

ERECTILE DYSFUNCTION

Food Insecurity May be an Independent Risk Factor Associated With Erectile Dysfunction in the United States: Analysis of the National Health and Nutrition Examination Survey Data



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ABSTRACT

Introduction: While food insecurity is a global public health problem associated with obesity, diabetes, hypertension and coronary heart disease, literature regarding the relationship between food insecurity and erectile dysfunction (ED) is scarce.

Aim: We aimed to determine the associations between food insecurity and ED in the National Health and Nutrition Examination Survey.

Methods: Data was extracted from 3,891 participants (aged ≥ 20 years) with ED in the 2001–2004 National Health and Nutrition Examination Survey. Multivariable logistic regression analysis with sampling weights was conducted to evaluate the associations.

Main outcome measure: Food security was assessed utilizing the Household Food Security Module. A single-question self-report from the Massachusetts Male Aging Study was utilized to evaluate ED status.

Results: Approximately 10.2% of individuals had food insecurity. Food insecurity was significantly associated with ED after full adjustment (odds ratio [OR] 1.56; 95% confidence interval [95% CI] 1.16–2.09; $P = .003$). Men with very low food insecurity had 59% higher risks of ED compared with those having high food security (OR 1.59; 95% CI 1.13–2.27; $P = .006$). Moreover, the associations were stronger in the old people (age ≥ 60) (OR 2.15; 95% CI 1.26–3.66; $P = .004$).

Conclusions: Food insecurity might be associated with higher risks of developing ED. **Wang W, Chen J, Peng L, et al. Food Insecurity May be an Independent Risk Factor Associated With Erectile Dysfunction in the United States: Analysis of the National Health and Nutrition Examination Survey Data. Sex Med 2022;10:100549.**

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Key Words: Erectile Dysfunction; Food Insecurity; NHANES; Diet; Nutrition

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent inability to attain and/or maintain an erection sufficient for sexual satisfaction.¹ ED is a common disorder that adversely impacts

approximately 30 million men in the United States.² Furthermore, ED has been regarded as age-dependent. It is estimated that the prevalence rate of ED ranges from 13% to 30% in men younger than 40 years, and the rate increases to 40–80% in men

Abbreviations: ED, erectile dysfunction; NHANES, National Health and Nutrition Examination Survey; CVD, cardiovascular disease; OR, odds ratio; CI, confidence interval; USDA, United States Department of Agriculture; BMI, body mass index; SD, standard deviation
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aged ≥ 70 years.^{2,3} ED not only significantly decreases the quality of life but also represents a critical indicator of subclinical cardiovascular disease (CVD). Increasing evidence indicated that ED severity was closely associated with CVD burden.⁴ Dong et al included 12 prospective cohort studies involving 36,744 individuals and found that men with ED were associated with increased risks of CVD (odds ratio [OR]: 1.48; 95% confidence interval [CI]: 1.25–1.74), coronary heart disease (OR 1.46; 95% CI 1.31–1.63), stroke (OR 1.35; 95% CI 1.19–1.54) and all-cause mortality (OR 1.19; 95% CI 1.05–1.34).⁵ Therefore, it is critical to identify modifiable risk factors, and to establish ED prevention or alleviation strategies.

Food insecurity is characterized by inadequate consistent access to safe food with essential nutrients, fruits, and vegetables. A recent study revealed that the prevalence rate of food insecurity ranged from 8% to 20% in developed countries.⁶ Additionally, the unprecedented coronavirus disease 2019 pandemic has significantly exacerbated food insecurity problems with the prevalence rate rising from 11% in 2018 to 38% in March 2020 in the United States.⁷ The individuals experiencing food insecurity often consume high energy-dense, nutrient-poor foods rather than fresh fruits and vegetables because of unpredictable food availability.

Increasing studies have demonstrated an independent relationship between food insecurity and end-stage renal disease, nonalcoholic fatty liver disease, cognitive impairment, diabetes, hypertension and coronary heart disease.^{8–11} Nevertheless, little is known regarding the relationship between food insecurity and ED. Thus, we utilized data from the 2001–2004 cycles of the National Health and Nutrition Examination Survey (NHANES), to determine whether food insecurity is independently associated with increased risks of developing ED.

METHODS

Study Design and Population

NHANES is one of a series of nationally representative surveys undertaken by the Centers for Disease Control and Prevention's National Center for Health Statistics in the United States. These surveys collected cross-sectional data from samples of the resident civilian adults and children utilizing a stratified, multi-stage probability sampling design.¹² In the current study, 2 cycles of data from 2001 to 2004 were obtained from NHANES. The 2001–2002 and 2003–2004 waves represent the only years in which questionnaire data concerning ED were available. The individuals with incomplete erectile function assessment, missing food insecurity data or a prior diagnosis of prostate cancer were excluded from our study. Ultimately, 3,891 participants aged ≥ 20 years were included in the final analysis. The study protocols were approved by the Ethics Review Board of the National Center for Health Statistics, and informed consent was signed by all individuals.

Measurement of Household Food Security

We utilized the Household Food Security Module to evaluate the food security status of participants. This module includes a standardized 10-item questionnaire specific to the households without children and an 18-item questionnaire for the households with children. The questionnaire assessed whether there was any food security-related condition or behavior occurring during the past 12 months and was detailed demonstrated in Supplementary Table 1. A score ranging from 0 to 10 was obtained by a summation of the affirmative responses of participants. The lower score indicated less food insecurity. Based on the United States Department of Agriculture, food insecurity was defined as low (scores 3–5) or very low food security (score 6–10), while full (score 0) or marginal food security (score 1–2) were categorized into food security.¹³

Outcome Assessment

A single-question self-report from the Massachusetts Male Aging Study was utilized to assess ED in the NHANES.¹⁴ This questionnaire can accurately identify the men with clinically diagnosed ED with the area under the curve values of 88.8%, making it useful for providing information regarding the prevalence rate of ED in the epidemiological studies.¹⁴ Men were asked whether they could get and keep an erection adequate for satisfactory intercourse. On the basis of previous studies,^{15–18} participants who responded “sometimes able” or “never able” were considered ED. In contrast, those who answered “always or almost always able” or “usually able” were regarded as having a normal erectile function.

Study Covariates

Baseline characteristics of participants consisted of age, race (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other race), the ratio of family income to poverty (< 1.5 , $1.5–3.5$ and > 3.5), an education level (less than high school, high school and above high school), marital status (married or living with a partner and living alone), body mass index (BMI) (< 20 , $20–25$, $25–30$, > 30 and missing), alcohol intake (non-drinker, light drinker, heavy drinker and missing), smoking status (nonsmoker, former smoker and current smoker), physical activity status, CVD, diabetes, hypertension and high cholesterol. Alcohol intake was defined as none (0 g/d), light (< 27.9 g/d), and heavy (≥ 28 g/d).¹⁹ Participants who smoked less than 100 cigarettes were considered nonsmokers; former smokers were those who responded to smoking more than 100 cigarettes in their whole life but did not smoke at the time of the interview; Individuals smoked more than 100 cigarettes in their lifetime and also reported smoking at the time of the interview, they were regarded as current smokers. Physical activity status was assessed by whether individuals engaged in more than 10 continuous minutes of moderate or vigorous activity in an average week. Men who responded to the previous diagnosis of angina, heart attack, or coronary heart disease were

regarded as having CVD. Individuals with a previous diagnosis of diabetes, or fasting plasma glucose concentration over 126 mg/dL, were considered as having diabetes. Hypertension was defined as the mean systolic pressure over 149 mm Hg or mean diastolic pressure over 90 mm Hg, taking antihypertensive medication, or self-reported a physician diagnosis of high blood pressure. Individuals with a total cholesterol level over 240 mg/dL, a previous diagnosis of high cholesterol, or a self-reported taking the lipid-lowering medication were classified as having hypercholesterolemia.

Statistical Analysis

Continuous and categorical variables were presented as mean ± standard deviation and proportions, respectively. The study analysis was adjusted for sampling weights, strata and primary sampling units. Baseline characteristics of participants between food-secure and food-insecure groups were compared by t-test and chi-square test. A multivariate logistic regression model utilizing weighted survey procedures was performed to evaluate the independent association between food insecurity and erectile function. 2 models were utilized in our study: (i) included adjustment for age, race, and BMI (model I); (ii) model I + the ratio of family income to poverty, education level, marital status, alcohol intake, smoking, physical activity status, CVD, diabetes, hypertension, and high cholesterol (model II). Results were demonstrated as adjusted OR with 95% CI.

We also conducted additional sensitivity analyses to assess the robustness of our results. Firstly, we categorized food insecurity into 4 groups (high, marginal, low, and very low) to examine whether there existed a dose-response association between increasing severity of food insecurity and ED. Secondly, As the association between age and ED has been well established,²⁰ age was treated as a prespecified potential effect modifier. An interaction test was utilized to evaluate the heterogeneity of associations between different subgroups (age ≥ 60, 40–59, 20–39). Additional stratified analyses by age categories were conducted. Missing values were replaced by median (continuous) or mode (categorical) of existing cases of that variable. All statistical analyses were conducted utilizing the R software (version 4.1.2) and Empower (www.empowerstats.com). Results were statistically significant for *P* values < .05.

RESULTS

A total of 3,891 participants were included in our analysis, 19.7% of whom were classified as ED. Baseline characteristics of participants by food security status were demonstrated in Table 1. Compared with food-secure individuals, Men in the food-insecure group were more likely to be younger, Mexican American, with a ratio of family income to poverty less than 1.5, less educated, living alone, alcohol drinkers and physically inactive (Table 1). Approximately 10.2% of individuals had food insecurity during the past 12 months.

Baseline characteristics of participants with or without a history of ED were presented in Table 2. The ED group tended to be older, and was more likely to be non-Hispanic white, have a lower socioeconomic status, be less educated, have a BMI higher than 30, be a former smoker and have a lack of exercise (all *P* < .05). Participants with ED were more likely to have a history of CVD, diabetes, hypertension and high cholesterol (all *P* < .001) (Table 2).

Table 1. Baseline characteristics of participants by food security status in NHANES 2001–2004

	Food secure	Food insecure	<i>P</i> value
Number	3,394	497	
Age, y	51.2 ± 18.8	42.8 ± 16.6	<.001
Race, n (%)			<.001
Mexican American	606 (17.9%)	184 (37.0%)	
Other Hispanic	96 (2.8%)	35 (7.0%)	
Non-Hispanic White	1,941 (57.2%)	172 (34.6%)	
Non-Hispanic Black	643 (18.9%)	95 (19.1%)	
Other race	108 (3.2%)	11 (2.3%)	
Ratio of family income to poverty, n (%)			<.001
Less than 1.5	772 (22.8%)	358 (72.1%)	
1.5–3.5	1,125 (33.1%)	115 (23.1%)	
Over 3.5	1,337 (39.4%)	7 (1.4%)	
Missing	160 (4.7%)	17 (3.4%)	
Education level, n (%)			<.001
Less than high school	851 (25.1%)	258 (52.0%)	
High school	840 (24.8%)	114 (23.0%)	
Above high school	1,703 (50.1%)	125 (25.0%)	
Marital status, n (%)			<.001
Married or living with partner	2,354 (69.3%)	302 (60.8%)	
Living alone	1,040 (30.7%)	195 (39.2%)	
BMI, kg/m ² , n (%)			.003
BMI < 20	116 (3.4%)	28 (5.6%)	
20 ≤ BMI < 25	850 (25.0%)	153 (30.8%)	
25 ≤ BMI < 30	1,395 (41.2%)	187 (37.6%)	
BMI ≥ 30	937 (27.6%)	119 (24.0%)	
Missing	96 (2.8%)	10 (2.0%)	
Alcohol intake, n (%)			<.001
Nondrinker	2,461 (72.5%)	326 (65.6%)	
Light drinker	374 (11.0%)	80 (16.1%)	
Heavy drinker	304 (9.0%)	62 (12.5%)	
Missing	255 (7.5%)	29 (5.8%)	

(continued)

Table 1. Continued

	Food secure	Food insecure	<i>P</i> value
Smoking, n (%)			<.001
Nonsmoker	1,407 (41.5%)	157 (31.6%)	
Former smoker	1,141 (33.6%)	124 (25.0%)	
Current smoker	846 (24.9%)	216 (43.4%)	
Physical activity status, n (%)			
Moderate			<.001
Yes	1,720 (50.7%)	185 (37.2%)	
No	1,674 (49.3%)	312 (62.8%)	
Vigorous			.180
Yes	1,134 (33.4%)	151 (30.4%)	
No	2,260 (66.6%)	346 (69.6%)	
History of cardiovascular disease, n (%)			.356
Yes	367 (10.8%)	44 (8.9%)	
No	3,027 (89.2%)	453 (91.1%)	
History of diabetes, n (%)			.580
Yes	356 (10.5%)	56 (11.3%)	
No	3,038 (89.5%)	441 (88.7%)	
History of hypertension, n (%)			.001
Yes	1,348 (39.7%)	160 (32.2%)	
No	2,046 (60.3%)	337 (67.8%)	
History of high cholesterol, n (%)			.114
Yes	1,241 (36.6%)	167 (33.6%)	
No	2,153 (63.4%)	330 (66.4%)	

BMI = body mass index.

The values are presented as weighted means \pm SD or unweighted counts (weighted %).

As shown in [Table 3](#), food insecurity was significantly associated with ED after adjusting for age, race and BMI (OR 1.99; 95% CI 1.53–2.60; $P < .001$). In addition, Men with low and very low food security had increased risks of developing ED when compared to those with high and marginal food security after full adjustment (OR 1.56; 95% CI 1.16–2.09; $P = .003$) ([Table 3](#)). We further conducted sensitivity analyses by categorizing food insecurity into 4 groups. Our result revealed a dose-response association between food insecurity and ED after adjusting for all confounding variables. Participants with very low food insecurity had 59% higher risks of ED compared with those having high food security (OR 1.59; 95% CI 1.13–2.27; $P = .006$) ([Table 3](#)).

[Table 4](#) presented a subgroup analysis of the association between food insecurity and ED stratified by age of the participants. There were no significant interactions between food insecurity and age in the association with ED (P for interaction = .112). After full adjustment, we found that the

Table 2. Baseline characteristics of participants with or without a history of erectile dysfunction in NHANES 2001–2004

	History of erectile dysfunction		<i>P</i> value
	No	Yes	
Number	2,742	1,149	
Age, y	43.4 \pm 15.7	66.0 \pm 15.4	<.001
Race, n (%)			<.001
Mexican American	553 (20.2%)	237 (20.6%)	
Other Hispanic	91 (3.3%)	40 (3.5%)	
Non-Hispanic White	1,439 (52.5%)	674 (58.7%)	
Non-Hispanic Black	563 (20.5%)	175 (15.2%)	
Other race	96 (3.5%)	23 (2.0%)	
Ratio of family income to poverty, n (%)			<.001
Less than 1.5	753 (27.4%)	377 (32.8%)	
1.5–3.5	827 (30.2%)	413 (36.0%)	
Over 3.5	1,044 (38.1%)	300 (26.1%)	
Missing	118 (4.3%)	59 (5.1%)	
Education level, n (%)			<.001
Less than high school	641 (23.4%)	468 (40.8%)	
High school	718 (26.2%)	236 (20.5%)	
Above high school	1,383 (50.4%)	445 (38.7%)	
Marital status, n (%)			<.001
Married or living with partner	1,814 (66.2%)	840 (73.1%)	
Living alone	928 (33.8%)	309 (26.9%)	
BMI, kg/m ² , n (%)			<.001
BMI < 20	104 (3.8%)	40 (3.5%)	
20 \leq BMI < 25	753 (27.4%)	250 (21.7%)	
25 \leq BMI < 30	1,118 (40.8%)	464 (40.4%)	
BMI \geq 30	729 (26.6%)	327 (28.4%)	
Missing	38 (1.4%)	68 (6.0%)	
Alcohol intake, n (%)			<.001
Nondrinker	1,900 (69.3%)	887 (77.2%)	
Light drinker	351 (12.8%)	103 (9.0%)	
Heavy drinker	296 (10.8%)	70 (6.1%)	
Missing	195 (7.1%)	89 (7.7%)	
Smoking, n (%)			<.001
Nonsmoker	1,212 (44.2%)	348 (30.3%)	
Former smoker	696 (25.4%)	569 (49.5%)	
Current smoker	834 (30.4%)	232 (20.2%)	
Physical activity status, n (%)			<.001
Moderate			<.001
Yes	1,430 (52.2%)	475 (41.3%)	
No	1,312 (47.8%)	674 (58.7%)	

(continued)

Table 2. Continued

	History of erectile dysfunction		P value
	No	Yes	
Vigorous			<.001
Yes	1,101 (40.2%)	184 (16.0%)	
No	1,641 (59.8%)	965 (84.0%)	
History of cardiovascular disease, n (%)			<.001
Yes	150 (5.5%)	261 (22.7%)	
No	2,592 (94.5%)	888 (77.3%)	
History of diabetes, n (%)			<.001
Yes	148 (5.4%)	264 (23.0%)	
No	2,594 (94.6%)	885 (77.0%)	
History of hypertension, n (%)			<.001
Yes	819 (29.9%)	697 (60.0%)	
No	1,923 (70.1%)	452 (40.0%)	
History of high cholesterol, n (%)			<.001
Yes	881 (32.1%)	527 (45.9%)	
No	1,861 (67.9%)	622 (54.1%)	

BMI = body mass index.

The values are presented as weighted means ± SD or unweighted counts (weighted %).

association between food insecurity and ED remained significant among the 3 groups (all *P* values < .05). Moreover, the old participants (age ≥ 60) who had food insecurity during the past 12 months were associated with a 115% higher risk of developing ED (OR 2.15; 95% CI 1.26–3.66; *P* = .004) (Table 4).

DISCUSSION

This is the first large population-based cohort study to determine the impacts of food insecurity on erectile function. Our

Table 4. Subgroup analysis of the association between food insecurity and erectile dysfunction by age in NHANES 2001–2004

Age group	OR (95% CI)*	P value	P for interaction
20–39	1.41 (1.05, 1.88)	.020	.112
40–59	1.29 (1.02, 1.73)	.039	
≥ 60	2.15 (1.26, 3.66)	.004	

*Adjust for age, race, ratio of family income to poverty, education level, marital status, BMI, Alcohol intake, smoking, physical activity, cardiovascular disease, diabetes, hypertension and high cholesterol.

results revealed an independent association between food insecurity and increased risks of ED after adjustment for all the confounding variables (OR 1.56; 95% CI 1.16–2.09; *P* = .003). In addition, we categorized food insecurity into 4 groups and found that individuals with very low food insecurity had 59% higher risks of ED when compared to those with high food security (OR 1.59; 95% CI 1.13–2.27; *P* = .006). Moreover, the associations were stronger in the old people (age ≥ 60).

While food insecurity was once regarded as a developing countries problem, more and more studies have reported this condition in developed countries such as Canada, Australia, the UK and the United States.²¹ Food insecurity is a serious public health concern leading to poor nutrient intake and has been shown to associate with many negative health consequences. Ver-cammen et al utilized the data of 13,518 adults from the NHANES 2007–2014, they found that individuals with very low food security had greater odds of excess predicted 10-year CVD risk (OR 2.36, 95% CI 1.25–4.46).²² Another study enrolled 15,499 immigrant individuals and revealed that food insecurity was significantly related to a 57% higher risk of coronary heart disease (*P* < .01), 81% higher risk of angina pectoris (*P* < .01), and 120% higher risk of heart attack (*P* < .01).²³ Similarly, Venci et al performed analyses of 33,014 adults sample and they found that the combined relative risks for men with very low food insecurity were 1.75 (95% CI 1.37–2.24) for coronary heart disease, 1.40 (95% CI 1.08–1.81) for heart attack, 1.42 (95% CI 1.22–1.65) for hypertension, and 1.23 (95% CI 1.02

Table 3. Association between food insecurity and erectile dysfunction in NHANES 2001–2004

Characteristic	OR (95% CI), P value	
	Model I	Model II
Food insecurity definition		
Low/very low food security (reference: high/marginal)	1.99 (1.53, 2.60), <.001	1.56 (1.16, 2.09), .003
Food insecurity by category (reference: high)		
Marginal food security	1.21 (0.84, 1.74), .313	0.92 (0.63, 1.36), .677
Low food security	2.01 (1.46, 2.77), <.001	1.44 (1.12, 2.25), .009
Very low food security	2.06 (1.35, 3.15), <.001	1.59 (1.13, 2.27), .006

Model I: adjust for age, race and BMI.

Model II: adjust for age, race, Ratio of family income to poverty, education level, marital status, BMI, alcohol intake, smoking, physical activity, cardiovascular disease, diabetes, hypertension and high cholesterol.

−1.48) for diabetes.²⁴ CVD and ED share many common risk factors including a sedentary lifestyle, physically inactive, hypertension, smoking, diabetes, obesity and hyperlipidemia.⁴ Furthermore, there exists an overlap in the pathophysiological mechanisms between CVD and ED such as endothelial dysfunction and inflammation.⁴ Accordingly, it is reasonable to speculate on the possible negative effects of food insecurity on erectile function. We found that food insecurity was independently associated with ED, and the association remained robust when we categorized food insecurity into 4 groups. The possible explanations for the associations were as follows: (i) On the one hand, individuals with food insecurity are more likely to consume a variety of energy-dense, high-fat, cheap foods, such as salty snacks and sugar-sweetened beverages, which can significantly increase the risk of obesity, diabetes and CVD.²⁵ Meanwhile, it is reported that a high-fat, high-sucrose diet can lead to an impairment of erectile function via uncoupling nitric oxide synthase.²⁶ On the other hand, food-insecure adults consume less fresh fruit, vegetables and micronutrients in their daily life. The high-quality products including fruits, vegetables and food legumes have high amounts of phytochemicals that possess antioxidant and anti-inflammatory effects.²⁷ Shiri et al included 312 diabetic patients and found that men who consumed fruit weekly or seldom had greater odds of ED when compared to those consuming fruit daily (OR 3.2).²⁸ Another study published by Espósito et al demonstrated an inverse association between higher consumption of fruit, nuts, monounsaturated lipids and ED (all $P < .05$).²⁹ (ii) Food insecurity is a persistent stressful experience and can dysregulate the allostatic load system.³⁰ The cumulative physiological and emotional toll from chronic stress was related to depression and poor physical function, and might finally result in ED.³¹

Food insecurity is the common consequence of poverty, low education and limited resources available for household food acquisition for young individuals. Besides, among elders it can also be caused by functional impairments that hinder them from shopping or being capable of preparing healthy foods. Our subgroup analyses showed the associations between food insecurity and ED were stronger in the older adults (age ≥ 60). This might be explained by that the health burden of food insecurity in old people might be more severe than in young individuals.³² Two-thirds of elders have multiple chronic diseases including diabetes, hypertension, asthma, coronary heart disease, depression and cognitive impairment, which puts them in poorer health status and increases the difficulties to complete activities of daily living.³³ Moreover, old people are related to postponing necessary medical care and poor medication adherence.³² Therefore, more attention should be paid to the old people.

The current study features several strengths: (i) We utilized a large nationally representative sample of United States individuals. It is one of the largest cohorts and well generalized; (ii) The food security status of participants was assessed by the standardized Household Food Security Module, which has been validated

in the previous studies^{8,9,11,19}; (iii) A multivariate logistic regression model was conducted controlling for multiple socio-demographic and health variables in our study. However, some limitations also exist in our study. Firstly, food insecurity status was evaluated at the household level, but ED was assessed at the individual level. Nevertheless, studies have shown that household food insecurity can affect almost all people in the household.⁸ Secondly, some unmeasured confounding variables such as neighborhood characteristics and food environment might lead to bias in the association. Thirdly, we cannot establish the causal association in our study due to the nature of cross-sectional studies.

CONCLUSIONS

In conclusion, the current study suggests that food insecurity might be associated with an increased risk of ED. Moreover, the association might be stronger among the old people. Our study calls for continued policies that improve accessibility and quality of food to alleviate food insecurity and establish ED prevention strategies.

DECLARATIONS

Ethical approval: Written informed consent was provided for each participant and the National Center for Health Statistics Research Ethics Review Board approved the project

Informed consent: The data of participants were obtained from the public dataset NHANES in an anonymous form. Thus, additional consents were waived in the present study.

DATA SHARING STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: NHANES.

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STATEMENT OF AUTHORSHIP

Conceptualization: WW, JWC. Data curation: LP, XSG, LDL. Formal analysis: YX, FXZ. Funding acquisition: YCM. Investigation: FQ, JHY. Methodology: WW, JHY. Project administration: WW, JHY. Resources: WW. Software: JWC. Supervision: JHY. Validation: LP. Visualization: LDL. Writing—original draft: WW. Writing—review & editing: WW, JHY.

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SUPPLEMENTARY MATERIALS

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