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Effect of marijuana use on cardiovascular and cerebrovascular mortality: A study using the National Health and Nutrition Examination Survey linked mortality file

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Abstract

Background: Reports associate marijuana use with cardiovascular emergencies. Studies relating marijuana use to cardiovascular mortality are scarce. Recent advance towards marijuana use legalization emphasizes the importance of understanding relationships between marijuana use and cardiovascular deaths; the primary ranked mortality. Recreational marijuana is primarily smoked; we hypothesize that like cigarette smoking, marijuana use will be associated with increased cardiovascular mortalities.

Design: The design of this study was based on a mortality follow-up.

Method: We linked participants aged 20 years and above, who responded to questions on marijuana use during the 2005 US National Health and Nutrition Examination Survey to data from the 2011 public-use linked mortality file of the National Center for Health Statistics, Centers for Disease Control and Prevention. Only participants eligible for mortality follow-up were included. We conducted Cox proportional hazards regression analyses to estimate hazard ratios for hypertension, heart disease, and cerebrovascular mortality due to marijuana use. We controlled for cigarette smoking and other relevant variables.

Results: Of the 1213 eligible participants 72.5% were presumed to be alive. The total follow-up time was 19,569 person-years. Adjusted hazard ratios for death from hypertension among marijuana users compared to non-marijuana users was 3.42 (95% confidence interval: 1.20–9.79) and for each year of marijuana use was 1.04 (95% confidence interval: 1.00–1.07).

Conclusion: From our results, marijuana use may increase the risk for hypertension mortality. Increased duration of marijuana use is associated with increased risk of death from hypertension. Recreational marijuana use potentially has cardiovascular adverse effects which needs further investigation.

Keywords

Marijuana, cannabis, hypertension, cardiovascular mortality, delta-9-tetrahydrocannabinol

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Introduction

Cardiovascular diseases (CVDs) rank first as a cause of mortality worldwide and most are preventable.[1] Cardiovascular mortality encompasses death from diseases, emergencies, or conditions associated with heart and blood vessels.[2] In 2013, one out of every four deaths in the USA was due to heart disease (HD), stroke or other CVDs.[3] Cardiovascular death rates declined in the USA from 2000, however this decline has reversed since 2011.[4] Decline in cardiovascular deaths is due to clinical and public health interventions that address healthy lifestyles[5] including smoking cessation,[6,7] physical activity, healthy diet, maintaining

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normal body mass index, and avoidance of harmful alcohol use.[8–10] Thus, the reversal of the decline in the USA cardiovascular deaths calls for an assessment of emerging lifestyles including substance use that may have a relationship with CVDs.[11]

Reports associate marijuana use with cardiovascular emergencies.[12,13] The marijuana-like cigarette is primarily smoked. Contrary to marijuana, studies on mortalities from CVDs due to cigarette smoking are extensive.[14–16] Recent advances towards the legalization of marijuana in the USA necessitate the determination of the association of marijuana use with cardiovascular mortality.

The active constituent of marijuana, delta-9-tetrahydrocannabinol (THC), accounts for some cardiovascular effects of marijuana.[17,18] Review literature and reports suggest that marijuana smoking increases heart rate from 20–100% for about 2–3 h,[19] is associated with postural hypotension, fainting, and ischemic stroke.[17,20,21] THC acts primarily on the endocannabinoid system which regulates cardiovascular function and exerts sympathetic stimulation. The endocannabinoid system includes cannabinoid receptors CB1 and CB2 which are distributed in the central nervous system, cardiovascular system, and peripheral tissues. Delineated cardiovascular effects of THC are increased heart rate, increased supine blood pressure, orthostatic hypotension,[19] increased cardiac output, reductions in left ventricular ejection time,[21] and increases in venous carboxyhemoglobin levels[22] which cause unhealthy cardiovascular and cerebrovascular outcomes. We hypothesize that, like cigarette smoking, recreational marijuana will be associated with increased cardiovascular mortality.

Methods

The National Health and Nutrition Examination Survey (NHANES) assesses the health and nutritional status of the civilian noninstitutionalized US population. About 5000 nationally representative participants are selected through complex, multistage probability sampling yearly. Participants were interviewed on marijuana use starting in 2005. Interviews were conducted by physicians and other healthcare professionals in participant's homes and examinations were conducted in a mobile center. We merged the results of interviews in the 2005 NHANES with the 2011 public-use linked mortality file of the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC)[23] of participants eligible for mortality follow-up. Mortality information on participants in the NCHS public-use linked mortality file is obtained from death certificates or probabilistic matching from the National Death Index (NDI). Causes of death occurring in the USA before 1999 were based on the 9th revision of International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-9) guidelines and subsequently recoded into comparable ICD-10 rubrics. Deaths relevant to this study were classified as due to diseases of the heart (001) and cerebrovascular diseases (005). Hypertension deaths were classified as death from multiple causes that include ICD-9 codes '401' or '403' or ICD-10 codes 'I10' or 'I12. Those assumed alive were left un-coded.

We selected participants eligible for mortality follow-up, aged 20 years and above, who answered ''yes'' or ''no'' to the question, ''Have you ever used marijuana or hashish?'' Participants who answered yes were classified marijuana users and those who answered no, as non-marijuana users. Duration of marijuana use was estimated by subtracting participant's age at marijuana use initiation from the age at the 2005 screen. Follow-up period for eligible participants was 1991–2011. This study collectively refers to marijuana use, cigarette smoking, and alcohol use as substance use. Participants who reported having smoked at least 100 cigarettes in their lifetime and still smoked were classified current smokers, with those who had ceased smoking classified as past-smokers. Those who never smoked or smoked 100 cigarettes in their lifetime were classified non-smokers. High-risk drinking was defined in dietary guidelines for Americans 2015–2020 as consumption of four or more drinks any day or eight or more drinks weekly for women (five or more drinks any day or 15 or more drinks weekly for men). Participants who confirmed ever having five or more drinks almost every day at a point in life were classified as alcohol users. Participants reported their age, gender, educational status, and race/ethnicity and prior diagnosis of hypertension, angina, congestive heart failure, heart attack, or stroke by a doctor or other health professional.

Statistical analysis

We estimated mortality rates and hazard ratios (HRs) with 95% confidence intervals (CIs) from Cox proportional hazards regression, for hypertension, heart disease, and cerebrovascular deaths among marijuana users and current cigarette smokers. Our main independent variables were marijuana use status and years of marijuana use. We controlled for cigarette smoking (non-smokers as reference), gender (female as reference), age (25 years and below as reference), race/ethnicity (non-Hispanic Whites as reference), having health insurance (not having health insurance as reference), alcohol use (not having had five drinks or more on some days in life as reference), diagnosis of hypertension (no diagnosis of hypertension as reference), or CVD: angina, heart attack, congestive heart failure, or coronary heart

disease (no diagnosis of CVD as reference), education and body mass index (BMI), were controlled using continuous increasing level. Age was dichotomized as 25 years and below, or above 25 years. Research shows the age cut-off point associated with illicit substance use, smoking, and heavy alcohol consumption is 25 years.[24] The interaction factor between smoking status and marijuana use status was not significant in the survival model, so the interaction factor was excluded. We estimated cumulative hazard for hypertension, heart, and cerebrovascular disease mortality by marijuana use or cigarette smoking status over the 20-year period of follow-up. Nelson-Aalen curves estimate cumulative hazard functions of censored data.[25] The follow-up was right censored at the end of 2011.

Results

Demographic characteristics, marijuana use, and cigarette smoking

There were 1213 total eligible participants with one observation ending on or before entry and 72.5% presumed alive. Person-years follow-up was 19,569. Average age at entry of participants was 37.7 ± 11.2 years. Average BMI for all participants was 29.0 ± 7.0, for marijuana users, 28.6 ± 7.1, and for cigarette smokers, 27.7 ± 6.9. Demographic distribution is shown in Table 1. Among all 1213 participants, 34.3% neither used marijuana nor smoked cigarettes, 20.9% used only marijuana, 20.0% used marijuana and smoked cigarettes, 15.6% used marijuana and were past-smokers, 4.8% were past-smokers and 4.4% smoked only cigarettes. Average duration of marijuana use was 11.5 ± 12.8 years and 10.1 ± 13.8 years for cigarette smoking.

Diagnosis of hypertension or other CVDs

Compared to 20.6% of non-marijuana users, 23.0% of marijuana users had a prior diagnosis of hypertension. Among current smokers, 21.8% had a prior diagnosis of hypertension compared to 23.4% of past-smokers and 18.7% of never smokers. Prevalence for prior diagnosis of any other CVDs was 3.8% among marijuana users and 3.6% for non-marijuana users, 6.1% for current smokers, 5.7% past-smokers and 1.9% for never smokers. Distribution of hypertension, heart, and cerebrovascular mortality is shown in Table 1.

Mortality incidence rates and ratios

For all-cause mortality among marijuana users, the incidence rate ratio was 1.29 (95% CI: 1.03–1.61) and among current smokers 1.16 (95% CI: 0.90–1.48). Mortality incidence rates by marijuana use and cigarette smoking stratified by cause of death are shown in Table 2.

Unadjusted and adjusted HRs

The unadjusted HR for hypertension mortality among marijuana users compared to non-marijuana users was 1.86 (95% CI: 0.95–3.66). Unadjusted HRs are shown in Table 3. For HD mortality, unadjusted HR was 1.21 (95% CI: 0.76–1.92) among marijuana users compared to non-marijuana users, and 1.01 (95% CI: 0.99, 1.03) for each year of marijuana use. For cerebrovascular disease mortality, all unadjusted HRs were non-significant for marijuana use and cigarette smoking (not shown in Table 3).

The adjusted HR for hypertension mortality among marijuana users compared to non-marijuana users was 3.42 (95% CI: 1.20–9.79), and for each year of marijuana use was 1.04 (95% CI: 1.00–1.07) (Table 3). All adjusted HRs for HD and cerebrovascular mortality showed non-significant estimates in this model for marijuana use and cigarette smoking in this model most likely due to sample size. The adjusted HR for HD mortality was: (a) 1.09 (95% CI: 0.63–1.88) for marijuana users compared to non-marijuana users and (b) 1.00 (95% CI: 0.98–1.02) for each year of marijuana use (Not shown in Table 3).

Cumulative hazard curves

Nelson-Aalen cumulative hazard estimates show that marijuana users have a higher risk for hypertension mortality than non-marijuana users (Figure 1(a)). For hypertension mortality, there are more flattened areas for smokers; non-smokers seem to have a higher risk. The cumulative hazard for all-cause mortality is higher among marijuana users and cigarette smokers than their counterparts (Figure 1(b)).

Discussion

Marijuana users had an increased risk of hypertension mortality even after controlling for prior diagnosis of hypertension. Opiates have more deleterious consequences on the cardiovascular system than marijuana,[26] but hypertensive crisis following marijuana use has been described.[27] Also, cases of myocardial infarction and stroke following marijuana use among normotensives and people lacking history of cardiovascular diseases have been described.[27–29] In our study, increase in risk for hypertension, HD, or cerebrovascular disease mortality associated with cigarette use was not significant. This is largely due to the small sample size ($n < 30$) of mortalities among cigarette smokers under investigation. The hazardous effect of cigarette smoking on the

Table 1. Sociodemographic characteristics of participants, showing overall prevalence (%) and mortality rates (%) from hypertension, heart diseases (HDs), and cerebrovascular (CBV) disease.

Variables	Participants		Total mortality	HBP	HD	CBV
	Sample	%	Sample	%	%	%
Age $\leq$ 25years	226	18.6	63	9.5	22.2	11.1
Age $>$ 25years	987	81.4	269	12.6	23.0	6.3
Total	1213	100.0	332	12.1	22.9	7.2
Male	550	45.3	168	8.3	23.2	4.8
Female	663	54.7	164	15.9	22.6	9.8
Total	1213	100.0	332	12.1	22.9	7.2
Non-Hispanic Whites	579	47.7	162	14.8	26.5	7.4
Non-Hispanic Blacks	286	23.6	76	7.9	19.7	10.5
Mexican Americans	246	20.3	63	7.9	22.2	3.2
Other Hispanics	45	3.7	11	27.3	18.2	0
Other Race	57	4.7	20	10.0	10.0	10.0
Total	1213	100.0	332	12.1	22.9	7.2
$<$9th grade	89	7.3	20	15.0	30.0	5.0
9th–11th grade	166	13.7	43	7.0	20.9	9.3
High school graduate	277	22.9	76	7.9	21.1	7.9
Some college/associate degree	394	32.5	112	15.2	19.6	8.0
$\geq$College graduate	286	23.6	81	13.6	28.4	4.9
Total	1212	100.0	332	12.1	22.9	7.2
Marijuana users	686	56.5	204	13.7	22.5	7.4
Non-marijuana users	527	43.5	138	9.4	23.4	7.0
Total	1213	100.0	332	12.1	22.9	7.2
Current cigarette smokers	296	24.4	89	10.1	15.7	9.0
Past-cigarette smokers	248	20·4	74	14.9	27.0	9.5
Non-cigarette smokers	669	55.2	169	11.8	24.8	5.3
Total	1213	100.0	332	12.1	22.9	7.2
Alcohol use	190	17.7	55	10.9	29.1	7.3
No alcohol use	882	82.3	243	11.1	22.6	6.2
Total	1072	100.0	298	11.1	23.8	6.4

HBP: high blood pressure.
Mortality rates shown are row percentages based on total mortality but do not add up to 100% because mortality rates of other diseases are not shown.

cardiovascular system has, however, been largely demonstrated in studies[14] and is established knowledge. Also, our study focuses on marijuana use, and initial selection criteria was based on responses to marijuana use among adults. Our assumption that marijuana use and cigarette use continue throughout the period of follow-up, may not be so. Taking into consideration the availability of smoking cessation programs, these behaviors may change with time or from participation in an intervention. Specific marijuana use cessation interventions are yet to be documented and self-reported illegal drug use is likely to be under-reported which could have affected the results of our study. Use of cocaine/heroin/methamphetamine or participation in rehabilitation was not statistically relevant in our model and was excluded. We, however, controlled for relevant demographic factors. The observed large CIs for marijuana use estimates can also be attributed to sample size.

Within our limitations, our results may be suggestive of a possible increased risk of mortality from CVDs related to marijuana use. Taking into consideration results of study by Aronow and Cassidy,[22] the results from longitudinal studies designed to investigate and compare cardiovascular risk associated with marijuana use and cigarette use would be of importance in addressing recreational substance use and cardiovascular health.

Table 2. Incidence estimates for mortality from hypertension, heart disease, and cerebrovascular disease by substance use among study participants.

Cause of mortality	Marijuana
Hypertension	
Incidence rate in exposed/1000	2.57
Incidence rate in unexposed/1000	1.39
Incidence rate in population/1000	2.04
Incidence rate ratio	1.85 (0.92–4.00)
Attributable fraction in exposed	46.0%
Attributable fraction in population	32.1%
Heart disease	
Incidence rate in exposed/1000	4.22
Incidence rate in unexposed/1000	3.47
Incidence rate in population/1000	3.88
Incidence rate ratio	1.22 (0.75–2.00)
Attributable fraction in exposed	17.8%
Attributable fraction in population	10.8%
Cerebrovascular disease	
Incidence rate in exposed/1000	1.37
Incidence rate in unexposed/1000	1.04
Incidence rate in population/1000	1.23
Incidence rate ratio	1.32 (0.54–3.43)
Attributable fraction in exposed	24.4%
Attributable fraction in population	15.2%

Table 3. Unadjusted and adjusted analysis showing hazard ratios for hypertension mortality among (a) marijuana users and (b) each year of marijuana use.

Substance use and demographic factors	Unadjusted hazards ratio (95% confidence interval)	Adjusted hazards ratio (95% confidence interval)
(a)		
Marijuana user	1.86 (0.95–3.66)	3.42 (1.20–9.79)[a]
Current smoker	1.06 (0.48–2.33)	1.06 (0.40–2.77)
Former smoker	1.56 (0.75–3.25)	1.33 (0.57–3.10)
Alcohol user	1.03 (0.43–2.50)	0.95 (0.37–2.45)
Body mass index	1.03 (1.00–1.08)[a]	1.05 (1.01–1.10)[a]
Age > 25 years	1.29 (0.54–3.08)	1.25 (0.42–3.67)
Education	1.19 (0.90–1.57)	1.00 (0.70–1.43)
Male	0.67 (0.35–1.29)	0.72 (0.35–1.49)
Blacks	0.51 (0.21–1.24)	0.42 (0.14–1.27)
Mexican Americans	0.49 (0.19–1.28)	0.91 (0.28–2.94)
Other Hispanics	1.58 (0.48–5.25)	2.51 (0.54–11.63)
Other race	0.92 (0.22–3.89)	1.23 (0.29–5.35)
Have health insurance	2.66 (1.04–6.79)[a]	2.24 (0.75–6.72)
Diagnosed with hypertension	0.86 (0.38–1.93)	0.81 (0.32–2.06)
Diagnosed with a CVD	2.18 (0.67–7.06)	1.94 (0.42–8.97)
(b)		
Each year of marijuana use	1.03 (1.00–1.05)[a]	1.04 (1.00–1.07)[a]
Current smoker	1.06 (0.48–2.33)	1.14 (0.43–3.01)
Former smoker	1.56 (0.75–3.25)	1.35 (0.57–3.20)

CVD: cardiovascular disease (angina, heart attack, congestive heart failure, or coronary heart disease).
In (a), hazard ratios are estimated based on substance use status; in (b) they are based on each year of marijuana use, controlling for the same variables as in (a).
[a]$p < 0.05$.

The 2016 European Guidelines on CVD prevention recommend a lifetime prevention approach tailored towards promoting a healthy lifestyle among people of all ages in the general population and addressing unhealthy lifestyles including smoking among at risk populations.[7] The guidelines stress that preventive measures including success of smoking legislation account for plummeting rates for cardiovascular diseases. Notable in their recommendations is the cessation of smoking of all tobacco or herbal products. They emphasis that smoking is evidently an independent cause of CVD and a lethal addictive disorder. This is worth considering in legalizing marijuana use, especially if marijuana is found to have a causal pathway to CVDs.

The 2020 goal of the American Heart Association is to improve the cardiovascular health of all Americans by 20%, and reduce mortality from CVDs and stroke by 20%. Public health and clinical interventions have helped to promote the seven indicators of good cardiovascular health: blood pressure control, increased physical activity, healthy diet, total cholesterol control, healthy weight, blood glucose control, and smoking cessation. These have contributed to plummeting age-standardized death rates from CVDs since 2009.[30] Smoking is still the leading cause of preventable disease and death, and since recreational marijuana is primarily smoked, its increased use may have contributed to increases in morbidities and mortalities.

Other factors of interest to be considered include the effects of marijuana use on cardiovascular mortality among the youth and people with existing chronic conditions. The youth, especially those aged 18–25 years are more liable to substance use[31] and adults are more likely to live with chronic conditions. This expands the demographic coverage of the possible poor health consequences of marijuana use. In the interest of individual health, population health, and lowering costs associated with healthcare, research and education on the adverse effects of recreational marijuana use should be

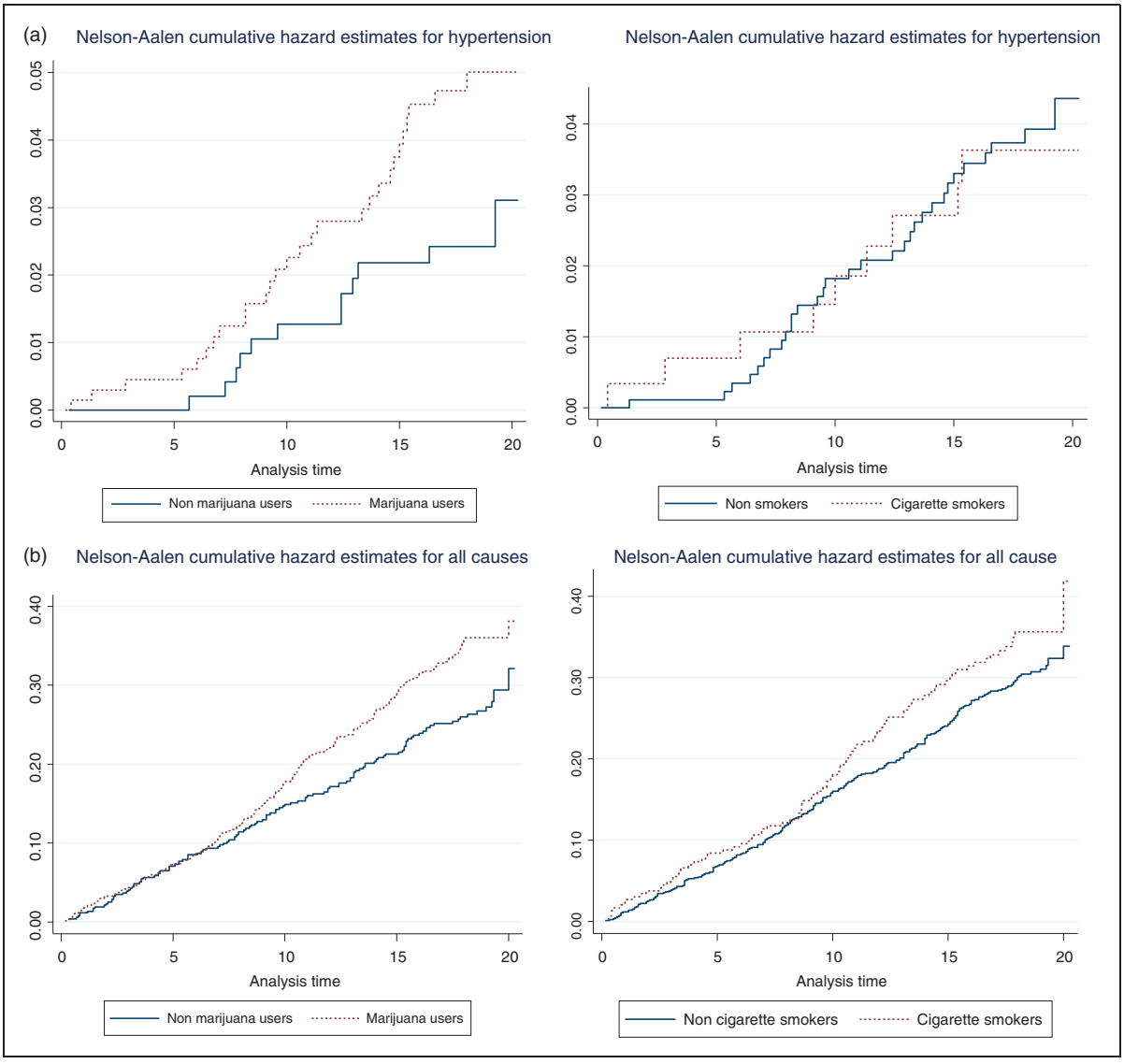

Figure 1. Nelson-Aalen cumulative hazard estimate of mortality from (a) hypertension and (b) all-causes associated with marijuana use and cigarette smoking. The *y*-axis shows cumulative hazard rate and *x*-axis shows follow-up time.

a priority as recommendations and advancements are made towards its legalization.

Conclusion

Marijuana use, especially prolonged years of use, may increase the risk of hypertension mortality. This cardiovascular risk associated with marijuana use, may be greater than the cardiovascular risk already established for cigarette smoking. We are not disputing the possible medicinal benefits of standardized cannabis formulations; however, recreational use of marijuana should be approached with caution. It is possible that discouraging recreational marijuana use may ultimately impact reductions in mortality from cardiovascular causes. A purposeful longitudinal study modeled with inclusion of listed relevant limitations is recommended to help evaluate this cause.

Author contribution

BAY, RBR, SS, KRW, and ISO, contributed to the conception or design of the work. BAY, RBR, SS, KRW, and ISO, contributed to the acquisition, analysis, or interpretation of data for the work. BAY drafted the manuscript. BAY, RBR, SS, KRW, and ISO critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of conflicting interests

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