Review

Chili pepper intake and all-cause and disease-specific mortality

A meta-analysis of prospective cohort studies

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Abstract: *Background:* Chili pepper has been used for the treatment and prevention of multiple diseases. This may be due to its abundance of bioactive components, such as carotenoids, which are well known for their antioxidant properties. To date, several prospective cohort studies have examined the association between chili pepper intake and mortality, but the results have not been consistent. This study aimed to clarify the association between chili pepper intake and all-cause and disease-specific mortality using a meta-analysis. *Methods:* PubMed, Embase, and ISI Web of Science databases were searched up to December 20, 2020, and reference lists of included studies were manually reviewed. All prospective cohort studies on the association between chili pepper intake and all-cause, cardiovascular disease (CVD)-specific, and cancer-specific mortality were included in this study. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated in the meta-analysis. Between-study heterogeneity was assessed using I^2 statistic and Q test. *Results:* A total of 4 cohort studies (N=564,748; all four studies had adjusted for important potential confounders such as demographic variables, dietary intake, and physical activity) were ultimately included in this meta-analysis. Among them, 31,527 died due to all causes, 10,184 died due to CVD, and 9,868 died due to cancer. Compared to none or rare consumption of chili pepper, consumption of chili pepper (ever or more than once a week) could significantly reduce the risk of all-cause mortality (summary adjusted HR: 0.87, 95% CI: 0.85, 0.90), CVD-specific mortality (summary adjusted HR: 0.89, 95% CI: 0.85, 0.93), and cancer-specific mortality (summary adjusted HR: 0.92, 95% CI: 0.88, 0.97). There was no significant between-study heterogeneity in the analyses (all-cause mortality: I^2=0.7%, P=0.389; CVD-specific mortality: I^2=21.8%, P=0.280; cancer-specific mortality: I^2=0.0%, P=0.918). *Conclusions:* The present meta-analysis confirmed that chili pepper intake could reduce the risk of all-cause, CVD-specific, and cancer-specific mortality, suggesting that chili pepper may be a beneficial ingredient in the diets in prolonging life.

Keywords: Chili pepper, mortality, meta-analysis, cohort studies

Abbreviations

CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio; RR: relative risk; TRPV1: Transient receptor potential cation channel sub-family V member 1; WMD: weighted mean difference.

Introduction

Chili pepper has been presented extensively in diets of different cultures around the world. In China, for example, regular consumption (≥3 days/week) of chili pepper was reported by 36.3% of the population [1]. Chili pepper not only adds color and flavor to the food but also has potential medicinal properties. Chili pepper contains a group of bioactive compounds, including carotenoids and capsaicinoids. They are responsible for the pungent flavor sensation and different colors of chili pepper [2, 3]. Animal studies showed that these compounds possessed anti-inflammatory, anti-oxidant, anti-cancer and cardiovascular disorder preventive properties [2, 3]. Studies in humans concluded that chili pepper intake may help to lose weight by increasing energy expenditure and lipid oxidation, and by reducing appetite [4, 5, 6]. However, the long-term effects of chili pepper consumption on health are not clear. To date, only few longitudinal studies have been performed to investigate the association between chili pepper consumption and mortality in the general population, and the magnitude of the association has not always been consistent, especially for cause-specific mortality including deaths due to cardiovascular disease (CVD) and cancer [1, 7, 8, 9].

Therefore, we performed a meta-analysis of all eligible population-based prospective cohort studies to clarify the association between chili pepper intake and all-cause, CVD-specific, and cancer-specific mortality [1, 7, 8, 9].

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Methods

We conducted the meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10] in the Electronic Supplementary Material (ESM) 1.

Search strategy

PubMed, Embase, and ISI Web of Science databases up to December 20, 2020, were used for article search. The following terms were used: ("chilli" OR "chili" OR "spicy" OR "paprika" OR "capsaicin" OR "pepper") AND ("mortality" OR "death") AND ("cohort" OR "prospective" OR "longitudinal" OR "follow up"). The references in relevant articles were manually searched. Subjects of the studies were limited to humans, and publication language was limited to English.

Titles and abstracts of the identified articles were examined by two authors (L.Y. and J.S.) independently; any disagreement was discussed and resolved with the third author (B.X.). The remaining articles were further screened through reviewing full text. Finally, 4 cohort studies on the association between chili pepper intake and mortality were included for this meta-analysis [1, 7, 8, 9].

Inclusion criteria

The inclusion criteria for this meta-analysis were as follows: (1) population-based prospective cohort study; (2) evaluation of the association between chili pepper intake and all-cause, CVD-specific or cancer-specific mortality; (3) estimates of the relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs).

Data extraction

The following information was extracted independently from each study by two authors (L.Y. and J.S.): name of the first author, publication year, study name, country, sample size, sex proportion, baseline age, follow-up duration, exposure assessment, exposure categories, numbers of outcomes, adjusted HR (or RR) with the corresponding 95% CI, and covariates adjusted in the analysis.

Study quality assessment

The quality of each study was evaluated by the Newcastle-Ottawa quality scale for cohort studies [11]. This scale assigned a maximum of 9 stars for each study. The following three broad aspects were considered: (1) selection of the cohorts (4 stars); (2) comparability of the cohorts (2 stars); and (3) outcomes of interest (3 stars).

Statistical analysis

The association between chili pepper intake and all-cause, CVD-specific, and cancer-specific mortality was estimated with pooled HRs and the corresponding 95% CIs and comparisons were made between chili pepper consumers versus none/rare consumers. In the meta-analysis, the degree of heterogeneity between studies was assessed using the Q test and quantified by I^2 statistics. A random-effects model was used to calculate the pooled HRs when $P<0.1$ or $I^2>50\%$; otherwise, a fixed-effects model was applied. Sensitivity analysis was performed by excluding each study from the model sequentially to examine the stability of the overall results. All analyses were performed using STATA version 11 (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of included cohort studies

Initially, 229 potentially relevant articles were identified, from which 4 articles finally met the inclusion criteria and were included in the meta-analysis of the association between chili pepper intake and all-cause, CVD-specific, and cancer-specific mortality [1, 7, 8, 9]. The literature search flow diagram is shown in Figure 1. The basic characteristics of the included studies are shown in Table 1.

There were 564,748 participants (mean age ranging from 46.6 to 55.1 years at baseline) who were followed up with the duration of 7.2 to 18.9 years in the included articles. Among them, 31,527 died due to all causes, 10,184 died due to CVD, and 9,868 died due to cancer. All included studies had adjusted for important potential confounding factors (number of adjusted confounders ranged from 12 to 17) and had high quality with the scores ranging from 7 to 8 (Table 2).

Association between chili pepper intake and mortality

Figure 2 shows the meta-analysis of the association between chili pepper intake and all-cause, CVD-specific, and cancer-specific mortality. Compared to those who did not, those who consumed chili pepper had a reduced risk of all-cause mortality (summary adjusted HR: 0.87, 95% CI: 0.85, 0.90; Figure 2A), CVD-specific mortality (summary adjusted HR: 0.89, 95% CI: 0.85, 0.93; Figure 2B), and cancer-specific mortality (summary adjusted HR: 0.92, 95% CI: 0.88, 0.97; Figure 2C). Fixed-effects models were used for all three outcomes as there was no significant between-study heterogeneity (all-cause mortality:

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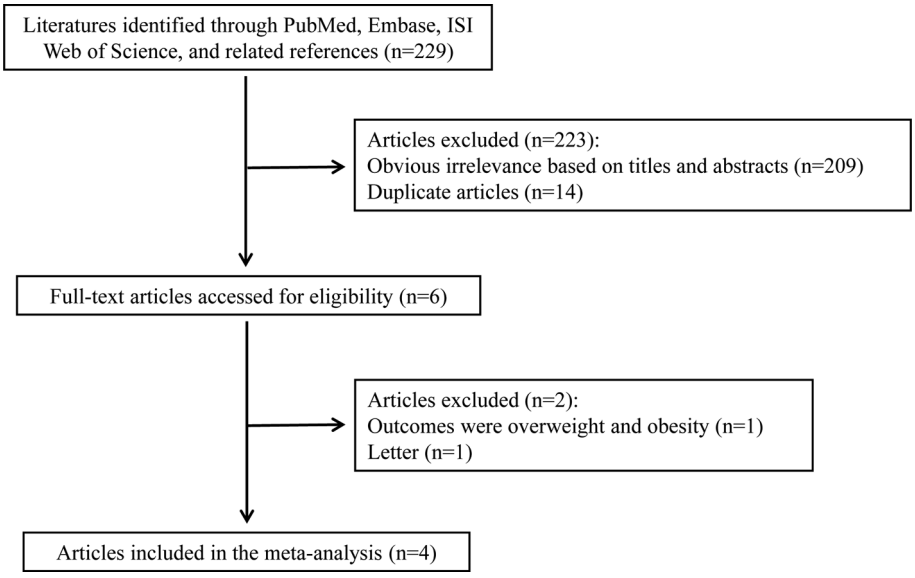

Figure 1. Flow chart of the literature search and article selection.

I^2=0.7%, P=0.389; CVD-specific mortality: I^2=21.8%, P=0.280; cancer-specific mortality: I^2=0.0%, P=0.918).

Sensitivity analysis

To investigate the impact of each study on the overall estimates, we removed every single study from the analysis. The results showed that the summary adjusted HR (95% CI) varied from 0.87 (0.84, 0.89) to 0.88 (0.84, 0.93) for all-cause mortality, 0.88 (0.83, 0.92) to 0.90 (0.83, 0.97) for CVD-specific mortality, and 0.89 (0.81, 0.99) to 0.93 (0.88, 0.97) for cancer-specific mortality, respectively, suggesting good stability of the results (Table 3).

Discussion

To the best of our knowledge, this is the first meta-analysis quantifying the association between chili pepper intake and all-cause, CVD-specific, and cancer-specific mortality. In this meta-analysis, compared to those who did not, those who consumed chili pepper had a 13% reduced risk of all-cause mortality, 11% reduced risk of CVD-specific mortality, and 8% reduced risk of cancer-specific mortality. This indicates that adding chili pepper to the diets might be recommended for prolonging life.

Comparison with other studies

Several systematic reviews and meta-analyses have confirmed the association between chili pepper consumption (mainly referred to its bioactive components) and the reduced risk of obesity [4, 5] and hypertension [12]. For example, a recent meta-analysis by Irandoost et al. [4] in 2021, including 13 randomized placebo-controlled clinical trials, showed that compared with placebo, capsaicinoids/capsinoids consumption per day could significantly increase resting metabolic rate (weighted mean difference [WMD]: 33.99 kcal/day, 95% CI: 15.95, 52.03), energy expenditure (WMD: 4.88 kcal/day, 95% CI: 1.75, 7.96), fat oxidation (WMD: 0.18 g/hr, 95% CI: 0.07, 0.29), and reduce respiratory quotient (WMD: −0.01, 95% CI: −0.02, −0.01) and carbohydrate oxidation (WMD: −1.42 g/hr, 95% CI: −2.67, −0.18), respectively. In another meta-analysis of 7 randomized clinical trials in 2021, Amini et al. [12] found that compared with the placebo, capsinoid and fermented red pepper paste supplement significantly reduced DBP levels (WMD: −1.90 mmHg, 95% CI: −3.72, −0.09), but not SBP (WMD: 0.55 mmHg, 95% CI: −1.45, 2.55). These data collectively suggest that chili pepper may have a beneficial influence on the morbidities of humans. However, the clear association between chili pepper and mortality has not been confirmed. In this meta-analysis, we pooled 4 population-based prospective cohort studies [1, 7, 8, 9] and found that chili pepper intake was associated with a reduced risk of all-cause, CVD-specific, and cancer-specific mortality, suggesting potential protective effects of chili pepper on human health.

Unfortunately, we did not evaluate the dose-response relationship between chili pepper intake and mortality because two of the included studies used different categories of chili pepper intake [1, 8] and the other two studies didn't provide this information [7, 9]. Lv et al. [1] showed that compared to participants who consumed spicy food <1 day per week, those who consumed 1–2 days, 3–5 days,

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Table 1. Characteristics of included cohort studies on the association between chili pepper and total, CVD-specific, and cancer-specific mortality

Author, year	Study name	Country	Sample size	Male, %	Baseline age, years	Follow-up duration, years	Exposure assessment	Chili pepper categories	Number of outcomes	Covariates adjusted for	Study quality*
Lv et al., 2015 [1]	China Kadoorie Biobank study	China	487,375	40.9	30–79 (mean: 51.1)	7.2	Self-reported	<1 day/week; 1–2 days/week; 3–5 days/week; 6–7 days/week	All causes: 20,224; CVD: 6,326; Cancer: 7,256	Age, sex, education, marital status, alcohol consumption, smoking status, physical activity, body mass index, intake frequencies of red meat, fruits, and vegetables, hypertension and diabetes at baseline, and family history of cancer, heart attack, stroke, or diabetes	8
Chopan et al., 2017 [7]	National Health and Nutritional Examination Survey	America	16,179	46.8	18–90 (mean: 46.6)	18.9	Self-reported	Do not consume chili peppers; Consume chili peppers	All causes: 4,946; CVD: 1,563; Cancer: 1,069	Age, sex, race, education, marital status, income, alcohol consumption, smoking status, frequencies of red meat, fruits, and vegetables, physical activity	7
Bonaccio et al., 2019 [8]	Moli-sani Study	Italy	22,811	47.7	≥35 (mean: 55.1)	8.2	Self-reported	Consumers vs. None/rare consumers; None/rare consumption; Up to 2 times/week; >2–4 times/week; >4 times/week;	All causes: 1,236; CVD: 444; Cancer: 482	Age, sex, energy intake, education, occupational class, smoking, leisure-time physical activity, cardiovascular disease, cancer, drugs for diabetes, lipid-lowering drugs, medication for hypertension, Mediterranean Diet Score (not including sweet pepper intake), sweet pepper intake (g/day, ordered quartiles), garlic, parsley, black pepper.	8
Hashemian et al. 2019 [9]	Golestan Cohort Study	Iran	38,383	42.2	40–75 (mean: 51.5)	11.1	Self-reported	Ever Versus Never Spice Consumption	All causes: 5,121; CVD: 1,851; Cancer: 1,061	Age, sex, place of residence, race, formal education, marital status, physical activity, wealth score, history of hypertension, diabetes mellitus, body mass index, smoking, opium use, energy intake, and Dietary Approach to Stop Hypertension index	8

CVD: cardiovascular disease. *Quality of each study was assessed based on the Newcastle-Ottawa quality scale.

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Table 2. Quality assessment of cohort studies

	Selection				Comparability		Outcome			
	1	2	3	4	5_a	5_b	6	7	8	Score
Lv et al., 2015	*	*	–	*	*	*	*	*	*	8*
Chopan et al., 2017	*	*	–	*	*	*	*	*	–	7*
Bonaccio et al., 2019	*	*	–	*	*	*	*	*	*	8*
Hashemian et al. 2019	*	*	–	*	*	*	*	*	*	8*

1: Representativeness of the exposed cohort; 2: Selection of the non-exposed cohort; 3: Ascertainment of exposure; 4: Outcome was not present at the beginning of study; 5a: Adjust for age; 5b: Adjust for additional factors; 6: Assessment of outcome; 7: Duration of follow-up was long enough; 8: Completeness of the follow-up. * indicates a score; – indicates no score.

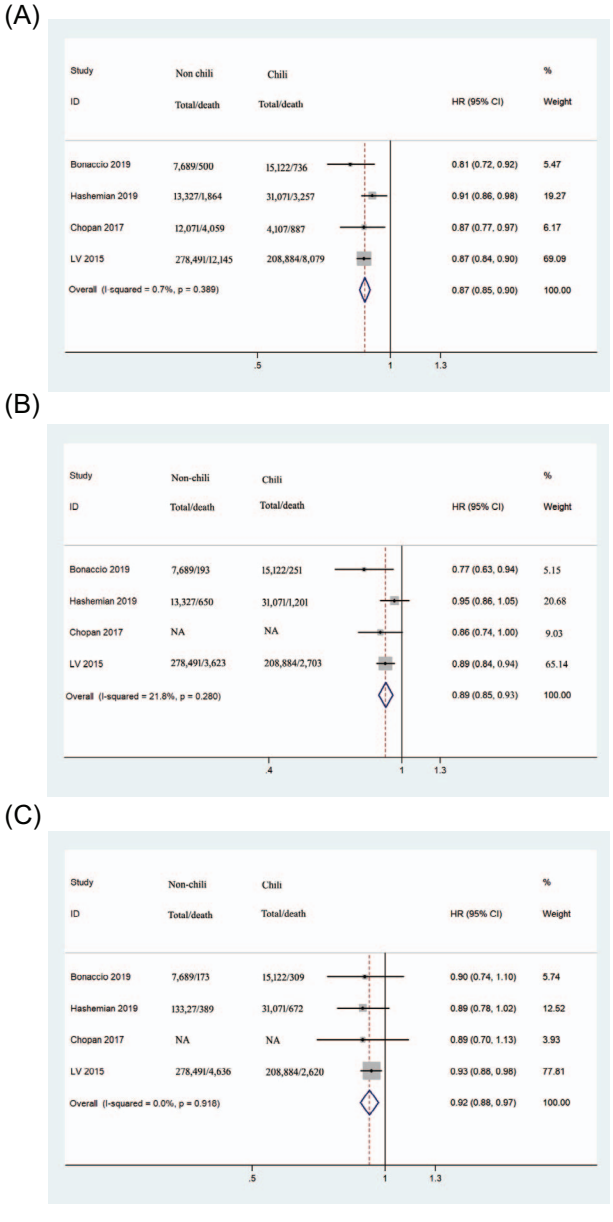

Figure 2. Meta-analysis of the association between chili pepper intake and (A) all-cause, (B) CVD-specific and (C) cancer-specific mortality. Note: CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio.

and 6–7 days had 10% (adjusted HR: 0.90, 95% CI: 0.84, 0.96), 14% (adjusted HR: 0.86, 95% CI: 0.80, 0.92), and 14% (adjusted HR: 0.86, 95% CI: 0.82, 0.90) reduced risk of all-cause mortality, respectively. Bonaccio et al. [8] reported that compared to participants who had none or rare chili pepper intake, those who consumed chili pepper 1–2 times/week, 3–4 times/week and >4 times/week had 14% (adjusted HR: 0.86, 95% CI: 0.73, 1.01), 18% (adjusted HR: 0.82, 95% CI: 0.70, 0.96) and 23% (adjusted HR: 0.77, 95% CI: 0.66, 0.90) reduced risk of all-cause mortality, respectively, suggesting a dose-response association between chili pepper intake and all-cause mortality. Further meta-analyses should consider the dose-response relationship between chili pepper intake and mortality when sufficient data are available.

Potential mechanism

The mechanism through which chili pepper could reduce the risk of mortality has not been fully understood. This may be attributed to the bioactive components of chili pepper. For example, capsaicin, which is the main ingredients of chili pepper (e.g., the contents ranged from 2.19 to 19.73 mg/g dry weight across sixteen different pepper genotypes [13]), can prevent obesity, reduce insulin resistance and low-density lipoprotein oxidation, protect endothelial function, and has antiplatelet and anticoagulant effects [14, 15]. All these effects may be ascribed to the actions of capsaicin on the transient receptor potential cation channel sub-family V member 1 (TRPV1) receptors [14]. Li et al. used a lipopolysaccharide-induced inflammation mice model showed that the secretion levels of IL-6, TNF-α, and NO by macrophages were much lower in the lipopolysaccharide plus capsaicin (100 μg/mL) group than that in the lipopolysaccharide group (i.e., IF-6: 204 vs. 436 μg/mL; TNF-α: 860 vs. 2024 μg/mL; NO: 19.89 vs. 52.4 μg/mL, all $P<0.05$), suggesting that capsaicin has anti-inflammatory effects [16].

In addition, chili peppers are a good source of carotenoids (e.g., β-carotene, β-cryptoxanthin, lutein, and zeaxanthin;

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Table 3. Sensitivity analysis of the effect of each primary study on the overall results

Study omitted	All-cause mortality	CVD-specific mortality	Cancer-specific mortality
Lv et al. 2015	0.88 (0.84–0.93)	0.90 (0.83–0.97)	0.89 (0.81–0.99)
Chopan et al. 2017	0.87 (0.85–0.90)	0.90 (0.85–0.94)	0.92 (0.88–0.97)
Bonaccio et al. 2019	0.88 (0.85–0.90)	0.90 (0.86–0.94)	0.92 (0.88–0.97)
Hashemian et al. 2019	0.87 (0.84–0.89)	0.88 (0.83–0.92)	0.93 (0.88–0.97)

CVD: cardiovascular disease. Data are expressed as hazard ratio (95% confidence interval); None or rare chili pepper intake used as the referent category.

the contents were found to range from 0.83 to 1.98 mg/g fresh weight in five Capsicum cultivars [17]). Carotenoids also possess important nutraceutical properties, including antioxidant effects (by removing free radicals and oxygen), prevention effects on cancer (by modulating apoptosis of cancer cells and multidrug resistance) [18], anti-obesity effects (by activating AMP-activated protein, accelerating fatty acids oxidation, or inhibiting lipogenesis) [19, 20], and prevention effects on cardiovascular risk factors (by increasing cholesterol efflux) [21]. All these beneficial effects in turn can reduce the risk of mortality. The ethanol extract of chili pepper could promote the expression of endogenous antioxidants via the Nrf-2 pathway [22]. More recently, studies showed that chili pepper may indirectly influence the host by altering the gut microbial community [23]. Microbial dysbiosis, referring to altered microbial composition and production of metabolites, has been shown to be related with an increased risk of obesity [24], CVD [25], diabetes mellitus [26], and cancer [27]. Thus, the beneficial alterations of gut microbiota may be beneficial in preventing these diseases, thereby reducing the risk of mortality.

Strengths and limitations

The strengths of the current study included the population-based prospective cohort design, the relatively long duration of follow-up, and the large sample size of the pooled included studies ensuring sufficient power to detect the association. However, several limitations should also be considered. First, because of the observational nature of the included studies, residuals and unmeasured confounding could not be completely ruled out. Second, as chili pepper consumption was evaluated only once at baseline, we could not account for the changes in chili pepper during the follow-up, which might have influenced the results. Further studies should assess the association based on repeated measurements of chili pepper. Third, chili pepper consumption was self-reported in all included studies, recall bias might exist. However, misclassification of exposure based on self-reported method usually causes regression dilution bias, and thus an underestimation of the magnitude of the real association [28]. Fourth, one included study (Hashemian) [9] did not delineate between black or chili pepper, and the other three articles [1, 7, 8] used chili pepper as the exposure of interest. However, pooled results of the three articles [1, 7, 8] were similar to the main results (data not shown). Finally, we defined chili pepper consumption as a low frequency (only more than once a week) in this meta-analysis which would underestimate its benefit since two of the included studies [1, 8] showed that the magnitude of mortality risk reduction was much larger for more frequent intake of chili pepper. In other words, there seemed to be a dose-response association between chili pepper consumption and mortality [1, 8]. However, due to differences in categories of chili pepper intake in the four included studies [1, 7, 8, 9], we could not evaluate the relationship between higher frequency of chili pepper intake and mortality. Further meta-analysis should be conducted to address this issue when sufficient data are available. In addition, because only four studies were included in the study, publication bias testing was generally considered to be underpowered and was not conducted in the study.

Conclusions

Our meta-analysis, based on cohort studies from diverse populations, demonstrates a beneficial effect of chili pepper intake on all-cause, CVD-specific, and cancer-specific mortality. The present findings support recommendations to add chili pepper to the diets for prolonging lifespan, although randomized controlled trials are warranted to confirm the observed relationship.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0300-9831/a000746

ESM 1. PRISMA 2020 Checklist

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Conflict of interest
The authors declare that there are no conflicts of interest.

Author contributions
B.X. and M.Z. designed the research; L.Y. and J.S. conducted the research; L.Y. and J.S. performed the statistical analysis; L.Y. and J.S. wrote the paper; and B.X. had primary responsibility for final content. All authors read and approved the final manuscript. Lili Yang and Jiahong Sun are co-first authors.

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