Association Between Passive and Active Smoking and Incident Type 2 Diabetes in Women

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OBJECTIVE—Accumulating evidence has identified a positive association between active smoking and the risk of diabetes, but previous studies had limited information on passive smoking or changes in smoking behaviors over time. This analysis examined the association between exposure to passive smoke, active smoking, and the risk of incident type 2 diabetes among women.

RESEARCH DESIGN AND METHODS—This is a prospective cohort study of 100,526 women in the Nurses' Health Study who did not have prevalent diabetes in 1982, with follow-up for diabetes for 24 years.

RESULTS—We identified 5,392 incident cases of type 2 diabetes during 24 years of follow-up. Compared with nonsmokers with no exposure to passive smoke, there was an increased risk of diabetes among nonsmokers who were occasionally (relative risk [RR] 1.10 [95% CI 0.94–1.23]) or regularly (1.16 [1.00–1.35]) exposed to passive smoke. The risk of incident type 2 diabetes was increased by 28% (12–50) among all past smokers. The risk diminished as time since quitting increased but still was elevated even 20–29 years later (1.15 [1.00–1.32]). Current smokers had the highest risk of incident type 2 diabetes in a dose-dependent manner. Adjusted RRs increased from 1.39 (1.17–1.64) for 1–14 cigarettes per day to 1.98 (1.57–2.36) for ≥25 cigarettes per day compared with nonsmokers with no exposure to passive smoke.

CONCLUSIONS—Our study suggests that exposure to passive smoke and active smoking are positively and independently associated with the risk of type 2 diabetes.

Diabetes Care 34:892–897, 2011

Smoking is one of the leading causes of avoidable death globally (1). The disease burden attributable to smoking already is enormous, with ~6 million premature deaths worldwide each year, and is projected to grow substantially across the century without an end to the pandemic (1). Diabetes also is a global health priority. The International Diabetes Federation has predicted that the number of individuals with diabetes will increase from 240 million in 2007 to 380 million in 2025 (2).

Accumulating evidence has identified a positive association between active smoking and risk of type 2 diabetes (3), whereas few studies had information on passive smoking. Data from the Third National Health and Nutrition Examination Survey 1988–1991 suggest that ~90% of nonsmokers have detectable levels of serum cotinine, a sensitive marker for tobacco exposure (4). Therefore, previous studies linking active smoking with diabetes risk might have underestimated the magnitude of the true association because individuals exposed to passive smoke would be in the reference group. The few studies that simultaneously examined the relative associations of passive and active smoking on diabetes risk (5,6) were limited by relatively short follow-up periods, limited information on potential confounders, and lack of information on smoking quantity or change in smoking behavior over time. Therefore, we prospectively investigated the association between passive and active smoking and the risk of incident type 2 diabetes over 24 years of follow-up among 100,526 women from the Nurses' Health Study (NHS).

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS—The NHS is an ongoing prospective cohort study of 121,700 registered nurses that began in 1976. Participants are followed via biennial questionnaires to update information on health-related behaviors and medical events. The follow-up for the cohort exceeded 90% through 2006. This study was approved by the institutional review board at Brigham and Women's Hospital.

The study population for this analysis comprised 100,526 participants of the NHS who did not have prevalent diabetes or cancer (except for nonmelanoma skin cancer) in 1982 when passive smoking was first assessed.

Assessment of status of smoking

The initial NHS questionnaire (1976) inquired of regular smokers at what age smoking began and the average quantity of cigarettes smoked per day. With each subsequent biennial questionnaire, participants reported whether they were current smokers. The intensity of smoking among current smokers was assessed by self-reported number of cigarettes per day in six categories (1–4, 5–14, 15–24, 25–34, 35–44, or ≥45). In the 1982 questionnaire (baseline of the present study), participants were asked, "Are you currently exposed to cigarette smoke from other people?" Responses were categorized into three levels: no exposure, occasional exposure, and regular exposure. Although we do not have direct validation of self-reported passive smoke exposure, we have previously reported that these women had higher toenail

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Received 3 November 2010 and accepted 31 January 2011.
DOI: 10.2337/dc10-2087

nicotine levels compared with women who reported no exposure to passive smoke (7).

Duration of smoking and years since quitting were calculated based on information from the initial and subsequent questionnaires. Pack-years of smoking (the equivalent of smoking 20 cigarettes a day for 1 year) was calculated by multiplying the number of packs smoked per day by the number of years of smoking.

Assessment of other covariates

Information on race, family history of diabetes, and waist circumference was obtained at baseline. BMI (calculated as weight in kilograms divided by the square of height in meters) and physical activity (metabolic equivalent tasks) were ascertained at baseline and updated with new information every 2 years. Total energy intake and intakes of alcohol, magnesium, calcium, vitamin D, total *trans* fat, fiber from cereal, and caffeine were ascertained first in 1980 using a semiquantitative food frequency questionnaire (FFQ) and then updated every 2–4 years from subsequent FFQs. The reproducibility and validity of the FFQ in the NHS has been documented (8). Except for total energy intake and intake of alcohol, nutrient values were adjusted for total energy intake by the residual method (9). Husband's education status, which was inquired in 1992, also was included in the analyses as an indicator of socioeconomic status because of the limited variability in the nurses' education attainment.

Assessment of diabetes

The baseline and biennial follow-up questionnaires asked participants to report whether a clinician had made a new diagnosis of type 2 diabetes during the preceding 2 years. Women who self-reported diabetes were then sent a supplementary questionnaire to confirm the diagnosis of diabetes; this questionnaire gathered information about symptoms, diagnostic laboratory test results, and diabetes treatment (10). Diagnosis of diabetes by the supplementary questionnaire in the NHS has been shown to be highly accurate (98.4% were confirmed by medical records), with a low percentage of false-negative self-reports (0.5%) (11).

Statistical analyses

Person-time was censored at the date of diabetes diagnosis, death, incident cancer diagnosis (except for nonmelanoma skin cancer), or the end of follow-up (June 2006), whichever came first. Participants who did not return the baseline FFQ were allowed to contribute person-time for later time intervals if they returned a subsequent FFQ.

In our primary analysis, participants were classified by smoking status at baseline (1982) and reclassified in each biennial follow-up cycle. Smoking status was analyzed in seven groups: *1*) participants who were consistent nonsmokers through June 2006 and who reported no exposure to passive smoke (which was the reference group); *2*) participants who were persistent nonsmokers through June 2006 but who occasionally were exposed to passive smoke; *3*) participants who were persistent nonsmokers through June 2006 but who were regularly exposed to passive smoke; *4*) past smokers; *5*) current smokers who smoked 1–14 cigarettes per day; *6*) current smokers who smoked 15–24 cigarettes per day; and *7*) current smokers who smoked ≥25 cigarettes per day. Exposure to passive smoke at baseline was carried forward in subsequent time intervals. Participants who never provided information on exposure to passive smoke and active smoking (9.5%) were included in the analysis as a separate missing group. Cox proportional hazards regression models were used to estimate relative risks (RRs) and 95% CIs. Multivariable models were constructed to adjust for potential confounding variables that have been previously associated with incident diabetes (age [continuous], race [Caucasian, American African, American Indian, and other], BMI [continuous], quadratic BMI [continuous], physical activity [quintiles], husband's education status [high school or less, Bachelor's degree, or higher than Bachelor's degree], family history of diabetes [yes or no], total energy intake [in quintiles], and intakes of alcohol [six categories], magnesium, calcium, vitamin D, total *trans* fat, fiber from cereal and caffeine, total fat and saturated fat [all in quintiles]). Proportional hazards assumptions were verified by testing the interaction with time using the likelihood ratio test ($P = 0.27$).

We also performed four additional analyses. First, to address the possibility of confounding by other markers of adiposity, we added baseline waist circumstance to the multivariable Cox proportional hazards regression model. Second, we analyzed the association between active smoking and diabetes using pack-years (in place of cigarettes per day) in the following categories: 1–9, 10–19, 20–29, 30–39, and ≥40 pack-years. Third, we divided past smokers into five groups based on the number of years since quitting (<5, 5–9, 10–19, 20–29, and ≥30 years), in order to assess cessation of active smoking on the risk of diabetes. Finally, to compare the results of our study more closely with the results reported by other investigators, we analyzed the association between active smoking and incident diabetes after redefining the reference group to include all nonsmokers (combining nonsmokers without passive smoke exposure and nonsmokers who were exposed to passive smoke); this reference group is more similar to the reference groups in most previous studies. All *P* values are two-tailed. Statistical tests were performed using SAS version 9.1 for Unix statistical software package (SAS Institute, Cary, NC).

RESULTS—During 24 years (1,539,278 person-years) of follow-up, 5,392 incident cases of physician-diagnosed type 2 diabetes were confirmed with the supplementary questionnaire. Participant characteristics by status of smoking are presented in Table 1. Compared with nonsmokers without exposure to passive smoke, women exposed to passive smoke had higher BMIs, were less physically active, were more likely to be Caucasian, were more likely to have a family history of diabetes, and were less likely to have a husband with a Bachelor's degree or higher. In contrast, BMI values were similar among current smokers and nonsmokers without exposure to passive smoke. The percentage of women with a positive family history of diabetes was lower among current smokers compared with nonsmokers without exposure to passive smoke. Current smokers also tended to have a lower intake of calcium and vitamin D and a higher intake of alcohol and caffeine.

Active and passive smoking were positively associated with the risk of incident type 2 diabetes (Table 2). Compared with nonsmokers without passive smoke exposure, the multivariable-adjusted RRs for nonsmoking women who were occasionally or regularly exposed to passive smoke were 1.10 (95% CI 0.94–1.23) and 1.16 (1.00–1.35), respectively. The risk of incident type 2 diabetes was increased by 28% (12–50) among past smokers. Current smokers had the highest risk of incident type 2 diabetes in a dose-dependent manner (*P* value for trend

<0.001). For women who currently smoked ≥25 cigarettes per day, the risk of type 2 diabetes was increased by nearly twofold (RR 1.98 [1.57–2.36]). Additional adjustment for waist circumference did not materially alter the results.

We also observed a dose-dependent association between active smoking and diabetes risk when cumulative pack-years were analyzed (Table 3). For participants with 1–9 pack-years of smoking, the adjusted RR for diabetes was 1.17 (95% CI 1.01–1.35) compared with nonsmokers with no exposure to passive smoke. The RR increased gradually across the categories and was 1.72 (1.48–1.98) for participants with ≥40 pack-years of smoking (*P* value for trend <0.001).

The risk of diabetes decreased gradually as the time since quitting increased (Table 3; *P* value for trend <0.001). For those who only recently quit (<5 years of abstinence), the risk remained high compared with nonsmokers without exposure to passive smoke (RR 1.88 [95% CI 1.59–2.23]). The RR decreased over time but still was elevated 20–29 years later (1.15 [1.00–1.32]). By the time 30 years had passed since quitting, the association was no longer significant (1.06 [0.90–1.24]).

In the secondary analysis in which the reference group was redefined to include all nonsmokers, the multivariable RR was 1.16 (95% CI 1.09–1.25) for past smokers and 1.50 (1.35–1.66) for current smokers. Among current smokers, the risk of type 2 diabetes increased from 1.29 (1.12–1.50) for women who smoked 1–14 cigarettes per day to 1.86 (1.56–2.20) for women who smoked ≥25 cigarettes per day.

Table 1—*Baseline characteristics by smoking status*

	Nonsmokers				Current smokers		
Variables	Reference*	Occasionally exposed to passive smoking	Regularly exposed to passive smoking	Past smokers	1–14 cigarettes per day	15–24 cigarettes per day	≥25 cigarettes per day
Age (years)	47 (41–54)	47 (41–54)	47 (41–53)	48 (42–55)	48 (42–54)	48 (42–54)	48 (42–54)
BMI (kg/m^2)	23.0 (21.2–25.8)	23.5 (21.6–26.6)	24.1 (21.9–27.4)	23.6 (21.6–26.6)	23.0 (21.1–25.7)	22.8 (21.0–25.4)	23.2 (21.2–26.1)
Alcohol consumption (g per day)	0.8 (0–4.3)	0.9 (0–5.3)	0.9 (0–4.7)	2.7 (0.8–11.0)	2.7 (0.8–11.2)	2.5 (0–11.6)	3.5 (0–14.6)
Physical activity (METs per week)	8.4 (3.2–19.9)	8.1 (3.1–19.2)	7.1 (2.4–16.9)	8.9 (3.1–20.5)	7.9 (2.7–20.2)	5.5 (2.2–15.9)	4.1 (1.4–11.6)
Caucasian (%)	96.2	93.8	93.1	94.9	93.5	95.2	95.9
Husband's education (%)†	53.0	44.7	35.9	44.0	39.6	35.0	35.0
Family history of diabetes (%)	17.3	18.2	19.9	17.4	16.4	15.8	16.6
Dietary factors (per day)							
Total calories (kcal)	1,519 (1,230–1,871)	1,534 (1,238–1,883)	1,529 (1,226–1,893)	1,495 (1,200–1,830)	1,473 (1,170–1,828)	1,481 (1,177–1,840)	1,511 (1,198–1,879)
Magnesium (mg)	285 (244–329)	280 (240–327)	277 (236–322)	293 (251–340)	289 (249–336)	291 (249–336)	292 (246–339)
Calcium (mg)	696 (531–918)	675 (519–885)	657 (497–877)	685 (526–894)	656 (500–862)	643 (483–851)	626 (470–840)
Vitamin D (IU)	252 (162–477)	239 (157–454)	232 (149–436)	241 (152–473)	222 (144–433)	216 (137–409)	213 (133–418)
Total *trans* fat (g)	4.0 (3.2–4.9)	4.0 (3.2–4.8)	4.0 (3.2–4.9)	3.8 (3.0–4.7)	3.8 (3.0–4.7)	4.0 (3.2–4.9)	3.9 (3.1–4.8)
Fiber from cereal (g)	2.5 (1.7–3.7)	2.3 (1.5–3.4)	2.1 (1.4–3.2)	2.2 (1.4–3.3)	2.0 (1.3–3.0)	1.9 (1.2–2.9)	1.9 (1.2–2.8)
Caffeine (mg)	234 (86–404)	331 (143–438)	358 (165–507)	375 (176–572)	392 (209–697)	455 (329–761)	569 (342–799)
Total fat (mg)	69 (60–78)	70 (61–79)	71 (62–79)	69 (60–78)	70 (61–79)	71 (62–80)	71 (61–81)
Saturated fat (mg)	27 (23–31)	28 (24–32)	28 (24–32)	27 (23–32)	28 (24–32)	29 (24–33)	29 (24–33)

Data are median (interquartile range) or percentage. *Participants who were consistent nonsmokers through June 2006 and who reported no exposure to passive smoke. †Percentage of those with a Bachelor's degree or higher.

CONCLUSIONS—In our prospective study of 100,526 women followed for 24 years, we found that exposure to passive smoke and active smoking were independently associated with the risk of developing type 2 diabetes. The association appeared dose dependent and remained significant after carefully controlling for multiple relevant lifestyle and dietary factors. After quitting, the risk of diabetes decreased gradually but still was significantly elevated 20 years later.

Several mechanisms may be involved in the increased risk of diabetes among smokers. First, cigarette smoking has been related to various systemic effects, including oxidative stress, systemic inflammation, and endothelial dysfunction, as reviewed by Yanbaeva et al. (12).

Each of these effects has been strongly implicated in insulin resistance (13) and diabetes risk (10,14,15). Second, even though smokers tend to have a lower mean BMI compared with nonsmokers, they have a more metabolically adverse fat distribution profile, with higher central adiposity (16). Finally, smoking could directly damage β-cell function (17) or induce chronic pancreatic inflammation (18). Those studies provide biological plausibility for a causal relation between smoking and diabetes.

There is fairly strong evidence supporting active smoking as a risk factor for type 2 diabetes. A recent meta-analysis (3) involving 25 prospective cohort studies reported a pooled adjusted RR of 1.44 (95% CI 1.31–1.58) for active smoking. However, our analysis, as well as previous studies (4,19), demonstrate that a large proportion of nonactive smokers (the reference group used in the recent meta-analysis [3]) may be exposed to passive smoke and that these participants are at increased risk of diabetes compared with individuals without any active or passive smoke exposure (5,6). Thus, the pooled RR of 1.44 reported in the meta-analysis may be a systematic underestimate of the true magnitude of the association, which is supported by our secondary analysis using all nonsmokers as the reference group (1.50 [1.35–1.66]). Furthermore, many of the studies included in the meta-analysis did not control for certain important lifestyle and dietary variables, such as alcohol intake and caffeine intake, which we and others have found to be important negative confounders in the association between smoking and risk of diabetes (20,21). The inability in the meta-analysis to account for these variables also would tend to produce an underestimate of the true association. That meta-analysis did not include main results from our cohort that showed a link between smoking and diabetes risk; these data, which were published nearly two decades ago (22), demonstrated an RR of type 2 diabetes among women who smoked ≥25 cigarettes per day compared with nonactive smokers of 1.49 (1.19–1.87) (22). Although women from that study also are included in the present analysis, we have expanded on the approach by taking passive smoke exposure into account, rigorously analyzing duration since quitting, adjusting for additional confounders, and also have 16 additional years of follow-up.

Several longitudinal studies investigated the association of smoking cessation on the risk of diabetes. Data from the Cancer Prevention Study suggested that quitting smoking reduced the rate of diabetes to that of nonsmokers after 5 years in women and after 10 years in men (23). Updated information of smoking status, lifestyle, and diet were not available in that study. Another study among middle-aged British men (24) indicated that starting from 5 years after smoking cessation, the risk of type 2 diabetes started to decrease compared with current smokers; however, the risk of diabetes was not equivalent to the risk among nonsmokers until 20 years after quitting (24). In our study, the risk of diabetes still was elevated 20 years after quitting, with an adjusted RR of 1.18 (95% CI 1.01–1.38). The same reasons for why the association between active smoking and diabetes were stronger in our analysis compared with the previous meta-analysis also may explain why a longer duration of quitting was required for risk equalization in our study compared with these previous two studies. Specifically, these two previous studies did not exclude passive smokers from the reference group and did not have information on all relevant confounders.

Our study has strengths and limitations that deserve mention. A major strength of this study, aside from its prospective nature and high follow-up rate, is the ability to control for various potential confounders and other known risk factors of diabetes. Confounding by time-varying covariates, especially lifestyle and dietary variables, is minimized by updating covariates every 2–4 years. Our study has limitations as well. For example, diabetes was self-reported. However, all of the participants were registered nurses, and self-reported diabetes was verified by a validated supplementary questionnaire (11). The possibility for residual confounding by unmeasured material and cultural factors, especially for the association between passive smoking and risk of diabetes, cannot be fully eliminated. In addition, our population was almost entirely white and exclusively female; thus, our results may not be generalizable to other populations. However, the relative homogeneity of the cohort in educational attainment and socioeconomic status actually may serve to enhance the internal validity of this study.

Another important limitation was the way in which we ascertained passive smoke exposure. First, we relied on self-reports of passive smoke exposure. Self-reports of exposure to passive smoke are

Table 2—*Smoking and risk of incident type 2 diabetes*

Variables	Nonsmokers			Current smokers		
	Reference*	Occasionally exposed to passive smoking	Regularly exposed to passive smoking	Past smokers	1–14 cigarettes per day	15–24 cigarettes per day	≥25 cigarettes per day
Person-years	98,156	276,208	191,074	609,811	90,945	97,884	55,186
Number of cases	259	887	756	2387	225	250	161
Age-adjusted RR	Reference	1.19 (1.04–1.37)	1.47 (1.27–1.69)	1.33 (1.17–1.51)	1.03 (0.86–1.23)	1.21 (1.02–1.44)	1.71 (1.40–2.08)
Age- and BMI-adjusted RR	Reference	1.09 (0.94–1.25)	1.17 (1.01–1.34)	1.15 (1.01–1.31)	1.27 (1.06–1.52)	1.49 (1.25–1.77)	1.81 (1.48–2.21)
Multivariable-adjusted RR†	Reference	1.10 (0.94–1.23)	1.16 (1.00–1.35)	1.28 (1.12–1.50)	1.39 (1.17–1.64)	1.68 (1.43–2.01)	1.98 (1.57–2.36)

Data are RR (95% CI). Participants who never provided information on exposure to passive smoke and active smoking were followed for 120,015 person-years with 467 incident cases of physician-diagnosed type 2 diabetes. *Participants who were consistent nonsmokers through June 2006 and who reported no exposure to passive smoke. †Adjusted for age, race, BMI (continuous BMI and quadratic BMI), physical activity, husband's education, family history of diabetes, total energy intake, and intake of alcohol, magnesium, calcium, vitamin D, total *trans* fat, fiber from cereal, caffeine, total fat, and saturated fat.

Table 3—*Active smoking, years since quitting of past smokers, and risk of incident type 2 diabetes*

Active smoking	Reference*	Cumulative quantity of active smoking (pack-years) 1–9	10–19	20–29	30–39	≥40
Person-years	98,56	265,386	166,200	130,001	108,726	164,809
Number of cases	259	795	519	394	431	804
Age-adjusted RR	Reference	1.13 (0.98–1.30)	1.18 (1.02–1.37)	1.19 (1.01–1.39)	1.51 (1.29–1.76)	1.60 (1.39–1.84)
Age- and BMI-adjusted RR	Reference	1.07 (0.93–1.23)	1.08 (0.92–1.25)	1.06 (0.90–1.24)	1.34 (1.15–1.57)	1.51 (1.31–1.74)
Multivariable-adjusted RR†	Reference	1.17 (1.01–1.35)	1.22 (1.06–1.40)	1.21 (1.04–1.41)	1.55 (1.30–1.83)	1.72 (1.48–1.98)

Yeas since quitting of past smokers	Reference*	Years since quitting (years) <5	5–9	10–19	20–29	≥30
Person-years	98,156	85,634	84,873	165,245	140,731	129,653
Number of cases	259	377	366	641	470	521
Age-adjusted RR	Reference	1.90 (1.62–2.22)	1.64 (1.40–1.92)	1.40 (1.21–1.62)	1.17 (1.01–1.37)	1.02 (0.88–1.18)
Age- and BMI-adjusted RR	Reference	1.65 (1.40–1.93)	1.32 (1.12–1.55)	1.14 (0.98–1.32)	1.03 (0.88–1.20)	0.96 (0.83–1.12)
Multivariable-adjusted RR†	Reference	1.88 (1.59–2.23)	1.50 (1.28–1.76)	1.29 (1.11–1.52)	1.15 (1.00–1.32)	1.06 (0.90–1.24)

Data are RR (95% CI). *Participants who were consistent nonsmokers through June 2006 and who reported no exposure to passive smoke. †Adjusted for age, race, BMI (continuous BMI and quadratic BMI), physical activity, husband's education, family history of diabetes, total energy intake, and intake of alcohol, magnesium, calcium, vitamin D, total *trans* fat, fiber from cereal, caffeine, total fat, and saturated fat.

only modestly correlated with biomarkers of tobacco-smoke exposure, such as serum cotinine (19,25). Part of the reason is the ubiquitous nature of passive smoke. A study of 663 subjects who never used tobacco and former tobacco users revealed that cotinine was found in the urine of 91% of participants, whereas only 76% reported exposure to passive smoke (19). Second, our assessment of passive smoke exposure was ascertained only at baseline in 1982, and it is likely that exposure to passive smoke changed over time because of individual factors (e.g., retirement) or societal factors (e.g., national interventions to reduce smoking). These two limitations would tend to result in misclassification, such that those women reporting little or no exposure in 1982 actually may have had important levels of exposure, whereas those reporting heavy exposure in 1982 may have had less exposure in the later years of follow-up. This type of misclassification would tend to produce weaker RR estimates than would hypothetically be observed in an ideal study. Therefore, we may have actually underestimated the true magnitude of the association between exposure to passive smoke and diabetes.

In conclusion, our prospective analysis suggests that smoking is strongly and independently associated with the risk of incident type 2 diabetes in a dose-dependent manner. Among former active smokers, the increased risk of diabetes persisted for 20 years after smoking cessation. Previous studies may have underestimated the magnitude and duration of the increased risk of diabetes associated with smoking.

Acknowledgments—This study was funded by the American Heart Association (Grant 0535401T), the National Institutes of Health (Grants CA-87969 and HL-079929), and the Beijing NOVA Program from the Beijing Municipal Science and Technology Commission. In addition, this work has been made possible through an International Society of Nephrology–Funded Fellowship (to L.Z.). The American Heart Association, the National Institutes of Health, the Beijing Municipal Science and Technology Commission, and the International Society of Nephrology had no role in the collection, management, analysis, or interpretation of data and had no role in the preparation, review, or approval of the manuscript.

No potential conflicts of interest relevant to this article were reported.

L.Z. wrote the manuscript and researched data. G.C.C. reviewed the manuscript and contributed to discussion. F.B.H. and E.B.R. contributed to discussion. J.P.F. researched data and reviewed the manuscript.

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