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ORIGINAL ARTICLE

Asthma and vitamin D in Brazilian adolescents: Study of Cardiovascular Risks in Adolescents (ERICA)

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ABSTRACT

Objective: To evaluate the association between asthma prevalence and serum levels of vitamin D in Brazilian adolescents. **Methods:** This was a cross-sectional, school-based study involving adolescents between 12-17 years of age from four large Brazilian cities located at different latitudes (Fortaleza, Rio de Janeiro, Brasília, and Porto Alegre). Information on asthma diagnosis, lifestyle, and sociodemographic characteristics was collected by means of self-administered questionnaires. Serum concentrations of calcifediol were dichotomized as sufficient (≥ 20 ng/mL) or insufficient/deficient (< 20 ng/mL) levels. Bivariate analyses were carried out between vitamin D levels and prevalence of active asthma (AA), as well as other variables in study, using the chi-square test. Generalized linear models were configured to analyze potential confounding factors (p < 0.20). **Results:** Between 2013 and 2014, 1,053 adolescents were evaluated. The prevalences of AA and insufficient/deficient levels of calcifediol were 15.4% and 21%, respectively. There were no statistically significant associations between AA and hypovitaminosis D. The prevalences of AA and vitamin D insufficiency were, respectively, 2.34 (95% CI, 1,28-4.30) and 3.22 (95% CI, 1.75-5.95) times higher in Porto Alegre than in Rio de Janeiro, regardless of possible confounding factors. However, no significant associations were found between the prevalence of AA and vitamin-D-related variables in any of the cities. **Conclusions:** No association was found between AA and low levels of vitamin D in adolescents living at different latitudes in Brazil.

Keywords: Adolescent; Asthma/epidemiology; Vitamin D.

INTRODUCTION

Asthma is a heterogeneous disease with several clinical phenotypes, being characterized by chronic inflammation of the lower airways. It is a global health problem with an increasing prevalence in recent decades.(1) According to the International Study of Asthma and Allergies in Childhood (ISAAC), the mean prevalence of asthma in Brazil in 2006 was 24.3% and 19.0% in children between 6 and 7 years of age and in adolescents, respectively, causing a significant burden on the health care system and the quality of life of patients and their families.(2) More recently, the *Estudo de Riscos Cardiovasculares em Adolescentes* (ERICA, Study of Cardiovascular Risks in Adolescents) revealed a prevalence of asthma of 13.1% in adolescents.(3)

The relationship between micronutrient deficiency and the etiology of asthma has been a subject of study in recent years.(4) Several studies have shown that vitamin D also participates in the pathogenesis of chronic, infectious, and autoimmune diseases.(5-7) There is an increasing number of studies pointing to a protective role of vitamin D and correlating its circulating levels with the severity and control of asthma.(5,6) However, the lack of consensus does not allow the general recommendation of using vitamin D as a supplement in asthma patients.(8,9)

Vitamin D deficiency is also considered a global public health problem, and its increased prevalence is closely related to changes in lifestyle, such as lack of exposure to sunlight, reduced intake of food sources of vitamin D, overweight/obesity, more indoor activities, and daily use of sunscreen. Low serum levels of vitamin D have been suggested to have a negative influence on lung function, number of exacerbations, and response to inhaled corticosteroids.(5,10,11) The aim of this study was to assess the association between asthma and serum vitamin D levels in adolescents in Brazil. Our hypothesis was that asthma might be more prevalent in adolescents with insufficient levels of this micronutrient.

METHODS

This study was an integral part of the ERICA project, a multicenter cross-sectional school-based study. The main objective of the ERICA was to estimate the prevalence of metabolic syndrome and cardiovascular risk factors in adolescents between 12 and 17 years of age, regardless of the sex, attending public or private schools in Brazilian

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cities with more than 100,000 inhabitants.[12] The study population was stratified into 32 geographical strata (27 capitals, including the Federal District of Brasília, and 5 sets with other municipalities in each macroregion of the country). A sample of 1,251 schools in 124 Brazilian municipalities was selected with a probability proportional to the population size. In each of the selected schools three combinations of shifts and grades were selected; within each of these combinations, one classroom was selected. All eligible students in the selected classrooms were included in the study. The design sampling weights were calculated by the product of the reciprocals of the inclusion probabilities in each sampling stage and were later calibrated considering the projections of the numbers of adolescents enrolled in the schools located in the geographical strata by sex and age. A total of 74,589 adolescents were evaluated. The ERICA sample has proven to be nationally and regionally representative, as well as in relation to each capital involved. Details of the sampling process have been described elsewhere.[13]

The sample of the present study was composed by a subsample of students who attended morning classes in 4 cities located at different latitudes: Fortaleza, Rio de Janeiro, Porto Alegre, and Brasília. Serum 25-hydroxyvitamin D levels were assessed.[12,13] The cities were selected because of their location and because their biorepositories were active during the study period. The participants were selected using proportional random allocation to ensure a thorough distribution of sex, age, skin color, season at data collection, and estimated sunlight exposure.[14]

Data collection included information on sociodemographic characteristics, such as sex, age, skin color, type of school (public or private), physical activity, season at blood sampling, and latitude according to the location of each city. Anthropometric measurements were taken.[12] Data were collected through a self-administered electronic questionnaire. The participants fasted for 12 h, and blood samples were collected at school, stored at −80°C, and subsequently analyzed at the same laboratory.[12] Variables regarding asthma were extracted from the written standardized questionnaire of the International Study of Asthma and Allergies in Childhood asthma module for the 13-to 14-year-old age group. The questionnaire had previously been translated to Portuguese and validated for use in Brazil.[15]

Active asthma (AA) was defined as the occurrence of at least one asthma attack in the last 12 months.[3] The other variables were categorized as follows: age range (12-14 years and 15-17 years); self-reported skin color (white, black, brown, yellow, or indigenous)[16] and categorized as "White" or "non-White"; type of school (public or private), and screen time (< or ≥ 2 h/day). The period of data collection was categorized according to the seasons (fall, winter, spring, or summer). Nutritional status and physical activity were also evaluated.[14,17,18] Physical activity was assessed using an adapted version of the self-administered Physical Activity Checklist, previously validated for Brazilian adolescents.[17] Participants performing ≥ 300 min/week of physical activity were classified as physically active.[17] Anthropometric measurements were performed with participants placed in a standing position, barefoot, and wearing light clothing, by means of an electronic scale (model P200M; Líder, São Paulo, Brazil) with a capacity of up to 200 kg (precision, 50 g) and a portable stadiometer (Alturaexata, Minas Gerais, Brazil; precision, 0.1 cm).[12] To assess the nutritional status of the participants, the WHO reference curves were adopted, the BMI-for-age being used according to sex. Those with a score of $+1 > Z \geq -2$ were considered to be of normal weight, whereas those with an index of $+2 > Z \geq +1$ or $Z \geq +2$ were considered to be overweight or obese, respectively.[19-21]

Calcifediol or 25-hydroxyvitamin D_3—25(OH)D—is produced in the liver by the hydroxylation of vitamin D_3 (cholecalciferol) by the vitamin D enzyme 25-hydroxylase and is the most stable form of vitamin D, maintaining high levels of vitamin D that reflect both sunlight exposure and dietary intake. Because 25(OH)D has a long half-life of approximately 24 h, it is routinely used to assess vitamin D status,[22] and its levels were measured by chemiluminescence microparticle immunoassay using a LIAISON 5000 series analyzer (DiaSorin Inc., Stillwater, MN, USA) and the DiaSorin kit. The coefficient of variation in percentage of this test varies from 3% to 8%, and its precision is 0.92 (95% CI, 0.90-0.94).[14] For analysis purposes, serum 25(OH)D levels were stratified into insufficient/deficient (< 20 ng/mL) or sufficient (≥ 20 ng/mL), based on the criteria adopted by the Department of Bone and Mineral Metabolism of the Brazilian Society of Endocrinology and Metabolism in 2017.[23]

Vitamin D dietary intake was assessed using a food record of all the meals consumed in the previous 24 h, including portion sizes and preparation methods. The data were collected using a software designed specifically for the ERICA.[14,18,24] After converting each food item to weight (g), the corresponding nutritional composition of each food was obtained by standardized tables, and the total diet of each participant was calculated. An intake of at least 400 IU/day of vitamin D was considered adequate.[25]

Statistical analyses were performed with the Stata statistical software package, version 14 (StataCorp LP, College Station, TX, USA), using the set of commands for analyzing survey data with a complex sample (survey). Considering the sample size and the high prevalence of asthma (> 10%), the associations between serum 25(OH)D levels, prevalence of AA, and other study variables were assessed by bivariate Poisson regression models, using prevalence ratio (PR) and respective 95% CI.[26] Then, generalized linear models with Poisson family distribution were set up to analyze associations between 25(OH)D levels adjusted for potential confounding factors in the bivariate analysis ($p < 0.20$). For comparison between the means of continuous variables, ANOVA and the Student's t-test were used. The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Institute of Studies in Public Health of the Federal University of Rio de Janeiro (Protocol no. 45/2008).

RESULTS

Between February of 2013 and November of 2014, 1,152 adolescents underwent serum 25(OH)D determinations in the selected cities. Those who did not answer the question about asthma were excluded, the final sample consisting of 1,053 participants (91.4%). The prevalence of asthma in the sample was 15.4%, and insufficient levels of vitamin D were detected in 21.4%. The sociodemographic characteristics of the sample are described in Table 1.

Table 2 shows the distribution of the prevalence of AA according to sociodemographic characteristics, serum 25(OH)D levels, and nutritional status. There was a significantly higher prevalence of AA among those between 15 and 17 years of age and studying at private schools. Rio de Janeiro had the lowest prevalence of asthma. There was no association between insufficient levels of 25(OH)D and asthma.

Table 3 shows the distribution of the variables related to vitamin D according to the cities studied. The city of Rio de Janeiro, when compared with the other cities, had the lowest prevalence of vitamin D insufficiency (< 20 ng/mL), the lowest level of inadequate vitamin D intake (< 400 IU/day), and the highest serum

Table 1. Sociodemographic characteristics of the sample.

Variable	n	%	95% CI
Active asthma			
Yes	162	15.4	13.2-17.5
No	891	84.6	82.4-86.8
Serum 25(OH)D level			
Sufficient	828	78.6	76.1-81.1
Insufficient	225	21.4	18.8-23.8
Sex			
Female	643	61.0	58.1-64.0
Male	410	39.0	35.9-41.8
Age bracket, years			
12-14	431	40.9	35.9-41.8
15-17	622	59.0	58.1-64.0
Skin color			
Non-white	564	54.1	51.1-57.1
White	478	45.8	42.8-48.9
Type of school			
Public	754	71.6	68.8-74.3
Private	299	28.4	25.1-34.4
Nutritional status			
Normal/low weight	761	72.5	68.8-74.3
Overweight/obese	288	27.4	25.1-34.4
Physical activity			
Active	517	52.3	49.2-55.4
Inactive	471	47.6	44.5-50.7
Season at blood sampling			
Spring	337	32.0	25.1-34.4
Summer	134	12.7	10.7-14.7
Fall	219	20.8	18.8-23.8
Winter	363	34.4	31.6-37.3
City (latitude)			
Fortaleza (03°43'02" S)	292	27.7	25.1-34.4
Brasilia (15°46'46" S)	241	22.8	20.3-25.4
Rio de Janeiro (22°54'23" S)	250	23.7	21.1-26.3
Porto Alegre (30°01'59" S)	270	25.6	22.9-28.2
Screen time, h/day			
≤ 2	375	37.7	34.7 - 40.7
> 2	619	62.2	59.2 - 65.2

25(OH)D: 25-hydroxyvitamin D_3.

Table 2. Prevalence of active asthma in relation to sociodemographic characteristics, nutritional status, and serum 25-hydroxyvitamin D_3 levels.

Variables	Active asthma[a]	No asthma[a]	PR	95% CI	p*
Serum 25(OH)D level					
Sufficient	83.2 (75.7-88.7)	83.1 (80.3-85.6)	0.99	0.66-1.50	0.98
Insufficient	16.8 (11.3-24.4)	16.9 (14.4-19.8)			
Sex					
Female	51.9 (44.1-59.7)	51.3 (50.1-52.4)	1.02	0.75-1.40	0.88
Male	48.1 (40.3-56.0)	48.7 (47.6-49.9)			
Age bracket, years					
12-14	41.9 (35.7-48.4)	50.7 (49.8-51.7)	1.37	1.05-1.78	0.021
15-17	58.1(51.6-64.3)	49.3 (51.6-64.4)			
Skin color					
Non-White	56.3 (47.1-65.0)	56.3 (54.8-57.8)	1.01	0.69-1.46	0.97
White	43.7 (35.0-52.9)	43.7 (42.2-45.2)			
Type of school					
Public	38.0 (27.9-49.3)	22.2 (15.9-30.1)	1.91	1.44-2.55	0.000
Private	62.0(50.7-72.1)	77.8 (69.9-84.1)			
Nutritional status					
Normal/low weight	70.6 (61.0-78.7)	72.9 (68.5-76.8)	1.09	0.74-1.60	0.66
Overweight/obese	29.4 (21.3-39.1)	27.1 (23.2-31.5)			
Physical activity					
Active	63.3 (54.8 -70.9)	53.7 (49.9-57.4)	1.38	0.98-1.94	0.063
Inactive	36.7 (29.1-.45.2)	46.3 (42.5-50.1)			
Screen time, h/day					
≤ 2	32.6 (24.6-41.7)	39.3 (35.6-43.0)	1.43	0.93-1.97	0.112
> 2	67.4 (58.3-75.4)	60.8 (57.0-64.4)			
Vitamin D Intake					
≥400 IU/day	3.2 (1.0-9.58)	5.4 (4.3-6.8)	1.35	0.99-1.06	0.19
< 400 IU/day	96.84 (90.4-99.0)	94.6 (93.2-95.7)			
City					
Porto Alegre	14.6 (11.2-19.0)	10.9 (10.4-11.5)	1.00		
Fortaleza	23.6 (18.6-29.4)	19.7 (18.9-20.5)	0.86	0.55-1.35	0.52
Brasília	35.6 (29.3-42.5)	20.8 (19.8-21.8)	1.24	0.80-1.93	0.33
Rio de Janeiro	26.2 (19.4-34.4)	48.6 (47.5-49.6)	0.41	0.24-0.72	0.002
Season at blood sampling					
Fall	14.3 (8.6 -22.8)	14.6 (9.2-22.4)	1.00		
Spring	37.5 (27.1-49.3)	38.9 (30.7-47.9)	1.02	0.64-1.62	0.949
Summer	20.1 (11.7-32.5)	18.8 (12.4-27.4)	0.95	0.52-1.74	0.87
Winter	28.1 (20.3-37.5)	27.7 (22.0-34.2)	0.97	0.61-1.55	0.90

25(OH)D: 25-hydroxyvitamin D_3; and PR: prevalence ratio. [a]Values expressed as % (95% CI). *Bivariate Poisson analysis.

25(OH)D levels, and such differences were statistically significant. Although vitamin D intake (µg/day) was also higher in Rio de Janeiro, this difference was not statistically significant when compared with the other cities. However, no significant associations were found between the prevalence of AA and vitamin D-related variables in any of the cities (data not shown).

When the total sample was analyzed, those with an intake < 400 IU/day had lower serum 25(OH)D levels than did those with an intake of ≥ 400 IU/day (ANOVA; $p < 0.001$) or those with vitamin D insufficiency (17.2% vs. 11.0%; PR = 1.18; 95% CI: 0.34-4.62). However, the latter association was not statistically significant.

The comparison between the participants in Porto Alegre and those in Rio de Janeiro regarding the prevalence of asthma and vitamin D-related variables remained significant regardless of adjustments for sex, age group, nutritional status, physical activity, and screen time (Table 4). In addition, the mean serum levels of 25(OH)D were significantly lower in Porto Alegre ($p < 0.0001$). However, vitamin D intake (µg/day) did not differ between the two cities ($p = 0.12$).

DISCUSSION

Despite the differences in the prevalence rates of asthma among the cities studied, no associations were

Table 3. Distribution of vitamin D-related variables according to the cities evaluated.

Variable	RJ	POA	FOR	BRA	PR	95% CI	p
VD insufficiency (< 20 ng), %	12.0	34.3	15.2	19.4	0.57	0.40-0.82	0.002*
VD intake (< 400 IU/day), %	93.3	96.3	95.6	96.7	0.97	0.94-0.99	0.041*
Mean serum VD level (ng/mL)	29.3	25.2	29.1	26.3			< 0.0001**
Mean VD intake (µg/day)	3.7	2.9	3.4	3.3			0.1869**

RJ: Rio de Janeiro; POA: Porto Alegre; FOR: Fortaleza; BRA: Brasília; PR: prevalence ratio; and VD: vitamin D. *Poisson regression comparing the prevalence of vitamin D insufficiency in RJ vs. other cities.**ANOVA.

Table 4. Comparison between Rio de Janeiro and Porto Alegre regarding the prevalence of active asthma and vitamin D-related variables.

Variable	PR	95% CI	p*	PRadj	95% CI	p**
Active asthma, %	2.24	1.42 - 3.52	0.001*	2.34	1.28 - 4.30	0.007
VD insufficiency (< 20 ng), %	2.90	1.87 - 4.48	0.000*	3.22	1.75 - 5.95	0.000
VD intake (< 400 IU/day), %	1.03	0.99 -1.08	0.126*	1.03	0.98 - 1.08	0.188

PR: prevalence ratio; PRadj: prevalence ratio adjusted for sex, age bracket, nutritional status, physical activity, and hours of screen time; and VD: vitamin D. *Bivariate Poisson analysis. **Poisson generalized linear models.

found between insufficient low levels of vitamin D and asthma in our sample.

A study carried out in the USA with adult patients demonstrated a positive correlation between serum vitamin D levels and lung function parameters (higher FEV_1 and FVC).[27] In the city of Viçosa, Brazil,[28] 124 patients in the 0-to 18-year age bracket were studied in order to correlate recurrent wheezing with serum vitamin D concentrations. There was an association between vitamin D deficiency and wheezing, and the authors raised the hypothesis that there is a greater susceptibility to acute respiratory tract infections with the onset of wheezing in the first year of life due to reduced serum levels of this vitamin and concluded that vitamin D supplementation was a protective factor for the studied population.[28]

Several studies have found evidence that vitamin D plays an important role in the pathogenesis of asthma by reducing airway inflammation through modulation of the immune system or improving the anti-inflammatory function of corticosteroids.[29-31]

Among the immunomodulatory properties of vitamin D, its action on innate immunity stands out: it reduces pro-inflammatory cytokines and increases autophagosomal and autophagic activity, as well as the adaptive immune response, characterized by the inhibition of T-cell proliferation (Th1, Th2, and Th17). Moreover, it reduces the expression of IL-2 and INF-γ, stimulates the suppression of cytotoxic T response, and increases the number of regulatory T cells, IL-10, and IgG4.[6,32,33] Clinically, a reduction in the incidence of infections, a better response to corticosteroids in asthma patients, and improvements in pulmonary function are observed, thus avoiding airway remodeling.[32] However, according to some authors,[34] the results of experimental studies that link specific dietary components to immunological changes and airway responses or inflammation rarely translate into consistent randomized controlled trials, and, so far, none has been recommended as a preventive or therapeutic agent for asthma.

A study carried out in 2017 and involving 289 children and adolescents (9-19 years) in the city of Lima, Peru, 137 of whom had asthma, raised the hypothesis that the free circulating form of vitamin D is biologically active and more associated with asthma and atopy than are total serum levels of vitamin D. The authors suggested that total serum levels of vitamin D might explain the contradictions in the results found in the literature.[35]

In our study, we adopted the new cutoff points for total serum levels of vitamin D recommended by the Brazilian Society of Endocrinology and Metabolism.[23] These current values started to be used after considerations of which serum levels truly reflected the greatest harm to health and, consequently, the real need for vitamin D supplementation. The current consensus is that vitamin D levels < 10 ng/mL present health risks and require supplementation. The previous criteria used in order to classify vitamin D insufficiency, deficiency, and sufficiency (< 20 ng/mL; ≥ 20 ≤ 29 ng/mL, and > 30 ng/mL, respectively) have been discussed by various medical societies due to the worldwide hypovitaminosis D "epidemic", regardless of the different sociodemographic and cultural characteristics of the studied populations.[23] However, there was no association between serum 25(OH)D levels and asthma in our sample, even when the old cutoff points were used (data not shown).

Exposure to sunlight is an important factor for the absorption of vitamin D. Brazil is a tropical country, of continental dimensions, and great heterogeneity of climate. Most of the country is located between the Equator and the Tropic of Capricorn, which makes it one of the largest countries in the world in terms of land with high exposure to solar radiation throughout the year.[36] Serum concentrations of 25(OH)D vary according to geographic region and latitude and are higher in countries located close to the Equator.[37]

Of the four cities studied, Fortaleza (latitude: 03°43′02″ S) and Rio de Janeiro (latitude: 22°54′23″ S) had the lowest prevalences of vitamin D insufficiency and higher serum 25(OH)D levels. In contrast, the prevalences of hypovitaminosis D were higher in Porto Alegre (latitude: 30°01′59″ S) and in Brasilia (latitude: 15°46′46″ S) than in the other two cities, and it could be explained by the large differences in latitude among them.[14]

The seasons also affect serum concentrations of 25(OH)D. When blood collection is performed in winter, the chance of hypovitaminosis D is greater.[14] In the present study, fewer blood samples were collected during summer due to school holidays. There is little seasonal variation in temperature in Rio de Janeiro and Fortaleza, whereas the climate is dry and there is little variation in solar radiation throughout the year in Brasília.[38] In Porto Alegre, however, climatic seasons are more clearly defined. In any case, there was no statistically significant association between the season at blood sampling and the prevalence of AA in our sample.

Interestingly, we found that the city of Rio de Janeiro, when compared with the other cities, showed significant favorable differences regarding vitamin D-related variables and the prevalence of AA. However, these findings were independent of the association between asthma and vitamin D levels.

Exploratory analysis comparing the distribution of these variables showed that the prevalences of asthma and vitamin D insufficiency was significantly higher in Porto Alegre (in southern Brazil) than in Rio de Janeiro (on the southeastern coast of Brazil) regardless of possible confounding factors. In addition to geographic distance, these two cities have important differences in climate, dietary habits, and rate of exposure to solar radiation.

In our sample, the lowest serum level of 25(OH)D was found among adolescents with a vitamin D intake of < 400 IU/day, suggesting a positive relationship between vitamin D intake and serum levels. Foods such as salmon, tuna, and cod liver oil, which are rich in vitamin D, are not usually consumed by Brazilian adolescents, who, in general, have shown a decline in healthy eating habits and consuming more processed foods.[14,39] Among the cities participating in the study, Porto Alegre had the lowest mean intake of vitamin D in µg, the highest rate of vitamin D insufficiency, and a high prevalence of asthma. Although proper nutrition is essential, it does not seem to be the only requirement for achieving acceptable levels of this vitamin.[37,40]

Cultural habits, the use of sunscreen, skin color, and the seasons of the year are among the factors that affect the absorption of vitamin D.[40] Rio de Janeiro showed higher vitamin D sufficiency, higher vitamin D intake (≥ 400 IU/day), and significantly higher serum levels of 25(OH)D when compared with the other cities studied, as well as showing a lower prevalence of AA. However, no significant associations were found between the prevalence of AA and vitamin D-related variables in any of the cities.

Some limitations of the study design should be considered, such as the impossibility of inferring causality for the associations found. The absence of lung function measurements due to the sample size and logistical issues made it difficult to compare our results with those of other studies that evaluated the association between asthma and vitamin D deficiency. On the other hand, the use of standardized procedures and trained staff ensured the good quality of the data. Furthermore, the random selection of participants and the sample size had sufficient power to ensure the reliability of the results obtained. Finally, the inclusion of geographic areas at different latitudes allowed the analysis of a large number of important confounding variables related to the association studied (exposure to sunlight, different lifestyles, and diet).

In conclusion, no association was found between AA and low levels of vitamin D in adolescents living at different latitudes in Brazil. Further studies are needed to elucidate whether this nutrient has any effect on asthma in a country with one of the highest incidences of solar radiation in the world.

AUTHOR CONTRIBUTIONS

CSFA: study conception and design; interpretation of results; and writing of the manuscript. EAOCJ and MMRF: analysis and interpretation of results. CLO and MCCK: manuscript review and final review of the submitted version. FCK: study conception and design; analysis and interpretation of results; manuscript review and final approval of the submitted version.

CONFLICT OF INTEREST

None declared.

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