (14.83)	<0.001
Current Smoker, No. (%)	1431 (15)	147 (6)	332 (13)	330 (18)	622 (22)	<0.001
Medication Use						
Statin Use, No. (%)	845 (9)	138 (6)	232 (9)	177 (9)	298 (11)	<0.001
ARIC Field Center						
Forsyth, NC, No. (%)	2343 (24)	603 (25)	642 (24)	441 (23)	637 (23)	<0.001
Jackson, MS, No. (%)	1955 (20)	256 (11)	570 (22)	424 (23)	705 (25)	
Minneapolis, MN, No. (%)	2902 (30)	892 (37)	777 (29)	511 (27)	722 (26)	
Washington County, MD, No. (%)	2529 (26)	632 (27)	663 (25)	504 (27)	749 (27)	
Social-Risk Factors						
Educational Attainment						
College or Above, No. (%)	3843 (40)	1063 (45)	1097 (41)	707 (38)	976 (35)	<0.001
High School/Some College, No. (%)	4110 (42)	1120 (47)	1132 (43)	738 (41)	1080 (39)	
No High School, No. (%)	1764 (18)	199 (8)	419 (16)	365 (19)	751 (27)	
ADI, median (IQR)†	102 (96.3-108.8)	100 (93.8-104.9)	101.9 (96.1-108.9)	102.5 (96.9-109.6)	103.2 (97.6-111.5)	<0.001

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein.

*Risk categories estimated using the Pooled Cohort Equations.

†Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants' 5-digit zip code; higher values represent higher area-level social deprivation.

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

Table 2. Event Counts and Incidence Rates Stratified by Predicted ASCVD, Education, and Area Deprivation Index.

ASCVD Predicted Risk*	Events	1,000 Person Years	Rate† Per 1,000 Person Years	Events	1,000 Person Years	Rate† Per 1,000 Person Years	Events	1,000 Person Years	Rate† Per 1,000 Person Years
	College or Above			High School/Some College			No High School Degree		
0%-5%	28	10.39	2.70	25	10.87	2.30	6	1.94	3.09
>5%-10%	45	10.41	4.32	62	10.66	5.72	32	3.91	8.19
>10%-15%	35	6.58	5.32	50	7.23	6.91	41	3.48	11.79
>15%	145	8.33	17.40	147	9.30	15.81	135	6.31	21.38
	Lowest ADI Quartile			Middle Two ADI Quartile			Top ADI Quartile		
0%-5%	19	9.68	1.96	24	8.29	2.89	16	5.23	3.06
>5%-10%	56	8.52	6.57	33	8.27	3.99	49	8.23	5.96
>10%-15%	30	5.45	5.51	37	5.45	6.78	59	6.39	9.24
>15%	119	6.62	17.96	127	7.80	16.29	181	9.57	18.92

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease.

*Risk categories were estimated using the Pooled Cohort Equations.

†Incidence rate of combined stroke and coronary heart disease was estimated over ten years.

‡Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants 9-digit zip code; higher values represent higher area-level social deprivation, and categories were defined using quartiles of distribution.

Risk Modification Analysis

Within each PCE predicted risk category, we evaluated if SES modified the relationship between PCE estimated risk and actual ASCVD 10-year observed incidence for each educational attainment level and neighborhood deprivation (college-educated and least deprived neighborhood as the referent) (Table 3). Large risk ratio differences (i.e., more than 10%) within stratum-specific PCE estimated risk categories by SES indicates risk modification. We found that the risk ratio was greater than 1 among those not having a high school degree for all PCE estimated risk categories. This result indicated a heavier burden of ASCVD than in college-educated participants independent of PCE estimated risk. This relative increase in ASCVD risk was statistically significant for groups with >5%-10% and >10%-15% PCE estimated risk; risk ratio 1.78 (95% CI; 1.16-2.76) and 2.15 (95% CI; 1.39-3.34) respectively. The risk of ASCVD in the most deprived neighborhoods (referent least deprived neighborhoods) was significantly higher only for the 10-year PCE estimated risk category >10%-15%, risk ratio 1.65 (95% CI; 1.05-2.59).

Table 3. Risk ratios comparing observed ASCVD incidence rates across education and ADI categories within each predicted risk category

	Education			Area Deprivation Index		
10-Year ASCVD Predicted Risk‡	**No High School RR (95% CI)**	**High School/Some College RR (95% CI)**	**College* or Above RR (95% CI)**	**Top ADI Quartile RR (95% CI)**	**Middle Two ADI Quartiles RR (95% CI)**	**Lowest† ADI Quartile RR (95% CI)**
0%-5%	1.16 (0.48-1.53)	0.84 (0.46-1.53)	1.00	1.61 (0.76-3.38)	1.51 (0.73-3.04)	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 (0.39-0.97)	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 (0.81-2.03)	1.00
>15%	1.22 (0.99-1.49)	0.92 (0.99-1.49)	1.00	1.07 (0.87-1.32)	0.93 (0.74-1.17)	1.00

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; RR, risk ratio.

*College or Above as referent.

†Lowest ADI as the referent.

‡Risk categories were estimated using the Pooled Cohort Equations.

In analyses stratified by educational attainment and neighborhood deprivation, participants without a high school degree who resided in the most deprived neighborhoods had a higher risk of ASCVD for all 10-year PCE estimated risk categories than other SES groups (Supplement Table 1 and Supplement Figure 1). At 10-year PCE estimated risk categories of 0%-5% and >10%-15%, having both individual and neighborhood measures of low-SES (without high school education and residing in the most deprived neighborhood) meant a substantially higher risk of ASCVD than either measure alone; risk ratio 3.64 (95% CI, 1.46-9.07) and 4.78 (95% CI, 1.62-14.09) respectively.

Observed 10-year absolute risk is presented for each education category, and ADI category across PCE estimated risk categories (Figure 1). We found heterogeneous differences in absolute risk (i.e., risk modification) by SES within stratum-specific PCE estimated risk categories. For example, the difference in absolute risk for participants without a high school degree (referent college-educated) rose by 6 percentage points for PCE estimated risk of >10%-15%; absolute risk difference decreased to 3.4 percentage points for PCE estimated risk >15% (Supplement Figure 2). Heterogenous differences in absolute risk for ADI categories were also noted, albeit smaller differences than educational attainment categories. Differences in absolute risk for participants living in the most deprived neighborhoods (referent least deprived neighborhoods) were 1.2 percentage points higher for PCE estimated risk of >5%-15%, and 1.6 percentage points higher for PCE estimated risk 10%-15%.

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

example, the likelihood ratio test comparing models 1 and 4, which included education and ADI categories, and their interaction with the PCE 10-year predicted ASCVD risk categories [Model 4: Prob(ASCVD) = β_0 + β_1(i.Score) + β_2(i.Education) + β_3(i.ADI) + β_4(i.Score x i.Education) + β_5(i.Score x i.ADI)] demonstrated a statistically significant model improvement when measures of SES was added as an interaction term with PCE estimated risk category (*p*-value <0.0001). Additionally, the Akaike information criterion was smaller, suggesting that educational attainment measures and area deprivation improved model fit for predicting 10-year ASCVD outcomes compared to the PCE predicted risk category alone.

Table 4. Comparison of models predicting ASCVD 10-year Incident events with and without measures of Socioeconomic Status

Model	Number	Akaike* Information Criterion	Bayesian† Information Criterion	Likelihood Ratio Tests P-Value
PCE‡	9728	2371	2386	--
i.PCE + i.Education§	9717	2366	2395	0.004
(i.PCE)x(i.Education)	9717	2331	2374	<0.0001
i.PCE + i.ADI‖	9728	2371	2400	0.14
(i.PCE) x (i.ADI)	9728	2346	2389	<0.0001
i.PCE + i.Education + i.ADI	9717	2366	2409	0.002
(i.PCE) x (i.Education)x(i.ADI)	9717	2328	2458	<0.0001

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohort Equations.

*Akaike Information Criterion measures goodness-of-fit between observed values and expected values; lower scores compared to referent indicate an improvement in prediction.

†Bayesian Information Criterion measures goodness-of-fit between observed values and expected values; lower scores compared to a referent model indicate an improvement in prediction.

‡Pooled Cohort Equations predicted risk was stratified into 4 categories of risk: 0-5%; >5-10%; >10-15%; >15%.

§Education was stratified into three categories: no high school; high school/some college; college or above (referent)

‖Higher Area Deprivation Index indicates higher neighborhood deprivation and was stratified into three categories according to the interquartile range: top ADI quartile; middle two ADI; lowest ADI quartile (referent)

#All models that added in the social deprivation factor as a risk factor was compared to the Pooled Cohort Equations without a social deprivation factor.

**All models that added in social deprivation as an interaction term was compared to the Pooled Cohort Equations model with social deprivation added as a risk factor.

Discussion

In the current study, we investigated whether SES's individual and neighborhood measures modify the association between the PCE risk score and actual 10-year ASCVD observed outcomes. We also described the excess burden of ASCVD events among low-SES populations relative to high-SES populations conditional on PCE estimated risk. The PCE estimated risk underestimated incidence of ASCVD events experienced among low-SES groups, and absolute differences in risk among SES measures became most pronounced at higher PCE predicted risk categories, indicating risk modification by measures of SES. Our results also suggest that SES factors' value in predicting incident ASCVD events may vary by PCE predicted 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.[19-22, 24] 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.[26, 34-37] 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

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.

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

identify underlying mechanisms. Many unknown factors exist along the socio-ecological paradigm that works in concert with individual behavioral and physiologic factors to lead to a 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 strategies in cholesterol management, hypertension management, and aspirin use.[16, 18, 42, 43] For example, at an estimated 10-year PCE risk of 7.5%, statin therapy is recommended for primary prevention of ASCVD.[18] We show that a higher SES is a risk-protecting factor, and the absolute risk of ASCVD does not cross the 7.5% threshold until a PCE 10-year risk of >15% (Figure 1). The use of SES in estimating an individual's risk can potentially improve the efficiency of resource use and more precisely target interventions to achieve population-level objectives to decrease the ASCVD burden globally and in the United States. However, drug therapy decisions for primary prevention of ASCVD should incorporate other qualifying factors such as patient preference and not base decisions solely on ASCVD risk estimates.

We don't advocate for the use of SES in the clinical decision of ASCVD preventive therapies for US patients without a validated ASCVD prediction model that incorporates SES. Our findings do suggest validation of an ASCVD prediction model that appropriately incorporates SES as an ASCVD risk modifier is warranted. Model validation comparison measures such as net risk reclassification –similar to Mosley et al. evaluation of PCE risk prediction improvement with adding a polygenic risk score – can help guide decisions on the utility of incorporating SES to guide clinical decision making.[44-45] In addition, what and how SES measures are incorporated into an ASCVD prediction model – e.g., summation of SES factors versus single SES factors – requires further exploration.[46-47]

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.[48] 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. While medication 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.

Conclusions

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.

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Competing Interests

None declared.

Ethics Approval

Institutional review boards at all ARIC centers in the United States approved study procedures. All participants gave written informed consent for the collection of data used in this study. This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board (IRB# 18-1187).

Contributors

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. All data relevant to the study are included in the article or uploaded as supplementary information.

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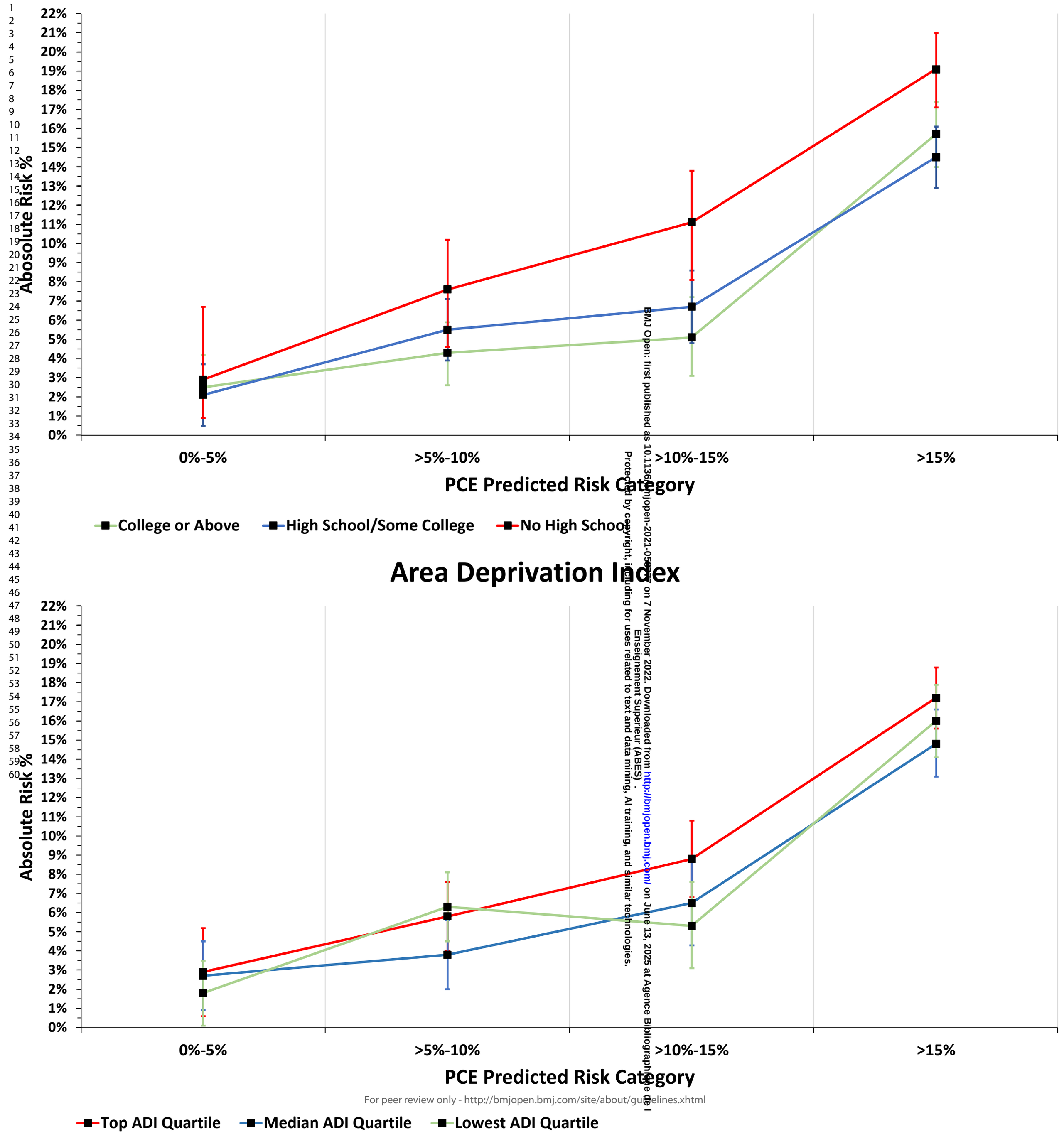
Figure 1. Observed 10-year incidence rate of ASCVD events by socioeconomic status. 10-year incidence rate of ASCVD events by education attainment (A) and Area Deprivation Index (B).

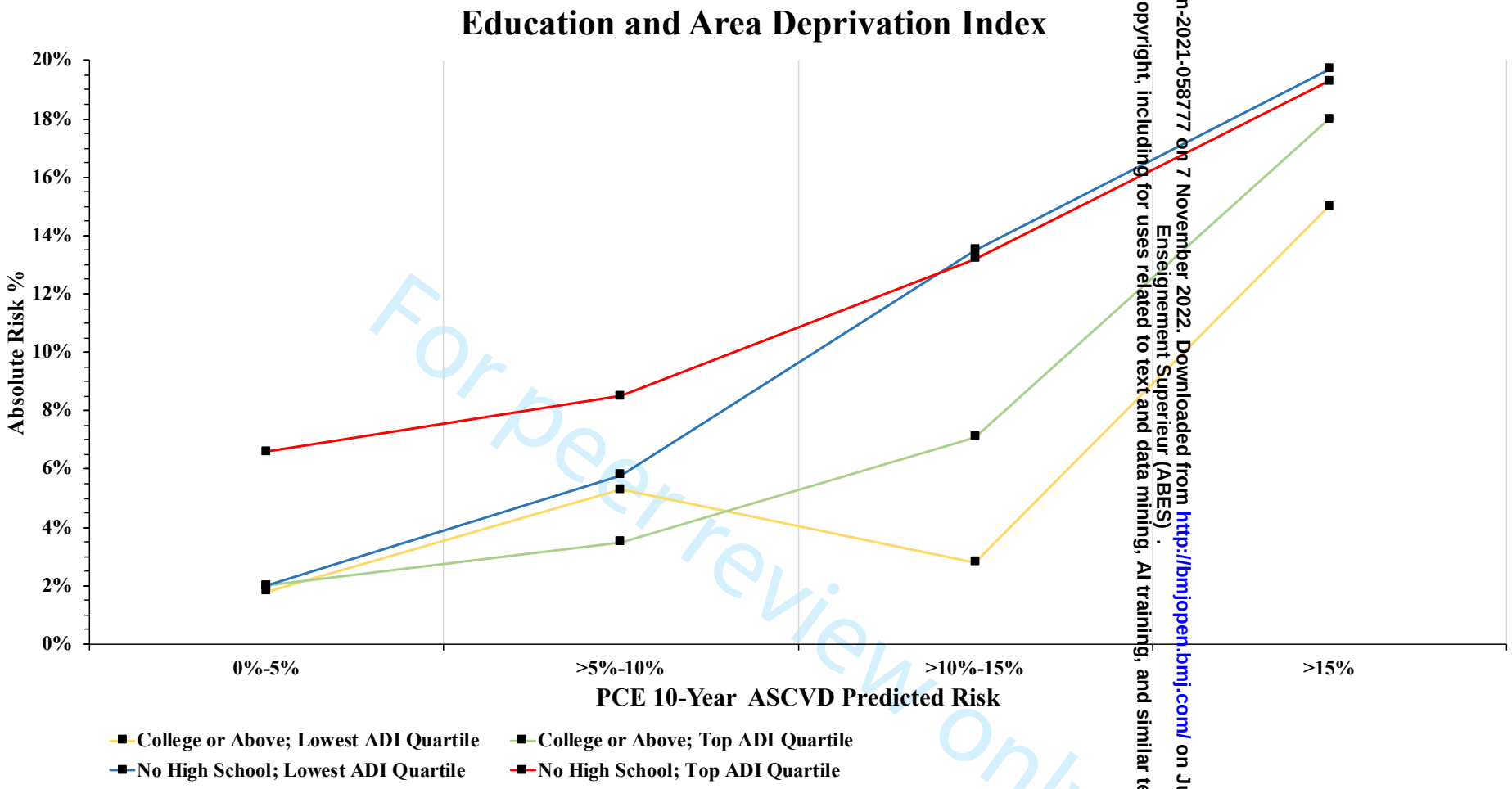
Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohort Equations

*Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants 5-digit zip code

1



SUPPLEMENTAL MATERIAL



Supplement Figure 1. Absolute risk of ASCVD accounting for dose response of both education attainment and Area Deprivation Index.
Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; PCE, Pooled Cohort Equations.
*Area Deprivation Index measures area-level social deprivation and estimated using the census-tract of participants' 9-digit zip code; higher values represent higher area-level social deprivation and categories were defined using quartiles of distribution.
†Analysis not powered to estimate the relationship between both socioeconomic status exposure variables simultaneously with absolute risk percentage; and convergence on 95% confidence interval point estimates were not obtained.

Supplement Table 1. Risk Ratios comparing 10-year incident ASCVD event rate across Socioeconomic Status (Education and Area Deprivation Index) within category of predicted risk

	10-Year ASCVD Predicted Risk											
	0%-5%			>5%-10%			>10%-15%			>15%		
	Area Deprivation Index			Area Deprivation Index			Area Deprivation Index			Area Deprivation Index		
	Top ADI Quartile RR (95% CI)	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)	Top ADI Quartile RR (95% CI)	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)
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)	1.28 (0.93-1.74)	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)	0.95 (0.68-1.34)	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	1.20 (0.85-1.69)	0.97 (0.67-1.40)	1.00

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; RR, relative risk.
*Risk ratio cannot be estimated for social deprivation category at a predicted risk of 0-5% due to lack of ASCVD incidence for category.

Education Attainment

PCE Risk Category	Absolute Risk % (95% CI)	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%
High 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%
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%)	

Area Deprivation Index

PCE Risk Category	Absolute Risk % (95% CI)	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%
Middle 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%
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%)	

Supplement Figure 2. Difference in 10-year absolute risk of ASCVD events between levels of socioeconomic status, conditional on predicted risk category.

Abbreviations: ADI, Area Deprivation Index; ASCVD, atherosclerotic cardiovascular disease

*Predicted risk categories were estimated using the Pooled Cohort Equations.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
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			
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, follow-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 modifiers. 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 without missing).

		(*e*) Describe any sensitivity analyses	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	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 on exposures 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	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (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 meaningful 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			
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 separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.