Prevalence and significance of risk enhancing biomarkers in the United States population at intermediate risk for atherosclerotic disease

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KEYWORDS
Risk enhancing biomarkers; ASCVD; CAC scores

Background: Pooled cohort equations (PCEs) estimate 10-year risk for atherosclerotic cardiovascular disease (ASCVD) in US adults. One use is to guide statin eligibility. However, PCEs risk estimate is inaccurate in some US subpopulations.

Objective: Recent cholesterol guidelines proposed addition of risk enhancing factors to improve risk assessment for selection of statin therapy. This study examines frequencies of several risk enhancing biomarkers in NHANES subjects at intermediate risk (7.5 - 20% 10-year risk for ASCVD) and considers how they may be used to better assess risk for individuals.

Methods: Prevalence of the following biomarkers were determined: elevations in apolipoprotein B-containing lipoproteins, i.e., LDL cholesterol (LDL-C) (160-189 mg/dL), non-HDL-cholesterol (non-HDL-C) (190-219 mg/dL), or total apolipoprotein B (apoB) (≥ 130 mg/dL), serum triglyceride (≥ 175 mg/dL), hemoglobin A1c (5.7-6.4%), high sensitivity C-reactive protein (2-10 mg/L), and waist circumference ≥ 102 cm, and abnormal estimated glomerular filtration rate (15 - ≤ 60 mg/min/1.73 m²).

Results: 25% of NHANES population had intermediate risk. In this subgroup, 85% had ≥ 1 biomarkers—similarly in women and men—with a third having ≥ 3 abnormal markers. Frequencies were not age-related, except in those 40-49 years, in whom > 40% had ≥ 3 abnormal biomarkers. It made little difference whether LDL-C, non-HDL-C or apoB was used as the atherogenic lipoprotein.

Conclusion: Three or more enhancing risk factors in intermediate risk subjects can complement PCE-estimated 10-year risk and guide the patient-provider discussion toward use of lipid-lowering medication. Future research is needed to integrate risk estimates by PCE and multiple risk enhancers.

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Introduction

Statins are the mainstay for cardiovascular risk reduction in patients with established atherosclerotic cardiovas-

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Submitted July 14, 2021. received in revised form October 20, 2021. Accepted for publication November 23, 2021.
duction in ASCVD events), safety, and cost-effectiveness. These RCTs implied that statin eligibility can be defined as a 10-year risk for hard ASCVD events of ≥ 7.5%. This level of risk for individuals is determined by a set of equations using major risk factors (cigarette smoking, hypertension, hypercholesterolemia, low HDL cholesterol [HDL-C], and advancing age); these equations were derived from 5 prospective studies carried out in the United States (pooled cohort equations [PCEs])².

In spite of this simple definition of statin eligibility, numerous extenuating circumstances can arise in clinical practice. Importantly, after publication of 2013 cholesterol guidelines¹, several reports³ showed that PCEs do not reliably predict risk in some subpopulations in the United States. Thus, in 2018, the 2013 cholesterol guidelines were updated by adding factors not included in PCEs¹. These were several emerging factors (risk enhancing factors) and coronary artery calcium (CAC). Risk enhancing factors include higher risk conditions (e.g., chronic inflammatory disease and metabolic syndrome) and several biomarkers that predict ASCVD independently of the major risk factors. CAC identifies the presence of subclinical atherosclerosis. CAC provides a counterweight to risk-enhancing biomarkers, because zero or low CAC scores can demonstrate reduced risk (5). The current study examines the frequencies of several so-called risk enhancing biomarkers in the NHANES population and considers how they may be used to favor statin therapy.

**Methods and subjects**

The objective of this secondary data analysis was to determine the prevalence of selected risk-enhancing biomarkers in Americans without ASCVD, in the age range of 40 to 75 years, whose 10-year risk for hard ASCVD, as determined by PCEs was in the range of 7.5% < 20.0 % (intermediate risk). Demography and histories of hypertension, diabetes, and smoking also were included. Reported intakes of hyperglycemic agents, hypolipidemic agents (statins and others) and anti-hypertensives were analyzed.

Data used for the analysis was derived from the de-identified NHANES database obtained during surveys conducted between 1999 and 2016. Briefly, the NHANES surveys are conducted following a complex design. Five thousand subjects are randomly selected yearly to represent the non-institutionalized population at large. Fifteen counties throughout the country are visited each year. Subjects are interviewed at home and a subset is invited to participate in additional testing including a physical examination, laboratory chemistries, dental and physiological measurements. The database and documentation of survey procedures is detailed in the NHANES database website (https://www.cdc.gov/nchs/nhanes/about_nhanes.htm).

In this analysis, the prevalence of the following biomarkers were determined: moderate elevations of apolipoprotein B-containing lipoproteins, i.e., LDL cholesterol (LDL-C) (160-189 mg/dL), non-HDL-cholesterol (non-HDL-C) (190-219 mg/dL), or total apolipoprotein B (apoB) (130-155 mg/dL); serum triglyceride (≥175 mg/dL); prediabetes (hemoglobin A1c 5.7-6.4%); high sensitivity C-reactive protein (hs-CRP 2-10 mg/L); estimated glomerular filtration rate (eGFR 15-60 mg/min/1.73 m²); and waist circumference ≥ 102 cm².

**Statistical analysis**

The descriptive statistics (median, percentiles, frequency, and proportion) for demographic data and other variables were summarized to describe the study population. The level of significance was set at 0.05. Weighted Mood’s median test⁵ and Rao-Scott chi-square test⁶ were employed to compare medians of continuous variables and categorical variables, respectively. All the statistical analyses were conducted according to NHANES guidelines using statistical software SAS 9.4 (SAS Institute Inc, Cary, NC).

Since NHANES has a complex study design, specific weight was assigned to each participant for the number of represented US adults. We incorporated the sample weight variables and the study design weight variables to adjust for the effects of the study design and calculate unbiased estimates for a valid inference to the general US population with and without ASCVD- and 10-year intermediate risk (ages 40-75 years).

**Results**

Approximately 9.5% of adults of the USA population aged 40 to 75 years had ASCVD (Fig. 1). Among the 90.5% without ASCVD, 66.6% had a low 10-year risk for ASCVD (< 7.5%), 25.0% had an intermediate risk (7.5% - < 20.0%) and 8.4% had a high risk (≥ 20%). This analysis focused on the prevalence of risk enhancing biomarkers in the non-ASCVD population with intermediate risk.

The characteristics of the population without ASCVD are summarized in Table 1. The study population had a median age of 66 and 58 years for women and men, respectively; the men were slightly younger than the women. The subjects were generally overweight and had a large waist circumference. Total cholesterol and non-HDL cholesterol (non-HDL-C) averaged in a borderline zone, and the HDL-C was within the normal range. Total apolipoprotein B (apo B) and the triglycerides averaged within the normal range. The median HbA1c was within the normal range as well as hs-CRP levels. The median estimated glomerular filtration rate (eGFR) averaged greater than 60 milliliters per minute per 1.73 m². The median systolic blood pressure was higher in women than in men and diastolic blood pressure was 71.3 and 75.2 mm Hg, respectively. The median PCE 10-year risk for ASCVD was around 11 % for each gender: Sex dimorphism was noted for most biomarkers except for non-HDL C, LDL C, triglycerides and total Apo B (Table 1).
Fig. 1 Schematic representation of study population (N). Subjects selected in the age range of 40 to 75 years were grouped according to history of atherosclerotic cardiovascular disease (ASCVD) and stratified according to the PCE 10-year risk for ASCVD. Thirty nine percent of ASCVD+ subjects and 25% of ASCVD- had a 10-y risk for ASCVD in the range of 7.5% - < 20%. This risk category is designated Intermediate Risk for ASCVD and the population without ASCVD is the focus of the current study.

The percent distribution of subjects was determined after weighing the data and they represent the distribution in the US population.

Table 1 Characteristics of Subjects without ASCVD and with PCE 10-year Intermediate Risk

<table>
<thead>
<tr>
<th>Women (n=9,062,401)</th>
<th>Men (n = 15,060,863)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.1 (53.4, 72.2)</td>
<td>58.2 (46.9, 66.9)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>29.5 (22.3, 39.6)</td>
<td>28.3 (22.9, 36.2)</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>100.7 (82.6, 121.2)</td>
<td>103.9 (88.3, 122.7)</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>211.4 (162.2, 269.9)</td>
<td>203.1 (153.3, 263.5)</td>
</tr>
<tr>
<td>non-HDL Cholesterol (mg/dl)</td>
<td>152.1 (105.5, 215.5)</td>
<td>155.5 (104.6, 217.6)</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dl)</td>
<td>53.5 (37.1, 78.8)</td>
<td>43.8 (31.6, 66.5)</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dl)</td>
<td>122.7 (79.5, 173.9)</td>
<td>123.6 (80.3, 174.3)</td>
</tr>
<tr>
<td>Total Apo B (mg/dl)</td>
<td>97.2 (70.7, 134.8)</td>
<td>100.3 (68.5, 138.4)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>142.3 (72.0, 291.6)</td>
<td>144.8 (99.8, 365.0)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 (5.1, 6.9)</td>
<td>5.5 (5.1, 6.7)</td>
</tr>
<tr>
<td>hs-C-Reactive Protein (mg/L)</td>
<td>3.3 (0.6, 12.5)</td>
<td>2.1 (0.4, 8.5)</td>
</tr>
<tr>
<td>Glomerular Filtration Rate (ml/min/1.73m²)</td>
<td>75.7 (54.6, 104.2)</td>
<td>83.1 (63.8, 111.5)</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>135.1 (114.1, 159.9)</td>
<td>127.3 (111.2, 149.8)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mm Hg)</td>
<td>71.3 (55.1, 86.1)</td>
<td>75.2 (60.6, 89.4)</td>
</tr>
<tr>
<td>PCE 10-year Risk for ASCVD (%)</td>
<td>11.4 (8.2, 17.6)</td>
<td>11.9 (8.1, 17.8)</td>
</tr>
<tr>
<td>% Smokers</td>
<td>23.4</td>
<td>33.4</td>
</tr>
<tr>
<td>% Diabetes</td>
<td>20.1</td>
<td>14.8</td>
</tr>
<tr>
<td>% Taking hypoglycemic drugs</td>
<td>16.1</td>
<td>11.0</td>
</tr>
<tr>
<td>% Taking hypolipidemic drugs</td>
<td>40.4</td>
<td>29.7</td>
</tr>
<tr>
<td>% Taking statins</td>
<td>29.7</td>
<td>21.2</td>
</tr>
<tr>
<td>% Taking antihypertensives</td>
<td>59.5</td>
<td>36.6</td>
</tr>
<tr>
<td>Race distribution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Non-Hispanic White</td>
<td>73.3</td>
<td>73.0</td>
</tr>
<tr>
<td>% Non-Hispanic Black</td>
<td>14.2</td>
<td>11.7</td>
</tr>
<tr>
<td>% Mexican-American</td>
<td>4.1</td>
<td>5.4</td>
</tr>
<tr>
<td>% Other Hispanic</td>
<td>4.3</td>
<td>4.3</td>
</tr>
<tr>
<td>% Other/Multi-Racial</td>
<td>4.1</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Women also had significantly higher prevalence of intake of treatment medications compared to men. Most women and men were non-Hispanic white.

Fig. 2A shows distributions of three 10-year risk categories (low, intermediate, and high) by gender and decade (as determined by PCEs). Most women showed low risk throughout fifth and sixth decades. In the seventh decade, approximately 50% had intermediate or high risk; and in the eighth decade, almost all were at intermediate or high risk. In men, the same pattern was observed but at a decade earlier. It may be of interest to compare these findings with reported distributions of CAC categories (zero, 1-99
Agatston units, and \( \geq 100 \) Agatston units) in women and men in the MESA study (Fig. 2B)\(^9\). In women ages 45-54, only about 15% had any detectable calcium; and very few had CAC \( \geq 100 \) Agatston units. Positive CAC scores essentially doubled in women 55-64 years; and after age 65, approximately half of women were CAC positive but only a quarter had CAC \( \geq 100 \) Agatston units. In contrast, men progressed to women’s CAC levels about a decade sooner.

Among subjects at intermediate risk for ASCVD, 85% had one or more risk biomarkers (Fig. 3A). Among these, percentages were similar for one, two, and three or more biomarkers between women and men. However, in both sexes, the prevalence of 3+ risk enhancing biomarkers was significantly high compared to the prevalence of zero risk enhancing biomarkers. Moreover, the prevalence of one or more risk markers as a function of age, occurred similarly between women and men (Fig. 3B and 3C). Among those in the age range of 40 to 49 years, more than 40% had 3 or more biomarkers.

The cohort aged 40 to 49 years, had a greater prevalence in \( \geq 3 \) risk biomarkers compared to the groups \( \geq 50 \) years old. In women aged 40 to 49 years, 3+ risk factors were associated with a higher waist circumference (mean 113.2 \( \pm \) 11.3 cm in the younger group vs. 108.7 \( \pm \) 12.8 cm in the older group, \( p = .001 \)), plasma triglyceride levels (433 \( \pm \) 740 mg/dl vs. 252 \( \pm \) 178 mg/dl, \( p < .0001 \)), non-HDL C (221 \( \pm \) 64 mg/dl vs. 185 \( \pm \) 47 mg/dl, \( p < .0001 \)), and high sensitivity C-reactive protein (10.6 \( \pm \) 6.5 mg/L vs. 5.6 \( \pm \) 3.2 mg/L, \( p = .0004 \)). In men, the group aged 40 to 49 years and 3+ Risk Enhancing Factors had higher levels of plasma triglyceride (group 40 to 49 years: 395 \( \pm \) 416 mg/dl vs. 280 \( \pm \) 169 mg/dl in the \( \geq 50 \) year group; \( p = .0001 \)), non-HDL C (215 \( \pm \) 56 mg/dl vs. 183 \( \pm \) 42 mg/dl, \( p < .0001 \)), high sensitivity C-reactive protein

![Fig. 2](https://example.com/fig2.png)  
**Fig. 2** Percent distribution of PCE 10-year risk for ASCVD categories in women and men as a function of age strata (panel A). Low risk (< 7.5%) (white bars), intermediate risk (7.5% - <20%) (black bars) and high risk (\( \geq 20\% \)) (gray bars). Most women reach an intermediate risk for ASCVD starting at age \( \geq 60 \) years and men start at age \( \geq 50 \) years (panel A). Panel B shows the distribution of CAC scores in women and men stratified by age. Data from reference no.9.
levels (5.1+/−3.2 mg/L vs. 3.9+/−2.6 mg/dL, p=0.0008) and HbA1c (6.1±1.5% vs. 5.9±0.9%, p=0.01) than the older men. The prevalence of risk biomarkers in subjects with intermediate risk were split into subgroups of PCE estimated risk 7.5% to 13.6% and 13.7% to 19.9% risk (Fig. 4). The prevalence of the number of risk enhancing factors was similar in women and men in the two categories of intermediate risk (Fig. 4A and 4B, respectively).

ApoB is often proposed as an additional risk enhancing biomarker. The prevalence of high apoB (≥130 mg/dL) was similar in men and women but was less than 15% (Fig. 5). Similarly, the prevalence of a high apoB level in combination with high levels of non-HDL cholesterol was similar to the prevalence of high apoB alone in both sexes. The prevalence of high LDL (160–189 mg/dL) was less than 15% and similar in both sexes. Importantly, the prevalence of a combination of high apoB and a lower level of non-HDL C was very low in both sexes. It has also been suggested that a high apoB is common in a subset of subjects with high triglycerides. In this survey, the prevalence of the combination of high apoB and high triglyceride was about 8 to 9% in both sexes (Fig. 5). This prevalence was higher than that of high apoB and low non-HDL C. The prevalence of high LDL C (160–189 mg/dL) and normal non-HDL C was very low in women and somewhat higher in men. Similarly, the prevalence of high Apo B and low non-HDL C was very low in both women and men.

Discussion

On the basis of primary prevention trials with statins, it is widely accepted that satins eligibility can be defined as a 10y-risk for ASCVD ≥7.5% as determined by PCEs. However, recent studies indicate that PCE inaccurately estimate risk in several subpopulations of USA 1,10. For this reason, 2018 cholesterol guidelines introduced risk enhancing factors. The guidelines proposed that additional risk enhancing

Fig. 3 Panel A shows the percent of subjects with intermediate (7.5% - < 20%) 10-year risk for ASCVD as a function of number of risk enhancing factors in women (white bars) and men (black bars). The percent of women or men increases progressively as a function of number of risk enhancing factors. There is no significant difference between men and women in the prevalence of biomarkers except for those with one risk enhancing factor (*P=.03). Sex-specific prevalence as a function of number of risk enhancing factors for each decade of age is shown for women and men in panels B and C, respectively. Within each decade of age, there is a significant increase in the prevalence of women or men with no risk enhancing factors (P=.0001). There is also a sex dimorphism in prevalence of zero (P=.02) and 3+ factors (P<.0001) in the 4th and 6th decade of age, respectively.

Fig. 4 Prevalence of risk enhancing biomarkers in women (panel A) and men (panel B) in the lower (7.5% - 13.6%) and upper (13.7 – 19.9%) levels of intermediate 10-year risk for ASCVD. Significant differences in the prevalence was noted in men with ≥ 3 factors (P=.03).
LDL-C, a predictor of atherogenic factors can be employed to identify a higher risk than estimated by PCEs. Likewise, the presence of increased coronary artery calcium can be used for the same purpose. Risk enhancing factors do not predict ASCVD as strongly as the major risk factors of PCEs. Still, they associate with ASCVD independently of major factors. Several of these factors are historical conditions. Others, here called risk biomarkers, can be gathered in laboratory work-up; they are the focus of the current analysis. In the NHANES population at intermediate risk, most subjects had at least one risk biomarker; thus, considering only one biomarker will add little incremental information for defining statin eligibility. This limitation has been discussed in detail in a critique of risk enhancing factors.

Addressing an aggregation of risk biomarkers factors in individuals is a different matter. The metabolic syndrome is a prime example of how a multiplicity of biomarkers can together predict ASCVD independently of the major risk factors. Among its components are dyslipidemia, pro-inflammatory state, prothrombotic state, moderately elevated blood pressure, and dysglycemia/insulin resistance. A clinical diagnosis depends on identification of three or more of the following: increased waist circumference (indicator of abdominal obesity), elevations in triglycerides (indicator of atherogenic, triglyceride-rich lipoproteins), prediabetes (indicator of insulin resistance), borderline high blood pressure, and reduced HDL-C. Although the quantitative contribution of each biomarker to ASCVD risk is not as great as major risk factors, for patients at intermediate risk, several markers together favor a higher risk. In the NHANES population, approximately one third of those at intermediate risk by PCEs had ≥ 3 risk biomarkers (Fig. 3).

All of the risk biomarkers examined here have been shown to be independent risk factors for ASCVD. Many of them can be considered metabolic risk factors, the same as or similar to those of the metabolic syndrome (a multiplex risk factor for ASCVD) and a designated risk enhancing factor. An increased waist circumference is one independent predictor in the metabolic syndrome. Recent cholesterol guidelines recognized moderate elevations of non-HDL-C, LDL-C, or apoB as a risk biomarker (Fig. 5); since these factors are highly correlated, the presence of more than one should not be double counted. Other biomarkers include hypertriglyceridemia, elevated lipoprotein (a), (not measured in NHANES), elevated hs-CRP, prediabetes, and reduced eGFR.

Since most intermediate-risk patients have at least one risk marker, the finding of only one marker should add little to risk assessment. In contrast, Akintoye et al. reported that ≥3 risk enhancing factors represents an optimum threshold for incremental risk prediction in pooled data from 3 epidemiological cohorts having 22,942 participants. Three or more risk enhancing factors is likely equivalent to the ≥ 3 metabolic risk factors of the metabolic syndrome, justification for starting statin therapy in patients at intermediate risk.

In the NHANES population, there was a high prevalence of ≥ 3 risk enhancing factors especially among men and women in the age range of 40 to 49 years (Fig. 3). The factors included high waist circumference, levels of plasma triglyceride, non-HDL C and levels of hs-CRP. In these subjects, lifestyle intervention can be implemented prior to or in addition to pharmacotherapy.

There is a growing body of evidence that CAC scoring is more predictive of ASCVD risk than individual risk factors. For example, in the absence of CAC but the presence of risk factors, the 10-year incidence of ASCVD is low. CAC is an indicator of subclinical atherosclerosis which is a step beyond atherogenic factors. Subclinical atherosclerosis is a stronger predictor of cardiovascular events than are individual risk factors. The predictive power of CAC is strongest when combined with multiple risk factors of the PCEs. This justifies CAC measurement in intermediate risk patients. Currently, CAC does not indicate utility of statins unless scores are > 100 Agatston units.

An alternate use of risk biomarkers is to support selection of patients for CAC measurement. Most risk biomarkers have been shown to associate with the level of CAC (Fig. 4). In patients with the metabolic syndrome, CAC scores increase progressively with the number of metabolic risk factors. Moreover, there is growing evidence that CAC is a powerful risk indicator that can favor statin therapy in patients at intermediate risk. Measurement of CAC has the advantage of identifying those at highest risk.
over risk factors by confirming established atherosclerotic lesions. Approximately one-third of intermediate-risk individuals have no coronary calcium, carry a low risk for ASCVD, and thus do not require current statin usage. Emerging risk factors alone do not give this important information. When uncertainty exists whether to measure CAC in patients with PCE-estimated 7.5-<20.0% 10-year risk, the finding of ≥ 3 risk biomarkers or higher risk historical factors at the least support CAC measurement. A high CAC score is basically a summation of multiplicative risk factors; risk enhancing markers are multiplicative.

As summarized by Grundy and Stone, when a patient has zero CAC, 10-year risk for ASCVD events is low (<5%); statin treatment can be delayed for up to a decade. Even in those with CAC 1-99 Agatston units, 10-year risk is usually <7.5%; there is some disagreement whether to initiate statins at this CAC level, but risk remains relatively low for up to 10 years; hence, it is reasonable to delay statins for up to 5 years before rescanning. But whenever CAC is ≥100 Agatston units, 10-year risk is at least 7.5% here, a statin can be initiated with confidence.

The analysis conducted in the current study does not extend to many diverse populations since the data are not available. Also, further development of risk assessment tools is needed to incorporate multiple risk enhancing factors along with established risks included in PCEs. There is need to acquire clinical trial evidence of benefit derived from treatment of risk enhancing factors with statins and non-statin drugs. In addition, more research is needed to determine the relative contribution of multiple risk enhancing factors to CAC scores. This has not been adequately studied.

In summary, the current paper poses the paradigm that multiple risk enhancing factors may be useful to guide statin therapy or CAC measurement. Additional research will be required to fully justify this paradigm. This paper also questions the utility of a single risk enhancing factor to justify statin therapy in an intermediate risk patient. In contrast, the presence of ≥ 3 risk biomarkers essentially equates to the metabolic syndrome as a multifactorial risk enhancing factor. As such it warrants adding a statin to a risk-reducing regimen in patents at intermediate risk for ASCVD. Moreover, for many years, cholesterol guidelines based risk assessment on population data. Yet, at every level of population risk, absolute risk for individuals can vary substantially. To better individualize risk, 2018 cholesterol guidelines introduced CAC measurements as well as risk enhancing factors. The latter can be used to either personalize risk estimation beyond PCE or to support CAC measurement. Their use to support CAC measurement may be preferable because of the power of CAC to better individualize risk assessment.

Authors’ contributions

Drs. Grundy and Vega designed, analyzed data and wrote the manuscript. Dr. Wang contributed to weighing and statistical analysis of the data. All authors agreed with the contents of the final version of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interests

None of the authors report any conflict of interests regarding the content of the publication.

Acknowledgements

The authors express appreciation for technical assistance of Ms. Liana Krishnt, B.S. and Aarthi Parvathaneni, B.S. Dr. Yi Pan, Ph.D. from the Centers for Disease Control and Prevention, provided the code for median analysis.

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