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Factors associated with lipid lowering therapy in the multi-ethnic study of atherosclerosis

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Abstract

Background Lipid-lowering therapy (LLT) plays a central role in managing atherosclerotic cardiovascular disease (ASCVD) risk, but its underuse is reported in over 40% of the qualified population in the United States. Studies on factors, particularly actionable factors associated with guideline-directed LLT are limited.

Methods This study evaluated participants from the Multi-Ethnic Study of Atherosclerosis (MESA) on their qualification for LLT at exam 5 (2010–2012) according to the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guideline on cholesterol management. Participants were categorized as on-LLT or off-LLT at the following exam (2016–2018). Multi-variable relative risk (RR) models were used to analyze between LLT usage and factors prior to 2013, including age, gender, race/ethnicity, education level and medical insurance, income, smoking, body mass index (BMI), diabetes, hypertension, and presence of coronary artery calcium (CAC).

Results Among the 2114 participants qualified for LLT at exam 5 with an average age of 70.7, 1,129 (53.4%) were on LLT while 985 (46.6%) were off LLT at exam 6. Black participants were less likely to be on LLT compared to the reference white participants (RR 0.80, 95% confidence interval CI 0.71–0.90). Higher BMI showed borderline significant association with LLT. Comorbidities of diabetes and hypertension were positively associated with LLT use (RR 1.39 and 1.23, 95% CI 1.27–1.52 and 1.10–1.36, respectively). CAC score > 0 as an indicator of subclinical ASCVD was strongly associated with LLT too, independent of other demographic or comorbidity factors (RR 1.38, 95% CI 1.21–1.56).

Conclusions This study identifies key factors influencing LLT use among MESA participants. Black participants were less likely to be on LLT, highlighting healthcare disparities. CAC presence was strongly associated with LLT use, suggesting that CAC measurement could be an actionable factor to improve adherence to LLT guidelines.

Keywords Lipid lowering therapy, Coronary artery calcium, Low density lipoprotein-cholesterol, Health disparity, Atherosclerotic cardiovascular disease

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Background

Hypercholesterolemia is a well-established risk factor for atherosclerotic cardiovascular disease (ASCVD), which remains the leading cause of death in the United States and many other regions of the world. Lipid-lowering therapy (LLT) is a cornerstone of prevention and management to reduce ASCVD risk. Studies have shown that LLT such as statins are under-used in up to 42.7% of individuals that are qualified [1–4]. Statin underutilization is associated with significantly higher LDL-C levels [2] and increased rate of ASCVD [4].

In the United States, the most current and widely adopted guideline on ASCVD prevention is the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Multi-Society guideline on management of blood cholesterol, which was an update from the 2013 ACC/AHA Cholesterol Guidelines [5]. Although multiple studies have demonstrated the role of race/ethnicity, education status and other social economic status in LLT underuse [6], limited data exists on factors associated with guideline-directed LLT, particularly on actionable factors that can potentially improve LLT usage. In addition to traditional ASCVD risk factors, coronary artery calcium (CAC) is recommended to facilitate ASCVD risk stratification that guides LLT [7], however, little is known regarding how the result of CAC measurement is used to improve LLT in qualified patients [8]. In the Multi-Ethnic Study of Atherosclerosis (MESA), CAC measurement results from study exams 1 (2000–2002) and exam 5 (2010–2012) were provided to participants and thus to their primary care physicians (PCP) too, but it is unclear how the knowledge of CAC results from MESA may influence LLT use.

We aimed to evaluate factors associated with LLT based on the 2013 ACC/AHA Multi-Society guideline on management of blood cholesterol, since the timing of the guideline publication closely followed MESA exam 5, when all participants had CAC measurements. Patient characteristics were collected from study baseline at exam 1 and up to exam 5, April 2010 through February 2012 prior to the publication of 2013 guideline, and LLT was documented post guideline publication at exam 6, September 2016 through March 2018, with the intention to understand contributing factors of LLT.

Methods

Study population

MESA is a multi-center cohort developed by the National Heart, Lung, and Blood Institute (NHLBI) to investigate atherosclerotic risk factors and subclinical disease progression. Between July 2000 and August 2002, 6814 participants aged 45 to 84 years and free of clinically apparent ASCVD from were recruited four ethnical/racial groups (White, Black, Hispanic, or Chinese American) at six centers in the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; St. Paul, MN). Full description of MESA can be found in previous publications [9] and on the MESA website [10]. The study was approved by all institutional review boards for the MESA field centers and all participants provided informed consent.

Participants with complete data for demographics, comorbidities, fasting lipid profiles at exam 5 (April 2010-February 2012) and self-reported use of LLT at exam 6 (September 2016-March 2018) were included in this study ($N=3054$). LLT qualification was determined based on the 2013 ACC/AHA multi-society guidelines for the management of blood cholesterol [5]. (1) Adults (40–79 years of age) with clinical ASCVD. (2) Adults with LDL-C ≥ 4.9 mmol/L (190 mg/dL). (3) Adults between 40 and 75 years of age with diabetes. (4) Adults with ≥ 7.5% estimated 10-year risk of ASCVD calculated by the Pooled Cohort Equation. Participants were then categorized by whether they were on- or off-LLT at exam 6 (Fig. 1).

Analysis variables

Key variables to assess the association with LLT included demographic factors of gender, race/ethnicity (White, Black, Hispanic, Chinese), education level and medical insurance at the MESA exam 1 (2000–2002), household income, smoking, body mass index (BMI), diabetes, hypertension, and CAC score at exam 5. In MESA, resting blood pressure (BP) was measured in a seated position after a 5-minute rest period by a certified trained technician using a Dinamap model Pro 100 automated oscillometric sphygmomanometer. Each participant had 3 BP measurements per visit, and the reported BP was the mean of the 2nd and 3rd measurements. Education and medical insurance status was divided into categorical groups. Household income was analyzed as a continuous variable from 1 to 13 representing total gross income ranging from < $5,000 to $10,000. The variable hypertension included treated hypertension and untreated hypertension with systolic blood pressure ≥ 140 mm Hg, and diabetes included treated diabetes and untreated diabetes based on fasting glucose ≥ 7.0 mmol/L (126 mg/dL) according to the American Diabetes Association criteria [11]. CAC was obtained using computed tomography imaging with either electron beam or multidetector scanners. The image acquisition protocol has been described previously [12]. Each participant was scanned twice, and the scans were interpreted at the core laboratory at the Los Angeles Biomedical Research Institute at Harbor the University of California Los Angeles Medical Center by experienced readers who were blinded to the clinical information for quantification using the Agatston method.

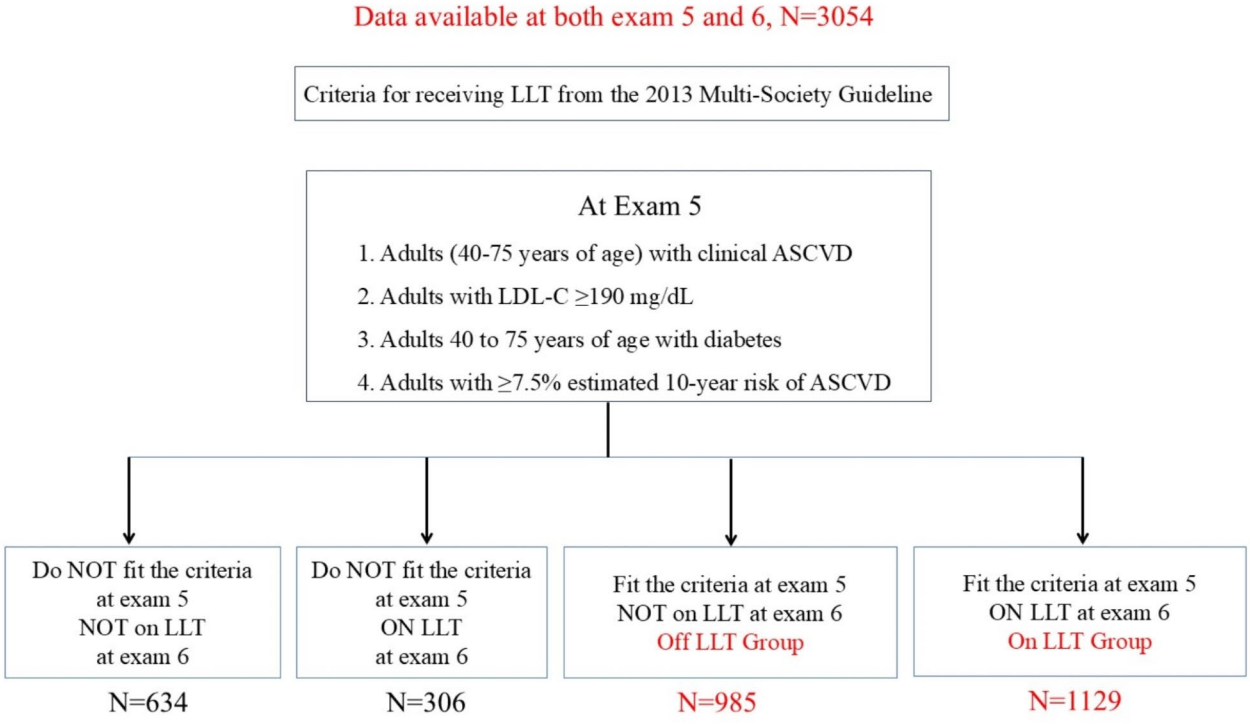

Fig. 1 Study design showing the number of MESA participants with demographic, co-morbidity and lipid lowering medication (LLT) data available and the criteria for grouping. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low density lipoprotein-cholesterol

Statistical analyses

The association between age, gender, race/ethnicity, household income, smoking, BMI, diabetes and hypertension at exam 5, and education level and medical insurance at exam 1 with LLT at exam 6 was evaluated in Relative Risk (RR) model 1. The association of MESA exam 5 CAC results in addition to factors in model 1 analysis were examined in RR model 2 on their associations with LLT usage. Participants with missing data were excluded and a complete case analysis was carried out. Missing data are small for most covariates except for CAC score: education level ($n=6$), household income ($n=62$), smoking status ($n=10$), BMI ($n=1$), and CAC score ($n=494$). A P-value<0.05 was considered statistically significant. Statistical analyses were performed using Stata 18.0 (Stata Corp, College Station, TX).

Results

A total of 3054 MESA participants had exam 5 and 6 demographic, comorbidity and LLT data available. We first sought to determine adherence to the 2013 ACC/AHA guidelines that were published post the completion of exam 5 (Fig. 1). Among those who fit the criteria of LLT ($N=2114$), 1129 (53.4%) self-reported to be on LLT and 985 (46.6%) were off LLT at exam 6. The characteristics based on LLT criteria are shown in Supplemental Table 1.

Next, we compared the demographic parameters and prevalence of co-morbidities in the On LLT ($N=1129$) and Off LLT ($N=985$) groups. Table 1 shows characteristics of participants at exam 1–5, stratified by whether they were on LLT at exam 6. Among participants qualified for LLT, Black participants were less likely to be on LLT at exam 6, while Chinese and Hispanics participants were more likely to use LLT compared to White participants. Having a higher BMI or co-morbidities of diabetes or hypertension favors LLT usage.

The association between demographic characteristics, co-morbidities and LLT usage was evaluated in subsequent multi-variable RR models (Table 2). Including CAC score (=0 versus >0) as an additional variable in model 2 reduced the number of data points to 1620 due to missing CAC scores. Characteristics of participants with CAC data available for model 2 analysis are shown in Supplemental Table 2. In both model 1 and model 2, Black race remained as a significant variable associated with LLT usage at exam 6, while income, education or insurance did not show association with LLT. BMI at exam 5 showed a borderline significant association with LLT at exam 6. Those with diabetes, hypertension have significantly higher prevalence of LLT usage at exam 6. The presence of CAC at exam 5 is a significant contributing factor to increased likelihood of LLT at exam 6 independent of all variables in RR model 1. The association between demographic characteristics, co-morbidities

Table 1 Characteristics of the On and off LLT groups at MESA exam 1–5. *P*-value from t-test (continuous variable) and Chi-square tes (categorical variable) are shown

	LLT at Exam 6		*P*-value
Exam 1–5 Variables	**On LLT**	**Off LLT**	
N	1129	985	
Age, mean (SD)	70.7 (7.9)	71.1 (8.2)	0.41
Male, N (%)	610 (54.0%)	534 (54.2%)	0.93
Race, N (%)			< 0.001
White	414 (36.7%)	377 (38.3%)	
Chinese	154 (13.6%)	108 (11.0%)	
Black	280 (24.8%)	316 (32.1%)	
Hispanic	281 (24.9%)	184 (18.7%)	
Education, Highest degree, N (%)			0.037
No degree	181 (16.0%)	117 (11.9%)	
High school/associate's degree	509 (45.1%)	448 (45.5%)	
Bachelor's degree	191 (16.9%)	189 (19.2%)	
Graduate degree	248 (22.0%)	231 (23.5%)	
Insurance, N (%)			0.28
No insurance	88 (7.8%)	61 (6.2%)	
Private insurance	193 (17.1%)	151 (15.3%)	
Medicare or Medicaid	815 (72.2%)	740 (75.1%)	
Other insurance	33 (2.9%)	33 (3.4%)	
Income, mean (SD)	9.1 (3.7)	9.2 (3.6)	0.34
Smoking, N (%)			0.53
Never smoked	498 (44.1%)	434 (44.1%)	
Previous smoker	547 (48.4%)	465 (47.2%)	
Current smoker	84 (7.4%)	86 (8.7%)	
BMI, mean (SD)	29.3 (5.4)	28.4 (5.4)	< 0.001
Diabetes, N (%)	403 (35.7%)	165 (16.8%)	< 0.001
Hypertension, N (%)	811 (71.8%)	599 (60.8%)	< 0.001

and LLT usage in subgroups of gender, race and education levels analyzed in multi-variable RR models is shown in Supplemental Table 3. CAC remained a significant factor associated with LLT in both genders, racial groups except Chinese, and in the 2 education groups.

Discussion

We reported that in this MESA population, black race was found to have an inverse association with LLT use. In contrast, higher BMI had a borderline positive association with LLT, while diabetes, hypertension and CAC score greater than 0 had a strong positive association with LLT use.

In the plan of NHLBI Division of Cardiovascular Sciences for implementing strategic vision on critical public health challenges, addressing social determinants of cardiovascular health and health inequities was identified as one of six pillars, while promoting cardiovascular health and preventing ASCVD across the life span was another pillar [13]. Better understanding of factors associated with disparities in dyslipidemia management, particularly actionable factors will greatly contribute to achieving these goals. In a 2006 MESA study that used the Third Report of the Adult Treatment Panel of the National Cholesterol Education Program to evaluate dyslipidemia management, men were more likely than women to be candidates of drug therapy but were less likely to be treated and have lipid level under control. Blacks and Hispanics had a comparable prevalence of hypercholesterolemia to Non-Hispanic Whites but were less likely to be treated and controlled. Ethnic disparities were attenuated substantially by adjustment for healthcare access variables, while gender disparities persisted after adjustment for ASCVD risk factors, social economical status (SES), and healthcare access variables [6]. We repeated the finding in the current study that Black race was associated with LLT underuse but education, income or insurance were no longer contributing factors. There could be explained by un-identified SES factor prevailing in Blacks that contribute to LLT underuse. For example, Black individuals are under-represented in the health care workforce which is associated with quality of health care for Black population [14].In the education group of bachelor's or higher degrees, Black race was only borderline associated with LLT (Supplemental Table 3). We also speculate that at this age range with average over 70, SES and healthcare access become less of disparity across race/ethnicity groups, because of the availability of Medicare.

Although our data did not show a strong association between race/SES and LLT, the finding that 985 out of 2114 qualified MESA participants were off LLT at the age around 70 (Fig. 1) is still alarming. This is in line with a recent report from the National Health and Nutrition Examination Survey that in 2017–2020, among those with an LDL-C level of 4.1–4.9 mmol/L (160–189 mg/dL), 42.7% were unaware and untreated, and in those with an LDL-C level of ≥4.9 mmol/L, the fraction was 26.8% [1]. Promoting guideline-compliant lipid control in patients at an older age will nevertheless benefit them in lowering risk of all-cause and cardiovascular mortality [15]. Statin was proven to be a cost-effective lipid-lowering treatment with efficacy and safety. Patients untreated or under-treated for dyslipidemia may be a result of perceived potential side effect, e.g., muscle-related statin intolerance was reported by 5–20% of patients and the cholesterol lowering effect of statin was thought to impair cognitive function too. However, these are more likely to be misinformation from the media rather than fact [16–19]. In situations of true statin-intolerance, proprotein convertase subtilisin/kexin type 9 serine protease inhibitors are considered for cholesterol lowering as an alternative to statin [20, 21]. With the availability of long-lasting lipid lowering medications [22], disparities in dyslipidemia management become even more modifiable by providing alternative treatment options.

Table 2 Association of exam 1–5 factors with LLT at exam 6. Relative risk (RR) and 95% confidence interval (CI) are shown

	Model 1 (*N* = 2114)			Model 2 (*N* = 1620)		
Exam 1–5 Variables	**RR**	**95%CI**	***P*-value**	**RR**	**95%CI**	***P*-value**
Age	1.00	(1.00–1.01)	0.60	1.00	(0.99–1.01)	0.82
Gender (male)	1.02	(0.94–1.10)	0.70	0.99	(0.90–1.08)	0.81
Race						
White, reference						
Chinese	1.11	(0.98–1.25)	0.11	1.05	(0.91–1.22)	0.48
Black	0.80	(0.72–0.89)	1.90E-05	0.80	(0.71–0.90)	1.60E-04
Hispanic	1.00	(0.90–1.11)	0.98	0.97	(0.86–1.10)	0.65
Education* (Highest degree)						
No degree, reference						
High school/ associate's degree	0.94	(0.84–1.06)	0.31	0.96	(0.84–1.10)	0.57
Bachelor's degree	0.91	(0.78–1.05)	0.19	0.91	(0.77–1.08)	0.26
Graduate degree	0.96	(0.83–1.11)	0.57	0.97	(0.82–1.14)	0.69
Insurance						
No insurance, reference						
Private insurance	0.96	(0.81–1.13)	0.59	0.96	(0.79–1.17)	0.68
Medicare or Medicaid	0.94	(0.82–1.09)	0.41	0.97	(0.82–1.16)	0.78
Other insurance	0.88	(0.66–1.16)	0.35	0.89	(0.64–1.22)	0.45
Income	1.01	(0.99–1.02)	0.23	1.01	(0.99–1.02)	0.46
Smoking						
Never smoked, reference						
Previous smoker	1.00	(0.92–1.08)	1	0.98	(0.90–1.07)	0.7
Current smoker	0.97	(0.82–1.15)	0.75	0.97	(0.81–1.16)	0.75
BMI	1.01	(1.00–1.01)	0.04	1.01	(1.00–1.02)	0.046
Diabetes	1.46	(1.35–1.58)	< 1.00E-16	1.39	(1.27–1.52)	1.70E-12
Hypertension	1.26	(1.14–1.38)	1.60E-06	1.23	(1.10–1.36)	1.50E-04
CAC presence				1.38	(1.21–1.56)	4.80E-07

Over the entire course of MESA study, race/ethnicity and SES still play a major role in all-cause mortality [11]. The persistent racial and ethnic differences in overall and ASCVD mortality are largely attributable to social determinants of health, emphasizing the need to identify and act on systemic factors that result in health disparities across racial and ethnic groups at early phase of life. Most patients that are not on target for ASCVD risk control were never offered the preventative treatment as needed when symptoms were absent or mild at a young age [16], and therefore the preclinical stage before clinical symptom manifestation should be the optimal window for making impactful intervention. There is evidence demonstrating the gap between patient perceived ASCVD risk and actual risk [23] so clinical evidence that minimizes this gap will benefit patients to be on track for LLT. We found that presence of co-morbidities including higher BMI, diabetes or hypertension is associated with LLT usage. In previous studies, the polypill approach was shown to be highly effective in these patients with multiple conditions [24]. In the MESA study, the finding of another subclinical "co-morbidity", positive CAC result showed strongly significant association with rate of LLT independent of other contributing factors. In the series of ACC/AHA guideline on lipid management from 2013 to 2018, CAC was recommended as a tool in addition to routine evaluations to guide LLT, our study is the first to demonstrate the association between CAC result and actual guideline-directed LLT use. Previously, the Nongated Chest Computed Tomography Scans to Improve Statin Rates, Incidental Coronary Calcification Quality Improvement Project (NOTIFY-1 Project) study screened patients without known ASCVD or statin prescription on a nongated chest CT scan for incidental findings of CAC using a deep learning algorithm. Notifying clinicians the opportunistic positive CAC screening results significantly increased statin prescriptions [8]. Our study and the NOTIFY-1 project both support that CAC measurement revealed the ASCVD risk that is not perceived by patients and/or their health care providers. Therefore, we advocate that CAC may be specifically promoted by PCP to raise awareness of actual ASCVD risk and to improve guideline-compliant LLT. Although CAC screen is not covered by most insurance payers [25], more and more health care systems are offering the test at an affordable rate [26], and performing the test is associated

with increased LLT and subsequently decreased risk of myocardial infarction and improved survival [27].

Limitations of the study include: (1) The time lapse from initial collection of education and medical insurance data at exam 1 to the time that income and comorbidity data were collected at exam 5, which may hide the changes in education and insurance over time. (2) MESA LLT data at exam 6 does not reveal the drug type or dose, although the most prevalence LLT during that period has been statins and ezetimibe. As a snapshot at the time of exam 6, the LLT data without duration or dosage does not allow lipid goal attainment assessment. (3) The LLT data also does not distinguish between physician factors in prescribing pattern versus patient factors. (4) Lastly, the CAC data were only available in 1620 out of the 2114 participants in the analysis, which may represent a selection bias.

Conclusion

In summary, our study evaluated factors associated with LLT in an elderly population of MESA based on qualification criteria in the 2013 ACC/AHA guideline. Black race showed a negative association with LLT use, revealing disparities in the quality of cardiovascular health care as reported in other studies too; higher BMI was mildly associated with LLT use, while diabetes, hypertension, and CAC score greater than 0 were strongly associated with LLT. The substantial impact of CAC result suggests the potential of CAC measurement as an actionable factor to improve guideline-compliant LLT.

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
BP	Blood Pressure
CAC	Coronary Artery Calcium
LDL-C	Low-Density Lipoprotein Cholesterol
LLT	Lipid-Lowering Therapy
MESA	Multi-Ethnic Study of Atherosclerosis
NHLBI	National Heart, Lung, and Blood Institute
PCP	Primary Care Physician
RR	Relative Risk
NOTIFY-1 Project	Nongated Chest Computed Tomography Scans to Improve Statin Rates, Incidental Coronary Calcification Quality Improvement Project

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-024-02363-y.

Supplementary Material 1

Supplementary Material 2: Table 1. Characteristics of the two LLT groups based on the 2013 ACC/AHA guideline. P-value from t-test (continuous variable) and Chi-square test (categorical variable) are shown. Table 2. Characteristics of the On and Off LLT groups in participants with CAC data available. P-value from t-test (continuous variable) and Chi-square test (categorical variable) are shown. Table 3. Association of Exam 1–5 factors with LLT at exam 6 in subgroups of race, gender, and education. Relative Risk (RR) and 95% confidence interval (CI) are shown.

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Author contributions

J.C. and M.Y.T. initiated the study proposal and contributed to study design, data acquisition, and manuscript writing; J.C., W.G. and S.O.N. contributed to data analysis and manuscript editing; J.C., W.G., S.O.N., H. S. B., P.K. G. and M. Y. T. contributed to the modification of study design and manuscript editing.

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Data availability

Access to MESA data can be requested at http://www.mesa-nhlbi.org upon approval of data analysis proposal.

Declarations

Ethics approval and consent to participate

MESA was approved by all institutional review boards for the 6 field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; St. Paul, MN). All participants provided informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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