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ORIGINAL ARTICLE

The association between dietary tryptophan intake and migraine

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Abstract

Migraineurs have been identified to have chronically decreased serotonin levels while its concentrations markedly increase during ictal periods. Regarding the importance of adequate tryptophan intake in regulating serotonin homeostasis and subsequent effect on migraine attacks, we designed the current study. The migraine group ($n = 514$, diagnosed according to the ICHDIII criteria) was recruited from a tertiary headache clinic. The controls consisted of 582 sex-matched healthy volunteers who were randomly selected from general population. After collecting demographic and anthropometric data, a validated 168-item semi-quantitative food frequency questionnaire (FFQ) was used for dietary intake assessments. Multiple regression models were applied to explore the relationship between migraine and tryptophan intake. The mean (SD) of the age of participants in the controls and migraine group was 44.85 (13.84) and 36.20 (9.78) years, respectively. The multiple regression models were adjusted for age (year), sex, body mass index (BMI) (kg/m^2), total daily energy intake (kcal/day), dietary intakes of total carbohydrates (g/day), animal-based protein (g/day), plant-based protein (g/day), total fat (g/day), saturated fat (g/day), and cholesterol (mg/day). It was shown that there is a negative association between tryptophan intake and migraine risk ((OR in the 3rd quartile = 0.46; 95% CI = 0.25–0.85) (OR in the 4th quartile = 0.40; 95% CI = 0.16–0.98) compared with the first quartile; P for trend = 0.045). Therefore, our results showed that subjects who had a median intake of 0.84–1.06 g of tryptophan per day had reduced odds of developing migraine by approximately 54–60%, relative to those consumed ≤ 0.56 g/day.

Keywords Dietary amino acids · Headache · Migraine · Serotonin · Tryptophan

Introduction

According to the reports of the Global Burden of Disease 2016, migraine is ranked as the first leading cause of disability in people aged less than 50 years [1]. This type of primary headaches has been proposed to be associated with different conditions including obesity, cardiovascular disorders, and gastrointestinal diseases [2–4]. The pathophysiological basis of this potentially debilitating disorder has not been fully described yet. Involvement of the trigeminovascular system, dysfunction of vascular system, mitochondrial dysfunction, neuroinflammation, and increased production of nitric oxide (NO) and the changes in the level of a number of neurotransmitters are some of the proposed underlying mechanisms [5–12].

Among the neurotransmitters, serotonin transmission has been suggested as a main factor involving in migraine pathogenesis [13]. Migraineurs have been identified to have chronically decreased serotonin levels between attacks and increased level during ictal period [14–16].

Also, increased sensitivity to serotonin agonists (triptans) might occur during attacks probably due to a defect in serotonin metabolism [16, 17]. Changes in serotonin turnover or the sensitivity of serotonergic receptors in the central nervous system (CNS) might participate in the interictal disturbances of sensory processes such as decreased habituation of cortical-induced responses in migraine sufferers [14]. On the other

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hand, augmented levels of serotonin have been found in plasma and cerebrospinal fluid (CSF) of patients during migraine attacks, probably reflecting the abnormalities in the turnover of serotonin in CNS [18, 19]. Thus, it is proposed that migraine headache might develop during a period of the attenuation in serotonin activity and consequent stimulation of serotonin receptors [19, 20]. On the other hand, serotonin depletion could augment the responses of cerebral and meningeal micro vessels to NO [21]. Triptans, considered as the first choice in acute treatment of migraine, are serotonin (5-HT) 1B and 1D receptor agonists [22].

Tryptophan is an essential precursor required for different metabolic reactions including serotonin production [23]. Once tryptophan concentrations diminished, it results in a short-term drop in neural serotonin level [13]. In an experimental study on rats, tryptophan-free amino acid formula or a low tryptophan diet reduced d-fenfluramine-induced or spontaneous discharge of serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) into the extra-cellular fluid of the hippocampus [24]. In a human study, tryptophan depletion noticeably decreased serotonin production in subcortical and cortical zones of the brain, traced by positron emission tomographic scanning using a 11C-methyl-L-tryptophan. Several hours post tryptophan depletion, CSF 5-HIAA dropped about 30%, demonstrated the substantial decrease of central serotonin turnover [25]. In addition, vestibular symptoms such as dizziness and nausea induced by optokinetic stimulus are reported to be greater in tryptophan-depleted individuals. Furthermore, hyper-excitability of the trigeminal nerves and augmentation of photophobia has been reported in tryptophan-depleted migraineurs [13, 26]. Therefore, it can be speculated that tryptophan depletion, which can occur consequent to decreased dietary tryptophan intake, might increase the susceptibility to migraine-associated symptoms. However, much uncertainty still exists about the association between tryptophan and migraine. Regarding the importance of adequate tryptophan intake in regulating serotonin homeostasis and subsequent effects on migraine attacks, we designed the current study to assess the relationship between dietary tryptophan intake and migraine headache risk.

Materials and methods

Study population and design

This case-control study was conducted between 2015 to 2018. Study participants were selected using convenience, consecutive sampling method. The case group ($n = 514$) were recruited from tertiary headache clinic of Sina University Hospital and a headache specialist's private clinic. Included migraineurs aged from 18 to 50 years old, and suffered from episodic and chronic migraine based on our expert headache-specialist neurologist's diagnosis according to the International Headache Classification (ICHDIII criteria, beta version) [27]. On the basis of these criteria, episodic migraine considered as having up to 14 headache days per month. Also, patients diagnosed as having chronic migraine if they have more than 15 headache days per month, with at least 8 days with migraine characteristics, for more than 3 months. Due to the fact that episodic migraine patients are less likely to be referred to our tertiary headache clinic, higher proportion of referred patients are diagnosed with chronic migraine. The control subjects consisted of 582 sex-matched healthy volunteers who were randomly selected from general population. All participants aged 18–60 years old and their body mass index (BMI) was between 18.5 and 35 kg/m^2. Also, participants were included in the study analysis if had a daily energy intake between 800 and 5000 kcal per day.

Suffering from any chronic diseases based on past medical history or physician's diagnosis such as gastrointestinal, liver or kidney disorders, diabetes mellitus, cardiovascular diseases, malignancy, tuberculosis, sarcoidosis, rheumatoid arthritis, psychiatric disorders, and any type of neurological diseases other than migraine including Parkinson, Alzheimer disease, multiple sclerosis, etc., was considered as the exclusion criteria for both groups. Also, pregnant or breastfeeding individuals or those who were following any specific diet over the prior year or the subjects suffering from substance/alcohol abuse or regular smokers were excluded from the study.

Demographic and anthropometric data

After fulfilling the inclusion and exclusion criteria, two trained researchers performed a structured interview. At the baseline visit, demographic data, past medical history, and anthropometric characteristics (including weight and height) were collected from all subjects.

With respect to the drug consumption in the migraine group in the current study, it is of note that since all studied patients were examined by the same expert headache-specialist neurologist, their prescribed medications were as follows: Abortive drugs for acute treatment of headache attack (i.e., nonsteroidal anti-inflammatory drugs (NSAIDs), other analgesics (codeine), and triptans), and prophylactic medications (i.e., propranolol (β-blockers), topiramate and sodium valproate/Depakine (antiepileptic drugs), selective serotonin reuptake inhibitor (SSRIs), in addition to tricyclic antidepressants (TCAs)).

Body weight was measured using a Seca 755 medical scale (weighing accuracy of 0·5 kg), and height was measured by a standard stadiometer (accuracy of 0.1 cm). BMI was calculated as weight (kg) divided by the square of the height (m^2).

Questionnaire data and dietary assessment

A validated 168-item semi-quantitative food frequency questionnaire (FFQ) was used by trained dietitians for dietary

intake assessment of participants [28]. The US Department of Agriculture (USDA) standard portion sizes (e.g., apple, 1 medium; bread, 1 slice; dairy, 1 cup) were used to specify the portion sizes of the consumed food and estimates were then converted to grams. When applying the USDA portion sizes was impossible, household measures (e.g., beans, 1 tablespoon; chicken meat, 1 leg or wing; rice, 1 large or small plate) were used alternatively [29]. The FFQ provides a measure for regular food intake based on a given standard serving size on a daily (e.g., bread), weekly (e.g., meat or rice), or monthly (e.g., soy) basis and therefore estimates usual dietary intakes. Then, data was converted to gram assuming each month equals 30.5 days. Since the Iranian food composition table (FCT) is incomplete and provides data only on a few nutrients, for calculating daily energy intake and nutrients (such as protein, carbohydrate, fat, and tryptophan), the Nutritionist-4 software (Nutritionist IV) and the USDA FCT that were adapted to Iranian food items were used [30]. Though USDA FCT did not contain some food items (such as some dairy products, i.e., Kashk, vetch, sweets, wild plum, mint, canned cherry), the Iranian FCT was applied alternatively for these food items [31]. For analyzing the nutrient and energy content of mixed food items (e.g., pizza), the usual restaurant recipes were used.

Statistical method

Analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software (version 21 (Chicago: SPSS Inc. IBM Corp.). All reported *P* values were two-sided and statistical significance level was set at *P* value less than 0.05. Total dietary intake of tryptophan of studied population was classified into quartiles. Baseline demographic, anthropometric, and dietary consumptions were compared according to these quartiles and reported as mean (standard deviation, SD) or number (percent) as appropriate. Linear regression models were applied to test the trend of continuous variables across quartiles of tryptophan. Also, adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were assessed for the relationship between intake of tryptophan and migraine headache risk. We used multiple logistic regression models with adjustment for age and sex in the first models, and adjustment for age (year, continuous), sex, BMI (kg/m^2, continuous), and total daily energy intake (kcal/day, continuous) in the second models. The fully adjusted regression models were additionally adjusted for dietary intake of a number of nutrients including total carbohydrates (g/day), animal-based protein (g/day), plant-based protein (g/day), total fat (g/day), saturated fat (g/day), and cholesterol (mg/day). The median value of each quartile of tryptophan intake was considered a continuous variable in order to test for linear trends across quartile.

Results

Overall, 582 sex-matched healthy subjects (94.5% were women) and 514 migraineurs (94.4% were women) were included in the present study. Sixty-one patients in the migraine group suffered from migraine with aura and 453 patients were without aura. Furthermore, 279 patients had chronic migraine and 235 patients suffered from episodic migraine. The mean (SD) of the age of participants in the controls and migraine group was 44.85 (13.84) and 36.20 (9.78) years, respectively. Regarding anthropometric measurements, the mean (SD) BMI of controls and cases was about 28.12 (4.80) and 25.91 (4.75) kg/m^2, respectively (*P* value < 0.001).

Table 1 provides an overview of baseline characteristics and dietary intakes of studied participants across quartiles of tryptophan consumption. It is apparent from this table that men were likely to consume higher amounts of tryptophan. Moreover, by increasing the intake of tryptophan, the daily consumption of total energy, carbohydrate, animal-based protein, plant-based protein, fat, saturated fatty acids, and cholesterol also significantly tend to increase (*P* value ≤ 0.05). Conversely, no significant association was found between age, and BMI and quartiles of tryptophan intake.

Table 2 reveals the ORs and corresponding 95% CIs for migraine according to quartiles of tryptophan intake. According to the age- and sex-adjusted regression models, a significant decrease in risk of migraine was only found in the last quartile of tryptophan intake (median intake = 1.06 g/day) versus the first quartile (median intake = 0.56 g/day) (OR = 0.63, 95% CI 0.43–0.90), while after considering BMI and daily energy intake in the first multiple regression models, this association became more apparent. It was indicated that the subjects in both the third (median intake = 0.84 g/day) and fourth quartiles of tryptophan had respectively 41% and 62% reduced risk of migraine in comparison with those in the lowest quartile (OR = 0.59, 95% CI 0.39–0.91 for the 3rd quartile; OR = 0.38, 95% CI 0.22–0.64 for the 4th quartile with the first quartile as reference; *P* for trend = 0.000). Furthermore, in the fully adjusted models in which dietary intakes of total carbohydrates (g/day), animal-based protein (g/day), plant-based protein (g/day), total fat (g/day), saturated fat (g/day), and cholesterol (mg/day) were also controlled for, the inverse association between tryptophan intake and migraine remained significant and was almost similar to that observed in the second models ((OR in the 3rd quartile = 0.46 95% CI = 0.25–0.85) (OR in the 4th quartile = 0.40 95% CI = 0.16–0.98) with the first quartile as reference; *P* for trend = 0.045) (Table 2 and Fig. 1).

Discussion

To the best of our knowledge, this is the first relatively large population-based investigation of the migraine headache risk

Table 1 Baseline characteristics and dietary intakes of study participants according to the quartiles of dietary tryptophan intake

Quartiles of tryptophan intake (g/day)					*P* for trend[1]
	1st quartile ($n = 274$)	2nd quartile ($n = 274$)	3rd quartile ($n = 274$)	4th quartile ($n = 274$)	
Female (%)	267 (97.4%)	261 (95.3%)	257 (93.8%)	250 (91.2%)	*0.014*
Age (years)	41.51 (13.58)	41.12 (12.39)	39.97 (12.63)	40.54 (12.77)	0.28
Body mass index (kg/m^2)	26.92 (5.10)	27.37 (4.86)	27.22 (4.78)	26.84 (4.86)	0.66
Dietary intakes (per day) (Mean (SD))					
Total energy (kcal)	1606.43 (352.60)	2007.28 (348.95)	2304.79 (428.79)	2832.25 (558.76)	*0.000*
Total carbohydrate (gr)	169.39 (57.98)	213.53 (61.36)	250.35 (73.94)	320.77 (102.74)	*0.000*
Total animal-based protein (gr)	26.98 (8.20)	35.17 (9.87)	43.88 (11.46)	53.17 (16.72)	*0.000*
Total plant-based protein (gr)	25.92 (7.39)	32.84 (7.96)	38.31 (10.00)	50.47 (14.05)	*0.000*
Total fat (gr)	66.39 (26.82)	96.82 (75.67)	117.96 (140.38)	114.35 (43.01)	*0.000*
Total saturated fatty acids (gr)	16.71 (7.39)	21.97 (9.36)	25.49 (11.29)	28.72 (10.16)	*0.000*
Total cholesterol (gr)	147.01 (65.22)	194.70 (72.90)	236.34 (79.66)	278.79 (127.08)	*0.000*

[1] *P* values were obtained using the linear regression model across quartiles of tryptophan intake for continuous variables and chi-square test for categorical variables. To test for linear trends for continuous variables across categories, the median value of each quartile of tryptophan intake (g/day) was used as a continuous variable

according to dietary tryptophan intake. Our results showed that subjects who had a median intake of 0.84–1.06 g of tryptophan per day had reduced odds of developing migraine by approximately 54–60%, relative to those consuming ≤ 0.56 g/day, even after controlling for potential confounders as well as daily dietary intakes of other nutrients. These findings therefore highlighted that considering enough intake of tryptophan rich foods such as flaxseed, salami, lentils, turkey, nuts, and eggs [32] within a healthy diet could lead to attenuating the odds of migraine among susceptible subjects. The Estimated Average Requirement (EAR) of tryptophan in adults is 4 mg per kilogram body weight that approximately equals to 300 mg (0.3 g) per day for a 75-kg healthy adult [32].

Our study demonstrated that the risk of having migraine attenuates by increased tryptophan intake. This observed relationship between migraine and tryptophan might be explained by the fact that tryptophan is the precursor of different components that might be involved in migraine pathogenesis including kynurenines, and serotonin, a well-known and important factor in the pathophysiology of migraine [14].

Migraineurs have been identified to have chronically decreased serotonin levels while its concentrations markedly increase during ictal periods. It has been shown that during headache attacks, serotonin releases from platelets which results in a short-term increase in plasma and brain levels of this neurotransmitter that may induce vasoconstriction of intracerebral arteries, initiating cortical spreading depression (CSD), and causing aura phase. Furthermore, experimental studies showed that the secretion of serotonin due to the periaqueductal gray area stimulation has analgesic effect by stimulating the inhibitory interneurons acting on dorsal horn neurons. Thus, the rise in brain serotonin level during migraine attack might be a pain-relieving and protective reaction [14, 15].

It is noted that reduction of the concentrations of serotonin might play a role in augmented cerebral and meningeal micro

Table 2 Odds ratio and 95% confidence interval for migraine according to the quartiles of dietary tryptophan intake

	Quartiles of tryptophan intake (g/day)				*P* for trend
	1st quartile	2nd quartile	3rd quartile	4th quartile	
Cases/non-cases	139/135	131/143	128/146	116/158	
Median (g/day)	0.56	0.70	0.84	1.06	
Age- and sex-adjusted model	1.00	0.86 (0.60–1.23)	0.75 (0.52–1.08)	0.63 (0.43–0.90)	0.010
Multivariable-adjusted model[a]	1.00	0.76 (0.51–1.13)	0.59 (0.39–0.91)	0.38 (0.22–0.64)	0.000
Multivariable-adjusted model[b]	1.00	0.66 (0.41–1.05)	0.46 (0.25–0.85)	0.40 (0.16–0.98)	0.045

[a] Additionally adjusted for body mass index (BMI) and daily energy intake (kcal/day)

[b] Additionally adjusted for dietary intakes of total carbohydrates (g/day), animal-based protein (g/day), plant-based protein (g/day), total fat (g/day), saturated fat (g/day), and cholesterol (mg/day)

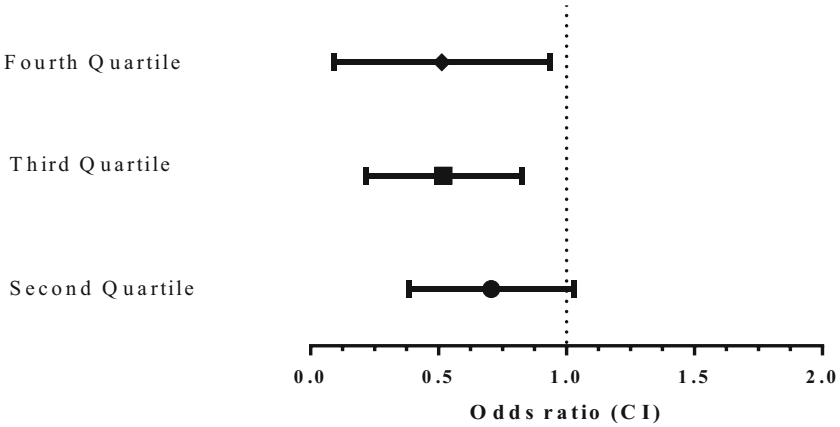

Fig. 1 Multivariable adjusted odds ratios and 95% confidence intervals for migraine by quartiles of tryptophan intake adjusted for age (year), sex, body mass index (BMI) (kg/m^2), total daily energy intake (kcal/day), and dietary intakes of total carbohydrates (g/day), animal-based protein (g/day), plant-based protein (g/day), total fat (g/day), saturated fat (g/day), and cholesterol (mg/day)

vessel responses to NO release, a messenger molecule with pivotal role in migraine pain genesis that acts through vasodilation effects by NO/cyclic GMP signaling pathway in addition to accelerating CGRP secretion [21]. Also, studies showed using medications such as reserpine and fenfluramine results in the release of serotonin that leads to depletion of its endogenous stores and provokes headache in susceptible individuals [21]. Infusion of 5-HT could terminate both spontaneous and reserpine-induced headaches and a polymorphism of the serotonin transporter gene promoter, a moderator of the brain serotonin homeostasis, that seems to be related to migraine with aura. Conversely, the decreased levels of serotonin interictally may occur due to its degradation and excretion. This process finally leads to extracerebral arteries' vasodilation and initiating pain sensitization in the head due to reducing the pain threshold. Besides, decreased serotonin concentration has also been described in some of the migraine comorbidities such as depressive disorders and tension-type headache [15, 33, 34].

In the same way, according to a recently published systematic review, decreased tryptophan level in the interictal period and its rise in the ictal phase in migraineurs have been confirmed in several studies [14]. As mentioned earlier, once tryptophan concentrations diminished, it results in a short-term drop in neural serotonin level [13]. Also, tryptophan produces other neuroactive metabolites through kynurenine pathway (KP), named as kynurenines. Thus, it would seem that restricted dietary tryptophan intake may be involved in migraine pathogenesis that could be related to both serotonin production and tryptophan-KP metabolites. Interestingly, it has been mentioned that chronic migraineurs might suffer from abnormal concentrations of the KP metabolites to some extent which were marked by increased xanthurenic acid and anthranilic acid levels, while other KP-related metabolites may decrease. The effects of KP derivatives particularly kynurenic acid on migraine pathophysiology could be explained through different mechanisms including antagonistic effects on glutamate NMDA receptors in the CNS and consequently suppression of CSD (especially in migraine with aura), suppressing CGRP release, antinociception activity, modulating inflammatory factors, and antioxidant properties [12, 35, 36].

Although several studies were conducted on the serotonergic mechanism of migraine headache, the investigations into dietary tryptophan intake and migraine risk are rare. Previous studies were mainly focused on the acute intake of tryptophan in ictal phase and they found discrepant results [13, 26, 37, 38]. Our result on chronic intake is not fully comparable with acute intake that assessed in previous studies. However, in concurrence to our results, administration of 200 mg/day tryptophan for at least 40 days was reported to be comparable with 2 mg/day methysergide. After the interruption of tryptophan administration, the intensity of attacks tended to regain [37]. In a case series on 10 migraineurs, 500 mg/day tryptophan in combination with 100 mg niacin, 500 mg calcium, 64 mg caffeine, and 650 mg acetylsalicylic acid (ASA) was prescribed at attack onset. The researchers hypothesized that tryptophan could reverse the falling of serotonin level, niacin could inhibit the conversion of tryptophan to kynurenine, ASA could dissociate tryptophan from binding proteins, and calcium can act as a vasoconstricting agent. Additionally, 9 out of 12 patients (75%) participating in the mentioned study reported 90–100% relief for most or all of their migraine attacks [38]. Also, Drummond compared amino acid mixture with or without tryptophan on migraine-associated symptoms and motion sickness. The tryptophan-containing drink had 2.3 g L tryptophan. Five and 8 h after consuming the amino acid drink, migraineurs who drank tryptophan-depleted drink reported more severe glare and light-induced pain. Eight hours after amino acid consumption, motion sickness was provoked. Thus, it was concluded that tryptophan depletion intensified headache pain and augmented nausea in migraineurs [13, 26].

In contrast to our results, a case series compared the regular diet containing 1.2 g/day tryptophan with tryptophan-restricted diet (350 mg/day) in 10 women with recurrent migraine-like headache, flush, and urticaria. Following the

low-tryptophan diet, migraine-like headache improved in 9 out of 10 patients [39]. The observed difference might be explained by the report of previous studies that patients who consume abortive medication more frequently would likely not benefit from tryptophan consumption that also includes patients with recurrent migraine.

Our research had some strengths and limitations. Among the strengths of the present study were investigating relatively high samples of migraineurs and also recruiting healthy non-headache subjects. In addition, all patients were examined by our expert neurologist-headache specialist and diagnosis was confirmed according to the ICHDIII beta criteria. Furthermore, we have applied a validated FFQ in order to estimate dietary intakes accurately.

Although to the best of our knowledge, this is the first study that explores dietary tryptophan intake of a relatively large sample of migraineurs compared with controls; it was limited in a number of ways. First, serum tryptophan levels were not investigated through the study which would help to interpret the results more accurately. Second, we attempted to consider the available data on confounding variables, though there would be some other contributing factors that we failed to assess and therefore could not fully exclude the effects of all confounders on the study results. Third, we did not assess the exact dosages and types of consumed medication, vitamins, nutraceuticals, or herbal remedies of migraineurs as well as headache-related features. Fourth, most of the enrolled participants in the present study consist of women. This may contribute to the fact that women suffer from migraine approximately twofold to threefold more than men. As such, this type of headache is often recognized in females while higher proportion of men with migraine remains underdiagnosed that may be associated with suboptimal treatment and thus less participation of males in the related studies [40].

Conclusion

Our findings suggest that subjects who had a median intake of 0.84–1.06 g of tryptophan per day had reduced odds of developing migraine by approximately 54–60%, relative to those consumed ≤ 0.56 g/day. These results are promising and should be validated by future large sample size cohort/case-control studies investigating tryptophan concentration in the plasma and CSF of migraineurs compared to healthy controls. Also, there is a need for well-designed clinical trials assessing the effects of tryptophan on migraine-associated symptoms.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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