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# The Interaction of C - Reactive Protein, Bisphenol A, & Cardiovascular Disease: A Demographical Analysis

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**Abstract**

**Objective:** The main objective of the study was to investigate the role of C-reactive protein on the relationship between Bisphenol A & Cardiovascular Disease, where the C-reactive protein has been taken as a moderating variable.

**Methods:** Quantitative research design has been incorporated for evaluating the role of C-reactive protein. Similarly, non-parametric Spearman correlation test has been conducted to assess the relationship between BPA and CVD. The data was taken out from the National Health and Nutrition Examination Survey (NHANES), which was collected in the year 2009-2010.

**Results:** The impact of urinary Bisphenol A on serum C-reactive protein was found statistically significant according to the Spearman correlation coefficient, $rs = .06$, $p = .015$. The scatter plots found that there is no relationship between the two variables; this observation held true after filtering the outliers from the plot.

**Conclusion:** The results might have positive change by contributing to the body of knowledge on bisphenol A and by rising scientific examination of substances used by the people in the daily life. Further research to identify other possible causes of CVD and elevation of CRP is recommended.

**Keywords:** bisphenol A, BPA, cardiovascular disease, coronary heart disease, environmental phenol, endocrine disruptor, heart attack, C-Reactive Protein, CRP, NHANES

## 1. Introduction

Bisphenol-A (BPA) is a synthetic substance used in polycarbonated plastic. BPA is mainly found in drinks, food packaging, and epoxy resin that are helpful in coating of cans within the food industry (Vogel, 2009). BPA is now enclosed in an extensive variety of customers' products from the plastic container, baby bottles, and the lining of cans for beverages (Rochester, 2013, pp.132-155). It has been observed that humans have increased levels of urine BPA because of using such products (Li et al, 2011).

There is an extensive human exposure to BPA; therefore, general public and regulatory agencies have paid much attention to the prospective risks that those BPA possess. A rapidly growing and emerging area in the research of bisphenol A's toxicity and its effects on the Cardiovascular system (CV) has been discussed. Numerous types of cardiovascular diseases including hypertension, angina, peripheral and coronary arterial disease and heart attack have been caused due to the concentration of higher urinary BPA in humans (Carwile et al., 2009). It has been observed in previous studies that the exposure of acute BPA usually supports the growth of arrhythmias in female rodent hearts (Gao & Wang, 2014). The chronic kidney disease is also a major illness caused by BPA, which is related to urinary Albuminuria and blood pressure. The progression of chronic kidney disease (CKD) among patients with primary hypertension can be caused by serum BPA (Hu et al., 2016, pp.332-337).

This research attempted to replicate and expand Melzer et al.'s (2010) results by inspecting the relationship between BPA with CVD. In this cross-sectional study, relationships of urinary BPA with CVD have been assessed, using a different data set (NHANES 2009/2010) than that used by Melzer et al. (2010). The addition of

C-reactive protein (CRP) to the analysis allowed exploring the mechanism by which BPA might cause CVD. According to Melzer et al. (2010), an association has been seemed between BPA and CVD; however, Melzer et al. (2010) did not pursue the mechanism by which BPA and CVD are related.

The researchers recommended the replication of study using a different set of data to confirm their findings. This study used multivariate analysis to evaluate the relationship between BPA and the presence of CVD, and the changes in reporting CVD after adjusting for CRP. According to Melzer et al. (2010), BPA might induce oxidative stress to normal vascular endothelial cells, leading to inflammatory changes. The research explored the inflammation as measured by CRP and to assess its relevance to CVD.

*1.1 Significance of the Problem*

The studies on Bisphenol A have been extracted from the NHANES (2009/2010) in the United States. Vandenberg et al. (2007) incorporated many studies showing the impacts of BPA on the development of human fetus, which acted as a disturbance for estrogen. Higher urinary concentrations of BPA are reflected because of higher BPA exposure, which is consistently related to the heart diseases in an adult population of United States. Recognizing the association among BPA, CRP, and CVD has posed a different perspective on chronic diseases leading to effective strategies for prevention of future chronic diseases. By creating potential positive social change, the study attempted to decrease the burden of financial costs associated with chronic disease.

*1.2 Purpose of the Study*

In this quantitative study, the association of urinary BPA with CVD has been explored. Urinary BPA was the independent variable, while reporting of CVD was the dependent variable with CRP, acting as a moderating variable.

*1.3 Research Questions and Hypotheses*

Is there an influence of C-reactive protein on the relationship between BPA and CVD, after adjusting for gender, age, ethnicity/race, urinary creatinine, arthritis? The null and research hypotheses are as follows:

Null Hypothesis ($H_0$): There is no influence of C-reactive protein on the relationship between Bisphenol A and CVD, after adjusting for gender, age, ethnicity/race, urinary creatinine, arthritis

Research Hypothesis ($H_A$): There is an influence of C-reactive protein on the relationship between bisphenol A and CVD, after adjusting for gender, age, ethnicity/race, urinary creatinine, arthritis

These hypotheses have been relied on the accuracy of detecting urinary BPA and serum CRP concentrations, and on honest reporting of the presence of heart attack, angina, coronary heart diseases, and congestive heart failure. Such accuracy was important to explore the research questions and to understand the relationship between BPA, CRP, and CVD. The challenge in the current study was to acquire accurate laboratory assessment of BPA and CRP. This was achieved through the selection of secondary data from NHANES collected in 2009/2010. As demonstrated by Teitel (2013), level of CRP was elevated among patients with chronic renal failure, obstructive sleep apnea, stroke, and severe peripheral vascular diseases. Acting as a systemic marker of inflammation, the level of CRP was interesting enough to use it as a marker for the effect of BPA on the body. There was no doubt that CRP, the substance that increased during all of these systemic diseases, was worth studying to investigate its level with the level of urinary BPA and reporting of CVD.

The relevance of CRP as the moderating variable was that inflammation, which is an active response of cardiovascular tissues to injury (Hennig et al., 2002, pp.95-102). This study attempted to examine if excessive exposure to BPA had an effect on triggering the inflammatory process in cardiovascular tissues. According to Melzer et al. (2010), excessive exposure to BPA might lead to oxidative stress on cardiovascular tissue and might lead to endothelial damage. The addition of CRP tested the hypothesis by Melzer et al (2010) through assessing serum CRP in the moderation analysis. To fully expand, the findings of these researchers, a robust research method, and design was indispensable fully to understand the interaction of BPA, CVD, and CRP.

The characteristics of BPA have been described in the study, within a representative sample of the United States population. The Larger sample size was desirable to maintain the reliability of the results (Hackshaw, 2008). According to Hackshaw, larger sample size would be helpful for narrow intervals, which usually emerges more precise results. The sample of the study always matters when comparison is done in between the concentration of urinary BPA and serum CRP. According to Hackshaw (2008), effect size can be measured by the relative risk or odd ratio. A possible bias in the study was the CRP, which was also elevated in other diseases. Efforts were made to include participants reporting only CVD. Providing empirical generalization to the larger population was the goal of this quantitative study.

## 3. Research Method

The cross-sectional quantitative research design has been used in the study, with a correlation approach to assessing the role of C-reactive protein on the relationship between Bisphenol A & Cardiovascular Diseases.

### *3.1 Population*

As per NHANES data collected in 2009/2010, 13,272 persons were selected for the sample. Only 10,537 individuals (79.4%) were surveyed (CDC, 2013a). The response rate differed between age group. The response rate fluctuated between 86.9% (for 16- to 19-year-old participants) to 55.2% (for participants over the age of 80 years). The sample selected represented the total U.S. population of all ages. To produce reliable results, oversampling was recommended for individuals age 60 and older, Hispanics, Asians, and African Americans. The oversampling was justified because the U.S. population is expanding exponentially with elderly people, Hispanics, Asians, and African Americans. As a result, these groups of individual play a dramatic role in the health trends of the U.S. population, and hence need to be replicated (CDC, 2013a).

### *3.2 Sample and Sampling Procedures*

Participants were selected based on gender, age, and ethnic/rational background. Once participants were selected, a unique health profile was created for each. No person could substitute for any missing or dropped participants. At any given time, participants had the ability to leave the survey with no retribution. Selected participants were provided with informed consent. NHANES participants were protected by the Public Health Act that deals with authorization for collecting information from participants.

### *3.3 Sample Size, Power, and Precision*

The preferred determined alpha level was set at 0.05 because adding more restriction (such as setting alpha at 0.01 or 0.001), when a sample size was fixed, would increase Type II error, failing to reject the null hypothesis when it was actually false. Therefore, the significance level was set to be 0.05. To conduct power analysis, the G*power 3.1.7 was used. The multiple binary logistic regression analysis was conducted, which was posed to have an identical number of covariates, and power analysis was conducted using a binary regression model with two tails.

This analysis was used to determine the power of the study given the original sample size. The OR was chosen to be 1.10 based on suggestions posed by Hsieh et al. (1998). Considering a multiple binary logistic regression with a very small effect size (OR = 1.10), a confidence level of 95% ($\alpha = .050$), a sample size of 1,465, the power was 0.31 (Faul et al., 2013). If the effect was of a medium size (i.e., OR of 3.5) the power was calculated to approach .99. Thus, there was sufficient power to reject the null hypothesis if it was false using such analyses.

### *3.4 Study Variables and Covariates*

A list of the dependent and independent variables and covariates are provided in Table 1. The urinary BPA was the independent variables, and reporting CVD was the dependent variable. NHANES interviewers conducted a brief interview to gather basic information such as race, age, sex, and general income level. A computer algorithm then selected all households, one or more, or none to participate in NHANES survey. Dropped participants were treated as missing data and could not be substituted by anyone, not even an immediate family member. Fifteen sample representatives were randomly selected and visited throughout the year to follow up on their dietary and health status (CDC, 2013b).

Table 1. Independent, Dependent, and Covariate Variables of the Study, NHANES 2009/2010

| Variable Type | Variable Name | Variable Source | Potential Responses | Level of Measurement |
|---|---|---|---|---|
| Independent variable | BPA | NHANES data file EPH_F.xpt | Values between 0.1-2.0 nanogram per deciliter | Continuous |
| Dependent variable | CVD | NHANES data file CDQ_F.xpt | 79.4% | Dichotomous |
| Moderating variable | CRP | NHANES data file CRP_F.xpt | More than 0.02 nanogram per deciliter | Continuous |

*3.5 Research Analysis*

Data was entered into SPSS version 21.0. Descriptive statistics were conducted to the research variables and the sample demographics. According to Howell, 2010, frequency and percentages were also calculated for nominal data such as instances of CVD, and means/standard deviations for continuous data, such as BPA and CRP levels. The urinary concentration of BPA was the independent variable, and reporting of CVD was the dependent variable. Serum concentration of CRP was a moderating variable. The plan was to assess how the amount of serum CRP affects the relationship between BPA and CVD.

## 4. Results

The final participants selected were 1,453, out of which 724 were male, and 729 were female (Table 2). The majority of the participants reported to not have arthritis (1,444, 99%), and the majority reported to not have CVD (1,360, 94%). Of those who were classified as having CVD based on the criteria, 35 (38%) reported being diagnosed with congestive heart failure, 46 (49%) reported being diagnosed with coronary heart disease, 28 (30%) reported at least one past heart attack, and 28 (30%) reported angina pectoris.

Table 2. Frequencies and Percentages for Sample Demographics

| Demographic | *n* | % |
|---|---|---|
| Gender | | |
| Male | 724 | 50 |
| Female | 729 | 50 |
| Non-Hispanic White | 661 | 46 |
| Other | 792 | 55 |
| Non-Hispanic Black | 253 | 17 |
| Mexican-American | 293 | 20 |
| Other Hispanic | 164 | 11 |
| Other/Multiracial | 82 | 6 |
| Arthritis | | |
| Yes | 9 | 1 |
| No | 1444 | 99 |
| CVD | | |
| No | 1360 | 94 |
| Yes (based on below classifications) | 93 | 6 |
| Congestive heart failure | (35) | (38) |
| Coronary heart disease | (46) | (49) |
| Heart attack | (28) | (30) |
| Angina pectoris | (28) | (30) |

The age of participants was from 20 years to 69 years with the mean of 43.56 years (*SD* = 14.10). The creatinine levels ranged from 4 mg/dL to 382 mg/dL with a mean of 127.08 and standard deviation of 75.71. BPA levels ranged from 0.28 ng/mL to 112.00 ng/mL with a mean of 3.29 and standard deviation of 5.71. Values for CRP ranged from 0.02 mg/dL to 8.76 mg/dL with mean of 0.39 and standard deviation of 0.65 (Table 3).

Table 3. Descriptive Statistics of Continuous Variables

| Continuous Variables | *Min.* | *Max.* | *M* | *SD* |
|---|---|---|---|---|
| Age | 20 | 69 | 43.56 | 14.10 |
| Creatinine (mg/dL) | 4 | 382 | 127.08 | 75.71 |
| BPA levels (ng/mL) | 0.28 | 112.00 | 3.29 | 5.71 |
| CRP (mg/dL) | 0.02 | 8.76 | 0.39 | 0.65 |

Moderation analysis with a binary logistic regression has been proposed to assess the research question. There was a significant relationship found between the independent variable (i.e., BPA) and the dependent variable (i.e., CVD) before including the moderator variable (i.e., CRP). Results indicated that the relationship between BPA and CVD was not statistically significant, so the moderation analysis could not be conducted. Thus, the null hypothesis could not be rejected, and there was no observed relationship found.

*4.1 Ancillary Analysis*

There might be an association between the study variable BPA and CRP, despite the inability to determine the relation with CVD. A single Pearson correlation was conducted in order to assess the potential relationship. Before the analysis was conducted, the assumptions of the Pearson correlation were evaluated. In order to determine the distribution of error, normality was assessed using a PP- plot. The plot indicated that the error was not normally distributed, and the assumption violated (Stevens, 2009). Additionally, in order to examine the homoscedasticity of the relationship standardized residual plot was used. These plots indicated that the linear relationship was heteroscedastic, and this assumption was also violated (Stevens, 2009). The Non-parametric equivalent of the Pearson correlation test was conducted.

Results of the Spearman correlation (Table 4) indicated that there was a significant relationship between measures of urinary BPA and urinary CRP levels ($r$s= .06, $p$ =.015). Though this relationship was found to be significant beyond the .05 level, examination of the Spearman correlation coefficient ($r$s) indicated that this represented a very weak association.

Table 4. Spearman's Correlation between BPA and CRP

| | | | Urinary BPA (ng/Ml) | CRP (mg/dl) |
|---|---|---|---|---|
| Spearman's rho | Urinary BPA (ng/Ml) | Correlation coefficient | 1.000 | .064* |
| | | Sig (2-tailed) | | .015 |
| | | N | 1453 | 1453 |
| | CRP (mg/dl) | Correlation coefficient | .064* | 1.000 |
| | | Sig (2-tailed) | .015 | |
| | | N | 1453 | 1453 |

*Note*. Correlation is significant at the 0.05 level (2-tailed).

In addition, upon examination of a scatter plot between the two variables, it was determined that significant findings might be due to the tendency of both variables to cluster around zero, and it has been observed that there is no linear relationship. This observation held true after filtering the outliers from the plot. A scatter plot between both variables was assessed with outliers in Figure 1 and further assessed without outliers in Figure 2.

To explore the relationship between BPA and CRP further, a logarithmic base scale of 10 transformations for these two variables was produced. Log base 10 transformation was the best transformation to use in this situation. The results of the logarithmic scale are depicted in Figure 1 and Figure 2.

The logarithmic 10-scale transformation did not show any linear relationship between BPA and CRP. There seemed to be a tendency towards a central cluster that might be skewing things to look like there was a relationship when the Spearman correlations were conducted. In an ancillary analysis, BPA and CRP were found to have a significant relationship using a Spearman correlation ($r$s= .06, $p$ = .015). Though, it was found that the relationship is significant beyond the 0.05 level, examination of the Spearman correlation coefficient indicated that this represented a very weak association. Further examination of a scatter plot between the two variables indicated that significant findings may be due to the tendency of both variables to cluster around zero, and therefore no linear relationship was observed. This observation held true after outliers were filtered from the plot.

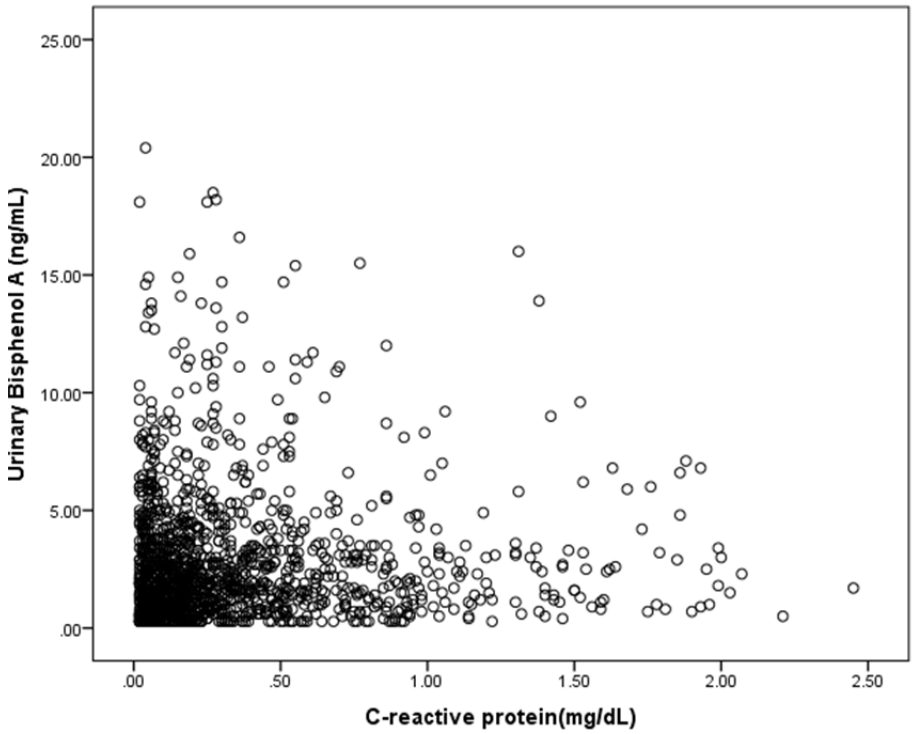


Figure 1. Scatterplot between urinary BPA and serum CRP measurements without outliers

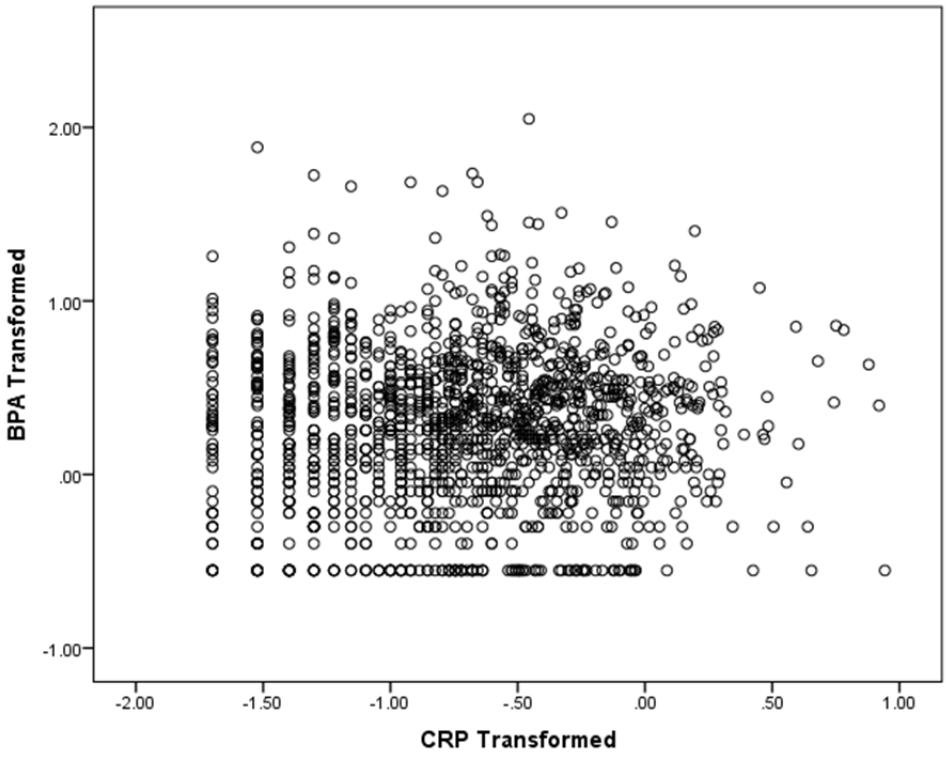


Figure 2. Scatterplot between urinary BPA and serum CRP transformed to base-10 logarithmic scale with outliers

## 4. Discussion

Teitel (2013) demonstrated the level of C-reactive proteins among patients, suffering from chronic renal failure, stroke, severe peripheral vascular diseases, and obstructive sleep apnea. The level of C-reactive protein was interestingly enough to use as a marker for the effect of Bisphenol A, acting as a systemic marker of inflammation on the body (Rezg et al., 2014). CRP was increased during certain systemic diseases that were worth examining to find out its level with the level of urinary Bisphenol A and reporting cardiovascular disease (Rancière et al., 2015).

Experimental studies have recommended that the exposure of Bisphenol A is correlated with insulin resistance and abnormal glucose metabolism (Tiwari et al., 2015). Though, data extracted from observational studies of humans sustaining an association between obesity and BPA, CVD and diabetes are still too inadequate in cross-sectional studies to make definitive statements of harm (Agarwal et al., 2015). It is essential that more potential studies, with careful measurements of socioeconomic status, urine dilution, and dietary intake, are conducted to recognize the possible impact Bisphenol An exposure in humans will have on the growth of chronic disease (Ye et al., 2013).

The results of the present study indicated the association between BPA and CRP, Spearman correlation for the two variables, BPA, and CRP, was .06 ($p$ = .015), indicating a significant association between BPA and CRP. The positive Spearman correlation indicated a positive association between BPA and CRP. As urinary BPA level increases, serum CRP level also increases. Though the relationship between BPA and CRP was found to be significant beyond the 0.05 level, examination of the Spearman correlation coefficient ($r$s) indicating a very weak association.

The focus of the association between BPA and CRP was later shifted to examine the cluster of the measurements of both BPA and CRP around the zero. To examine such cluster fully, a logarithmic 10-scale was conducted with outliers and without outliers. The logarithmic 10-scale transformation did not show any linear relationship between BPA and CRP. Further investigation of the association between BPA and CRP using a scatter plot also indicated a weak association, although the scatter plot was later scaled at a 10 logarithmic scale.

The current study ascertained that an association between BPA and CRP existed but not at a significant level

using Spearman correlation ($r$s = .06, $p$ = .015). Spearman correlation coefficient ($r$s) of .29 and below indicates the weak association. Spearman correlation coefficient ($r$s) between .3 and .39 constitutes a medium strength correlation and that of 0.5 and above indicates high strength association. Spearman correlation coefficient for BPA and CRP in the current study was .06 ($p$ = .015), indicating a very weak association.

The secondary data has been used; therefore, the current study is limited and was conducted under the auspices of the CDC. The sample size after the data processing and filtering was 1,465 participants. In order to reflect the reliability of the data, the larger sample size was desired. The resulting sample size used in the logistic regression conveyed the high level of power and hence the sample size was verified to be valid and trustworthy. The other limitation of the study is that the level of CRP is also raised in other conditions. To limit this confounder, the study controlled for age, gender, race/ethnicity, arthritis, and urinary creatinine. The reporting of CVD is also limited to heart attack, angina, coronary heart diseases, and congestive heart failure, with an exclusion of many other heart conditions.

NHANES has undergone extensive testing and demonstrated criterion validity, predictive validity, content and construct validity, internal consistency, measurement invariance, test-retest reliability to assure validity and usefulness of the data presented to researchers. Through the training of individuals conducting the interviews, performing the laboratory testing, and analyzing the findings, threats to validity were controlled.

## 5. Conclusion

In an ancillary analysis, there seemed to be an association between BPA and CRP ($r$s= .06, $p$ = .015); however, upon further analysis, it was determined that the association was not statistically significant. Similarly, no linear relationship was observed due to the tendency of both variables, and. Although no significant association was found between BPA and CRP in the study, further investigation is needed to confirm such results and to include more confounders and to increase sample sizes and hence to increase the reliability for possible generalization to the whole US population. A different perspective was provided by the study of chronic diseases, especially CVD. While the factors contributing to CVD have been established (complex interaction between diet, genetic, and lifestyle factors), the contribution of environmental contaminants such as BPA received poor attention from researchers. There was a need for research such as this to shed new light on the causes of CVD and contribute to the development of more effective strategies for prevention.

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## Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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