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BRIEF REPORT

Effect of Smoking on Longitudinal Interferon γ Release Assay Results Among Close Contacts of People with Pulmonary Tuberculosis

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Diagnosis of *Mycobacterium tuberculosis* infection in close contacts is critical for tuberculosis control. Smoking is a risk factor for *M. tuberculosis* infection and tuberculosis disease but its effect on longitudinal interferon γ release assay (IGRA) results remains unknown. We conducted a multisite prospective study in Brazil between 2015 and 2019, among close contacts of adults with culture-confirmed pulmonary tuberculosis. IGRA was performed at baseline, at month 6 if results were negative at baseline, and at months 24–30 after enrollment. IGRA results were categorized as IGRA positive (maintained from baseline to the last visit), IGRA conversion (from negative to positive at any time), IGRA reversion (from positive to negative at any time), and IGRA negative (maintained from baseline to the last visit). Associations between IGRA results and smoking status at baseline (current/former vs never) in contacts were evaluated using propensity score-adjusted logistic regression models. Estimated propensity score was used as a covariate in models, which regressed the outcome (IGRA positive, IGRA conversion, IGRA reversion) on smoking status. Of 430 close contacts, 89 (21%) were IGRA positive, 30 (7%) were converters, 30 (7%) were reverters and 22 were indeterminate. Smoking frequency was 26 (29%) among IGRA-positive contacts, 7 (23%) in converters, and 3 (10%) in reverters. Smoking in contacts was associated with lower odds of IGRA reversion (adjusted odds ratio, 0.16 [95% confidence interval, .03–.70]). We did not detect associations between smoking and IGRA positive or IGRA conversion. Our findings highlight the importance of smoking on longitudinal IGRA results. This has implications for clinical care and clinical trials in which IGRA status is monitored or used as an outcome.

Keywords. interferon γ release assays; IGRA; tuberculosis; close contacts; smoking.

Diagnosis of *Mycobacterium tuberculosis* infection in close contacts of persons with tuberculosis is critical for tuberculosis control. Interferon γ release assays (IGRAs) are used to diagnose *M. tuberculosis* infection, but the test is limited by assay variability, including the conversion (negative to positive) and reversion (positive to negative) of IGRA responses that may not always reflect changes in *M. tuberculosis* infection status [1]. Age and low peripheral lymphocyte count are among the factors that affect IGRA results [2]; smoking is a risk factor for *M. tuberculosis* infection [3, 4], tuberculosis disease, and death in persons with tuberculosis. [5].

In 2020, approximately 22% of the world population used tobacco [6]. In addition, smoking affects numerous biomarkers in the human body; however, studying this effect in a longitudinal cohort may provide more insight, by assessing the temporality of IGRA responses [5]. In this study, we evaluated a Brazilian longitudinal cohort of contacts of persons with pulmonary tuberculosis to investigate the association between smoking and longitudinal IGRA results.

METHODS

This was a substudy of a multisite prospective study in Regional Prospective Observational Research in TB (RePORT)–Brazil between 2015 and 2019 among close contacts (defined in this study as those with >4 hours per week of exposure to the index case patient) of adults with culture-confirmed pulmonary tuberculosis [7]. The RePORT-Brazil protocol was approved by the institutional review boards at each study site and at Vanderbilt University Medical Center. In the main cohort of

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1847 close contacts, IGRA was performed at baseline (within 40 days of treatment initiation for the tuberculosis index case). If the contact had a negative or indeterminate result, the IGRA was repeated at month 6. Contacts with a positive IGRA result at baseline did not undergo repeated testing at month 6.

QuantiFERON-TB Gold Plus IGRA testing was performed according to the manufacturer's instructions. IGRA results were categorized as IGRA positive (maintained from baseline to last visit), IGRA conversion (from negative to positive at any time), IGRA reversion (from positive to negative at any time), and IGRA negative (maintained from baseline to last visit). Participants with indeterminate IGRA results were excluded from this study. Details of the cohort of contacts of individuals with diagnosed pulmonary tuberculosis in RePORT-Brazil have been published elsewhere [8].

Alcohol use, illicit drug use, and smoking were self-reported and classified as current or former or never used. Categorical variables were displayed as frequency and proportions and compared using 2-sided Pearson's χ^2 or Fisher 2-tailed tests. Continuous variables were presented as median with interquartile range and compared using Kruskal-Wallis tests (between ≥2 groups).

Due to the low number of events, associations between IGRA results and smoking status at baseline (current or former vs never) in contacts were evaluated using logistic regression models adjusted for propensity score [9]. This was a 2-step procedure. In the first step, a propensity score model was constructed by regressing smoking status on a set of covariates available at baseline, from both contacts and tuberculosis index case patients. Estimated propensity scores, based on the fitted model, were calculated for each participant. For the low number of smokers, we used the least absolute shrinkage and selection operator (LASSO) regression with a logit link to identify variables to calculate propensity scores for each IGRA group separately. Characteristics included in LASSO regression for close contacts were age (in years), sex, alcohol use, illicit drug use, BCG vaccine scar, passive smoking (person inhaling smoke exhaled by a smoker or smoke from the tip of a lit cigarette), and tuberculosis-preventive treatment (initiated after enrollment in the study), and characteristics included tuberculosis case patients were age (years), sex, alcohol use, positive sputum smear, passive smoking, cavity on chest radiograph, illicit drug use, and glycated hemoglobin (hemoglobin A1c [HbA1c]). In a second step, the logit of the estimated propensity score was used as a covariate in the main outcome model, which regressed the outcome (IGRA positive, IGRA conversion, or IGRA reversion) on our exposure of interest, smoking status at baseline (current or former vs never) (see more details in Supplementary Table 1).

Information on participants was fairly complete, with only 6 variables containing missing data, with a maximum missingness of 2.9% (BCG scar among close contacts). Two types of sensitivity analyses were performed: since the amount of missing data was low, we performed single imputation as a sensitivity analysis. In addition, we repeated all analyses after excluding variables with any missing information. All results were similar to the complete case analysis (Supplementary Tables 2 and 3), which ignored participants with missing observations.

RESULTS

IGRA Testing Results Among Tuberculosis Close Contacts

Of 1847 close contacts enrolled in RePORT-Brazil, 500 were in follow-up at the start of this substudy; of the 500, 430 were reconsented and included in this substudy. IGRA was performed on these contacts 24–30 months after enrollment, regardless of the IGRA result at baseline or month 6.

In total, 430 close contacts of 139 tuberculosis case patients were included. Of the contacts, 89 (21%) were IGRA positive, 30 (7%) were converters, 30 (7%) were reverters, and 259 (60%) were IGRA negative; 22 (5%) had an indeterminate result at any time. When all IGRA result groups were compared, contacts with IGRA conversion had a higher body mass index ($P = .02$) tuberculosis index case patients for the IGRA-positive group were more frequently female ($P = .01$) and more likely to have a cavity on a chest radiograph ($P < .001$). Furthermore, contacts with IGRA reversion were older ($P < .001$) and their tuberculosis index patients had a higher bacillary load ($P < .001$). In addition, the frequency of smoking among contacts was 26 (29%), 7 (23%), and 3 (10%) in IGRA-positive, IGRA-conversion, and IGRA-reversion groups, respectively ($P = .24$). The IGRA-positive group had a higher frequency of current smokers, and IGRA converters were more likely to be former smokers, while in the IGRA-reversion group, 2 (6.7%) were current smokers and 1 (3.3%) was a former smoker ($P = .24$). See details in Table 1.

LASSO Regression and Propensity Score of Smoking

Characteristics identified using LASSO to estimate the propensity scores of close contacts for positive, conversion, and reversion IGRA groups were age (years), sex, alcohol use, illicit drug use, BCG scar, and tuberculosis-preventive treatment. The characteristics of tuberculosis index patients identified for conversion and reversion IGRA groups were sex, alcohol use, illicit drug use, passive smoking, positive sputum smear, cavity on chest radiograph, and HbA1c, and those identified for the IGRA-positive group were positive sputum smear and cavity on chest radiograph.

Association of Smoking With IGRA Result in Close Contacts of Patients With Active Tuberculosis

Multivariable logistic regression was used to test for the association between smoking status in close contacts with each outcome separately, adjusting for the logit of the estimated propensity scores (Figure 1). Model 1 demonstrates that smoking in contacts was significantly associated with lower

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Table 1. Characteristics of Tuberculosis Contacts and Tuberculosis Index Case Patients at Baseline, by Interferon γ Release Assay Result

Characteristic	Contacts or Case Patients by IGRA Result, No. (%)[a]					
	Total[c] (n = 408)	Negative (n = 259)	Conversion (n = 30)	Reversion (n = 30)	Positive (n = 89)	*P* Value[b]
Tuberculosis contacts						
Age, median (IQR). y	31.8 (13.7–46.3)	27.5 (12.1–43.3)	31.3 (18.5–42.6)	41.1 (24.6–54.4)	40.7 (20–49.7)	.001[d]
Female sex	245 (60)	149 (57.5)	20 (66.7)	20 (66.7)	56 (62.9)	.27
Race/ethnicity						
White	68 (16.7)	45 (17.4)	6 (20)	4 (13.3)	13 (14.6)	.47
Black	71 (17.9)	39 (15.1)	3 (10)	9 (30)	20 (22.5)	
Asian	2 (0.5)	0 (0)	0 (0)	0 (0)	2 (2.2)	
Pardo	264 (64.2)	173 (66.8)	21 (70)	17 (56.7)	53 (59.6)	
Indigenous	3 (0.7)	2 (0.8)	0 (0)	0 (0)	1 (1.1)	
BCG vaccine scar	378 (95.5)	242 (96.4)	29 (96.7)	29 (100)	78 (90.7)	.07
Literate	375 (87.2)	221 (85.3)	26 (86.7)	28 (93.3)	83 (93.3)	.03[d]
Income						
More than minimum wage	130 (32.3)	84 (32.8)	7 (23.3)	13 (46.4)	26 (29.2)	.78
Equal to or less than minimum wage	175 (43.4)	110 (43)	16 (53.3)	9 (32.1)	40 (44.9)	
Unknown	4 (1)	2 (0.8)	1 (3.3)	1 (3.6)	0 (0)	
Without income	94 (23.3)	60 (23.4)	6 (20)	5 (17.9)	23 (25.8)	
Smoking status	90 (22.1)	54 (20.8)	7 (23.3)	3 (10)	26 (29.2)	
Current	40 (9.8)	23 (8.9)	1 (3.3)	2 (6.7)	14 (15.7)	.24
Former	50 (12.3)	31 (12)	6 (20)	1 (3.3)	12 (13.5)	
Never	318 (77.9)	205 (79.2)	23 (76.7)	27 (90)	63 (70.8)	
Secondary smoking	120 (28)	75 (29)	8 (26.7)	8 (27.6)	22 (24.7)	.45
Alcohol consumption	201 (49.3)	122 (47.1)	13 (43.3)	16 (53.3)	50 (56.2)	.13
Illicit drug use	48 (11.8)	30 (11.6)	2 (6.7)	3 (10)	13 (14.6)	.54
TPT	89 (20.7)	8 (3.1)	6 (20.7)	17 (56.7)	50 (56.2)	<.001[d]
TPT status						
Incomplete	50 (56.2)	5 (62.5)	4 (66.7)	8 (47.1)	26 (52)	<.001[d]
Complete	39 (43.8)	3 (37.5)	2 (33.3)	9 (52.9)	24 (48)	
BMI, median (IQR)[e]	24.3 (19.3–28.9)	23.4 (18.3–28.8)	27 (20.3–31.2)	26.4 (20.8–31.2)	25.5 (22.3–28.6)	.02[d]
HIV infection	11 (2.7)	8 (3.1)	1 (3.3)	0 (0)	2 (2.2)	.51
ART (if HIV infected)	10 (83.3)	7 (87.5)	1 (100)	0 (0)	1 (50)	NA
Tuberculosis case patients						
Age, median (IQR), y	33 (23–41)	33 (24–40)	35 (20–56)	31 (22–39)	33 (22–42)	.96
Female sex	174 (67.2)	80 (31.5)	15 (50)	17 (56.7)	45 (50.6)	.01[d]
Race/ethnicity						
White	48 (11.9)	33 (13.2)	1 (3.6)	4 (13.8)	10 (12)	.21
Black	67 (16.7)	32 (12.8)	7 (25)	6 (20.7)	19 (22.9)	
Asian	2 (0.5)	2 (0.8)	0 (0)	0 (0)	0 (0)	
Pardo	280 (69.7)	180 (72)	19 (67.9)	18 (62.1)	54 (65.1)	
Indigenous	5 (1.2)	3 (1.2)	1 (3.6)	1 (3.4)	0 (0)	
BMI, median (IQR)[e]	19.7 (17.9–21.4)	20.1 (18–21.4)	20.5 (18–22.5)	19.4 (16.3–23)	19.4 (17.9–21.3)	.86
HbA1c, median (IQR), %	6 (5.7–6.6)	6.1 (5.8–6.4)	6.1 (5.6–6.8)	5.8 (5.3–6.6)	6 (5.7–6.6)	.42
Smoking (current or former smoker)	175 (42.9)	108 (42.5)	10 (33.3)	15 (51.7)	42 (50.6)	.16
Secondary smoking	109 (26.1)	64 (25.2)	9 (30)	3 (10.3)	27 (32.5)	.44
Alcohol consumption	312 (76.5)	194 (76.4)	23 (76.7)	21 (72.4)	68 (81.9)	.41
Illicit drug use	170 (41.7)	115 (45.3)	9 (30)	12 (41.4)	34 (41)	.43
Cavity on chest radiograph[f]	136 (33.3)	62 (24.4)	15 (50)	12 (41.4)	41 (49.4)	<.001[d]
AFB grade[g]						
Negative	108 (26.9)	79 (31.1)	4 (13.3)	6 (20.7)	19 (22.9)	<.001[d]
Scanty	62 (15.5)	47 (18.5)	3 (10)	0 (0)	7 (8.4)	
1+	90 (22.4)	55 (21.7)	7 (23.3)	6 (20.7)	22 (26.5)	
2+	45 (11.2)	28 (11)	4 (13.3)	5 (17.2)	8 (9.6)	
3+	96 (23.9)	45 (17.7)	12 (40)	12 (41.4)	27 (32.5)	
DST results						
Sensitive	351 (90.5)	225 (90.7)	27 (90)	25 (86.2)	74 (91.4)	NA
Rifampicin-isoniazid resistance	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	

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Table 1. Continued

Characteristic	Contacts or Case Patients by IGRA Result, No. (%)[a]					
	Total[c] (n = 408)	Negative (n = 259)	Conversion (n = 30)	Reversion (n = 30)	Positive (n = 89)	*P* Value[b]
Rifampicin resistance	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Isoniazid resistance	37 (9.5)	23 (9.3)	3 (10)	4 (13.8)	7 (8.6)	
Cough at baseline	383 (93.9)	241 (93.1)	30 (100)	28 (93.3)	84 (94.4)	.64

Abbreviations: AFB, acid-fast bacilli; ART, antiretroviral therapy; BMI, body mass index; DST, drug-susceptibility testing; HbA1c, hemoglobin A1c (glycated hemoglobin); HIV, human immunodeficiency virus; IGRA, interferon γ release assay; IQR, interquartile range; NA, not applicable; TPT, tuberculosis-preventive treatment.

[a]Data represent no. (%) of contacts or case patients unless otherwise specified. Missing information was identified in 4 variables of tuberculosis contacts: BCG vaccine scar (missing in 12 [2.9%]), income (missing in 5 [2.9%]), secondary smoking (missing in 1 [0.2%]), HIV infection (missing in 7 [1.7]); and 2 variables of tuberculosis cases: BMI (missing in 4 [1%]), and HbA1c (missing in 12 [2.9%]).

[b]Continuous variables were compared using Kruskal-Wallis tests, and categorical variables using χ^2 tests.

[c]Twenty-two close contacts with indeterminate IGRA result were excluded.

[d]Significant at P < .05.

[e]BMI calculated as weight in kilograms divided by height in meters squared.

[f]Cavity on chest radiograph was defined as an air-filled space within lung consolidation or within a mass or nodule on a chest radiograph, identified by a radiologist.

[g]Positive sputum smear was defined as AFB seen with auramine-rhodamine fluorescence microscopy.

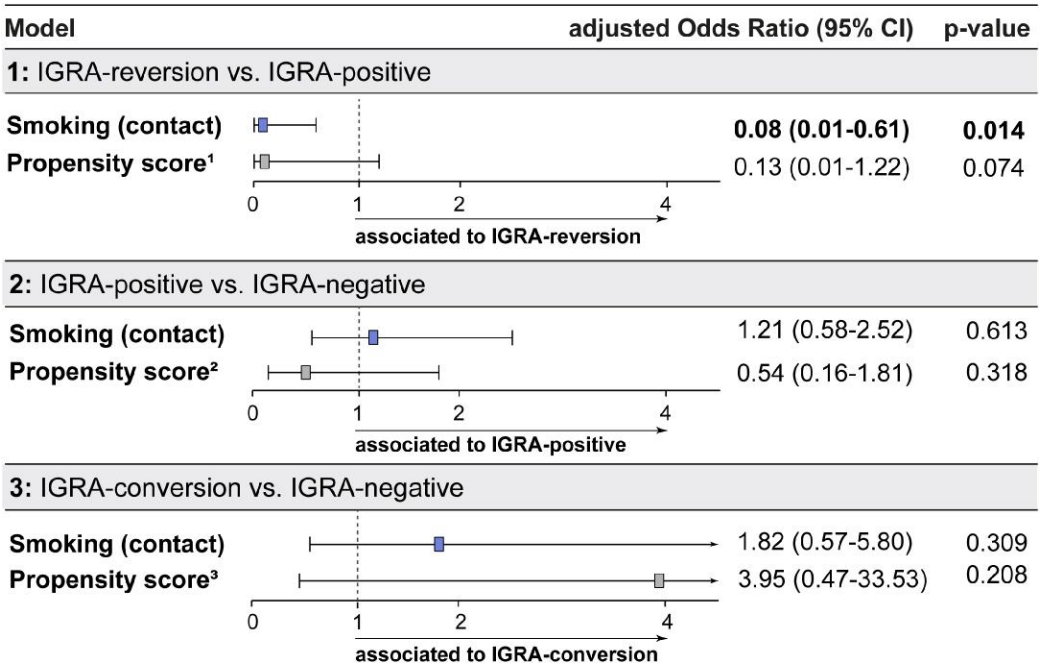


Figure 1. Logistic regression analyses were used to test associations between smoking and reversion, conversion, and positive interferon γ release assay (IGRA) results among close contacts of pulmonary tuberculosis case patients. For "smoking" (current/former), "never smoking" was used as the reference. Least absolute shrinkage and selection operator (LASSO) regression was used to select variables included in the propensity score for smoking. In model 1, the following variables were used for contacts: sex, alcohol consumption, illicit drug use, tuberculosis-preventive treatment (TPT), BCG scar, and age; and the following for tuberculosis case patients: sex, alcohol consumption, positive sputum smear, illicit drug use, cavity on chest radiograph, and hemoglobin A1c (HbA1c). In model 2, the following variables were used for contacts: sex, age, alcohol consumption, illicit drug use, BCG scar, and TPT; and the following for case patients: positive sputum smear and cavity on chest radiograph. In model 3, the following variables were used for contacts: sex, alcohol consumption, illicit drug use, TPT, BCG scar, and age; and the following for case patients: sex, alcohol use, smoking, positive sputum smear, illicit drug use, cavity on chest radiograph, and HbA1c. For IGRA-reversion and IGRA-conversion groups, comparisons were performed considering the initial result of those groups: IGRA reversion (from positive to negative at any time) versus IGRA positivity (maintained from baseline to last visit) and IGRA conversion (from negative to positive at any time) versus IGRA negativity (maintained from baseline to last visit). IGRA-positive and IGRA-negative groups were compared since both maintained the given result throughout the visits. Boldface type represents a statistically significant association. Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

odds of IGRA reversion versus IGRA positivity (adjusted odds ratio, 0.16 [95% confidence interval, .03–.70]; $P = .02$). In models 2 and 3, we did not detect significant associations between smoking status and increased odds of IGRA positivity (adjusted odds ratio, 1.18 [95% confidence interval, .57–2.44]; $P = .65$) or IGRA conversion (1.44 [.44–4.70]; $P = .54$).

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DISCUSSION

The use of IGRA testing for the diagnosis of *M. tuberculosis* infection is important for the control of tuberculosis. In this longitudinal study, smokers (current or former) had lower odds of reverting from an IGRA-positive to an IGRA-negative result. Furthermore, using conversion and reversion definitions recommended by the Centers for Disease Control and Prevention [10], the proportion of close contacts who remained IGRA positive was 21%; the proportion with conversion at any time, 7%; and the proportion with reversion at any time, 5%.

These results differ from the results of a clinical trial in adolescents, a longitudinal cohort in which adolescents with BCG vaccination had an IGRA conversion proportion of 6% and IGRA reversion in 36% [11]. Meanwhile a study from Spain identified 10% with IGRA reversion and 24% with persistently positive IGRA results [12]. Previous studies have reported that with use of simple definitions of conversion and reversion (without considering the thresholds of the quantitative IGRA results), such as negative to positive and positive to negative, respectively, their rates may be higher with IGRAs than with tuberculin skin tests [13]. The absence of standardized definitions of conversion and reversion is noteworthy.

In our study, the number of smokers with IGRA reversion was low (n = 3 [10%]). Although the clinical relevance and etiology of IGRA reversion has not yet been established, there is information suggesting that this reversion could be due to elimination *M. tuberculosis* infection [11, 14]. In addition, smoking can alter the interferon γ response and T-cell function [3, 4], which are significantly reduced among smokers. This could lead to false-negative or indeterminate IGRA results [5], although there is still controversy regarding these results [5]. Conversely, the low number of smokers in the IGRA-reversion group and the exclusion of indeterminate results in our analyses strengthen our hypothesis of the inability to clear *M. tuberculosis* infection (or IGRA response) in smokers.

This study had limitations. First, smoking and comorbid conditions were self-reported, and we did not obtain information on the frequency and quantity of cigarettes smoked or the specific type and diagnosis time of the indicated comorbid condition. Second, conditions such as human immunodeficiency virus infection or the use of concomitant medications were infrequent in this study. Finally, this study used a convenience sample, possibly introducing selection bias. Nevertheless, this is the first longitudinal cohort study to explore the association between smoking and IGRA results, using IGRA conversion and reversion as end points.

In conclusion, contacts who reported smoking (current or former) had lower odds of reverting from an IGRA-positive to an IGRA-negative result, after adjustment for multiple potential cofounders in both the close contact and the tuberculosis index patient. Our findings highlight the importance of smoking in longitudinal IGRA results. This has implications for clinical care and clinical trials in which IGRA status is monitored or used as an outcome, such as tuberculosis vaccine trials. Due to our findings and the limitations of previous research, additional studies are needed to elucidate the gaps in knowledge about specific immunological mechanisms between smoking and serial IGRA results.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. Conceptualization: G. A. and T. R. S. Data curation: M. B. A., G. A., M. C. F., C. S., and T. R. S. Investigation: M. B. A., G. A., M. C. F., C. S., and T. R. S. Formal analysis: M. B. A. and G. A. Financial support acquisition: M. C. F., A. L. K., M. C. S., V. C. R., B. B. A., and T.R.S. Methodology: M. B. A., G. A., and T. R. S. Project administration: M. C. F., C. S., and T. R. S. Resources: M. B. A., G. A., B. B. A., and T. R. S. Software: M. B. A., G. A., and T. R. S. Supervision: V. C. R., B. B. A., and T. R. S. Writing—original draft: M. B. A., G. A., and T. R. S. Writing—review and editing: All authors. All authors have read and agreed to the submitted version of the manuscript.

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Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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