Development and Progression of Diabetic Retinopathy in Adolescents and Young Adults With Type 2 Diabetes: Results From the TODAY Study

TODAY Study Group*

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OBJECTIVE

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study reported a 13.9% prevalence of diabetic retinopathy (DR) in youth with mean ± SD type 2 diabetes duration of 4.9 ± 1.5 years. After 7 years of additional follow-up, we report the risk factors for progression of DR in the TODAY cohort.

RESEARCH DESIGN AND METHODS

Retinal photographs (n = 517) were obtained in 2010–2011 and again in 2017–2018 (n = 420) with standard stereoscopic seven-field digital fundus photography. Photographs were graded centrally using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. A total of 367 patients with gradable fundus photographs in at least one eye at both assessments were included in analyses of progression of DR, defined as an increase of three or more steps on the ETDRS scale.

RESULTS

With mean ± SD age of 25.4 ± 2.5 years and diabetes duration of 12.0 ± 1.5 years, there was a 49% prevalence of any DR among participants. Prevalence by DR stage was as follows: 39% for very mild or mild nonproliferative DR (NPDR), 6% moderate to severe NPDR, and 3.8% proliferative DR. Compared with nonprogressors, participants who progressed three or more steps had significantly lower BMI, higher HbA_{1c}, higher blood pressure, increased triglycerides, decreased C-peptide, and higher prevalence of other comorbidities. Multivariate analysis demonstrated that HbA_{1c} was the dominant factor impacting DR progression.

CONCLUSIONS

Poor glycemic control of youth-onset type 2 diabetes imparts a high risk for progression of DR, including advanced, sight-threatening disease by young adulthood.

Diabetic retinopathy (DR) remains the leading cause of blindness in working-age adults and the fifth most common cause of preventable blindness (1). Prevention of DR relies on effective management of hyperglycemia with the goals of attaining near-normal glycemia as soon as possible after diagnosis and continuing to achieve target range HbA_{1c} over time (2–4). Clinical trial data suggest that β-cell decline

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**Members of the TODAY Study Group Writing Committee are listed in the APPENDIX. A complete list of the TODAY Study Group members can be found in the supplementary material online.*

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See accompanying articles pp. 1038, 1046, 1056, 1065, and 1073.

occurs more rapidly and failure to achieve glycemic targets using oral agents is more common and occurs sooner in patients diagnosed with youth-onset type 2 diabetes compared with those with onset of type 2 diabetes later in life (5,6). The challenge of managing youth with type 2 diabetes effectively is compounded by the social and economic burdens of these youth, largely representing underserved, racial and ethnic minorities (7). Thus, physiology and socioeconomic barriers combine to place youth with type 2 diabetes at very high risk for rapid worsening of glycemic control and potentially more rapid progression of diabetes-related complications, including DR.

In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study and its follow-up observational study, TODAY2, participants were monitored with longitudinal assessments of diabetes management and DR progression from 2004 to 2020. Two rounds of standard stereoscopic seven-field digital fundus photography were performed in 2010–2011 and ∼7 years later in 2017–2018. Although with only a brief mean duration of diabetes at the time of the first fundus photography (mean of 4.9 years, range 2–8), TODAY participants had a 13.9% prevalence of DR (8). The TODAY/TODAY2 study investigators recently published the longitudinal prevalence of complications over a mean follow-up period of 10 years, reporting that the prevalence of all complications had risen and DR prevalence increased to 49% (9). With the DR prevalence rising markedly and the presence of sight-threatening lesions, understanding the modifiable risk factors driving progression of DR during the transition from youth to young adult with type 2 diabetes is critical to preserve vision long-term, which is essential to future physical functioning, financial employment opportunities, and overall quality of life. We now report the risk factors associated with DR progression in youth-onset type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Design

The study design and results of the TODAY study have previously been published (10,11). Briefly, a total of 699 participants enrolled in the TODAY clinical trial over the course of 4.5 years and were followed for 2.0–6.5 years. After the TODAY trial ended in 2011, 572 participants enrolled in the TODAY2 observational follow-up study. In the last year of TODAY (2010–2011), stereoscopic color fundus photographs were collected from 517 participants, with results previously reported (8). During the TODAY2 observational follow-up study, fundus photographs were collected in 2017–2018 from 423 participants. A subset of 367 participants had gradable photographs in at least one eye at both assessments.

Standard Seven-Field Fundus Exams

All photographs were graded centrally at the University of Wisconsin-Madison Fundus Photography Reading Center by graders masked to treatment, age, duration of diabetes, glycemic control, and other clinical characteristics, using the final Early Treatment Diabetic Retinopathy Study (ETDRS) grading scale (12). Retinopathy progression was defined as the occurrence of a 3-step or more progression in the ETDRS grading scale from the level of retinopathy at the end of TODAY to the repeat fundus photographs at follow-up, representing a reproducible measure of clinically important worsening as previously described (13,14). All outcomes are reported as participant-level retinopathy severity (i.e., severity of the eye with more advanced disease determines the specific retinopathy grade). Clinically significant macular edema (CSME) was graded with color fundus photography and categorized as absent, definite, questionable, or ungradable.

Grading Based on ETDRS Scale

In addition to the 3-step progression, a condensed numeric retinopathy score was assigned at the University of Wisconsin-Madison Fundus Photography Reading Center. The condensed grading is obtained by collapsing the patient-level ETDRS scale into 8 levels: 1 = "no definitive diabetic retinopathy," 2–3 = "very mild NPDR," 4–5 = "mild NPDR," 6–7 = "moderate NPDR," 8–9 = "moderately severe NPDR," 10–11 = "severe NPDR," 12–15 = "early or stable, treated PDR," and 16–23 = "high risk PDR," where NPDR is nonproliferative DR and PDR is proliferative DR.

Risk Factors

During the randomized trial phase of the TODAY study, participants were seen every 2 months for the first year after randomization and quarterly thereafter. During TODAY2 (2011–2020), participants were seen every 3 months for 3 years and annually for 6 years thereafter until the end of the study. Demographic, detailed medical history, self-reported medication usage, physical examination, and fasting laboratory studies were collected as previously described (9,11). Blood and spot urine samples were obtained after a 10- to 14-h overnight fast and processed and analyzed immediately at the TODAY central biochemistry laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, WA). Hypertension and indices of nephropathy (urine albumin-to-creatinine ratio [ACR] ≥30 mg/g, ACR ≥300 mg/g) were evaluated longitudinally (9). Participants self-reported cigarette smoking, categorized as either "yes" (used within the past month) or "no" (never used/not used within the past month).

Statistical Analyses

All participants with gradable fundus exams in at least one eye at both exams were included in the analysis. All descriptive data are presented as mean ± SD, median [IQR], or *n* (%). Cohort characteristics are presented at both baseline and the final follow-up fundus exam. The final follow-up exam characteristics are summarized using time-weighted means up to the time of the exam for continuous values, and time-dependent categorical characteristics (comorbidities, medication usage, and smoking) were considered present if they had been at or before the time of the follow-up fundus exam. The same approach is used to present baseline characteristics for the full TODAY cohort. The number and percentage of participants in each of the condensed ETDRS classifications are presented for the cohort with images at both occasions and for the cohort with images only at follow-up. Participants with images at both occasions were categorized based on whether they had progressed at least

3 steps based on the ETDRS classifications. Participant characteristics were compared between the two groups with use of the Fisher exact test for categorical variables and Student *t* test for continuous variables. Skewed variables were normalized by log-transformation prior to testing. Risk factors for at least a 3-step progression were analyzed using univariate and multivariate logistic regression. Age and any statistically significant ($P < 0.05$) risk factors from the univariate model were selected as variables for the multivariate analysis. Results for the risk factor analysis are presented as odds ratios and 95% CIs with associated *P* values for the logistic regression coefficients. Analyses were performed using R (version 4.0.2) and considered exploratory, with statistical significance defined as $P < 0.05$.

RESULTS

A total of 367 participants completed both assessments and were included in the subsequent risk factor analyses. At the time of the second assessment, participants were on average (mean ± SD) 25.4 ± 2.5 years of age with diabetes duration 12.0 ± 1.5 years, HbA_{1c} 7.9 ± 1.9%, and BMI 36.1 kg/m^2 (Table 1). Approximately 60% of participants had hypertension, 58% had moderate or severe albuminuria, and 30% had been treated with lipid-lowering medications (15) (Table 1). Baseline characteristics at the start of the TODAY study in 2004 among the 367 participants with repeat fundus examinations were similar to those of the original full TODAY cohort (Supplementary Table 1).

Table 1—Characteristics of participants with type 2 diabetes ($n = 367$) at time of first (TODAY) and second (TODAY2) fundus exam

Characteristic	TODAY (2010–2011)	TODAY2 (2017–2018)
Female sex	236 (64.3)	
Race/ethnicity		
Hispanic	146 (39.7)	
Non-Hispanic Black	126 (34.3)	
Non-Hispanic White	71 (19.3)	
Other	24 (6.5)	
Age (years)		
At baseline	13.7 ± 2.0	
At Fundus exam	18.4 ± 2.5	25.4 ± 2.5
Diabetes duration (years)	4.9 ± 1.5	12.0 ± 1.5
BMI (kg/m^2)	35.8 ± 8.0	36.1 ± 7.8
HbA_{1c} (%)	7.1 ± 1.7	7.9 ± 1.9
Blood pressure		
Systolic (mmHg)	115 ± 9.1	116.7 ± 8.9
Diastolic (mmHg)	68.4 ± 6.7	70.5 ± 6.8
Cholesterol		
LDL (mg/dL)	89.7 ± 23.9	94.8 ± 23.6
HDL (mg/dL)	40.9 ± 8.6	42.3 ± 9
Triglycerides (mg/dL)	103.7 [32.7, 748.6]	113 [36.0, 907.2]
Fasting C-peptide (ng/mL)	3.2 [0.7, 9.6]	2.9 [0.5, 10.1]
Fasting glucose (mg/dL)	129.7 [76.8, 249.8]	149.3 [80.4, 295.1]
Comorbidities (%)		
Hypertension	162 (44.1)	224 (61.0)
ACR ≥30 mg/g	74 (20.1)	166 (45.2)
ACR ≥300 mg/g	16 (4.4)	48 (13.1)
Medications		
History of any hypertensive medication	125 (34.0)	216 (58.8)
History of any lipid-lowering medication	47 (12.8)	118 (32.2)
Ever smoked	48 (12.8)	161 (43.8)

Data are means ± SD, median [IQR], or *n* (%).

Progression of DR and CSME

Among participants with repeated fundus photography, 315 (85.8%) participants had no signs of DR at the first exam with mean diabetes duration of 4.9 years, (Fig. 1 and Supplementary Table 2), and 52 (13.9%) participants had very mild NPDR (3). No participant had mild NPDR or worse. Seven years later, the percentage of participants with no retinopathy had decreased to 51% ($n = 187$). Among those who progressed, 5 (1.4%) had severe NPDR, 10 (2.7%) had early or stable treated PDR, and 4 (1%) had high risk PDR (Fig. 1 and Supplementary Table 2). CSME was not present in the original cohort. Seven years later, 14 participants (3.8%) had developed CSME affecting the center subfield (Fig. 1 and Supplementary Table 2).

Risk Factors for Progression of DR

Twenty-five percent ($n = 93$) of participants progressed ≥3 steps on the ETDRS scale (Table 2). Participants who progressed had significantly lower mean BMI and mean C-peptide as well as significantly higher mean HbA_{1c}, mean blood pressure, mean concentration of triglycerides, mean fasting glucose, and prevalence of comorbidities over the course of TODAY and TODAY2 (Table 2). In univariate analyses, a 1-unit increase in HbA_{1c} (e.g., from 7 to 8%) increased the probability of retinopathy progression by 2.3-fold. The presence of other comorbidities such as hypertension and kidney disease was associated with a two- to four-fold increased likelihood of retinopathy progression. Other factors associated with the probability of progression of retinopathy, in descending order of odds ratio, were diastolic blood pressure, fasting glucose, and mean triglycerides. A 5 kg/m^2 increase of BMI reduced the probability of progression by ∼18 ± 8% (Table 3) (all $P \leq 0.02$). Sex, HDL, and LDL were not significantly associated with retinopathy progression. In the multivariate analyses, only HbA_{1c} had a significant impact on the progression of DR (Table 3) ($P < 0.001$).

CONCLUSIONS

After ∼10 years of follow-up and an average diabetes duration of 12 years, nearly one-half of the TODAY study participants developed DR. In the 7 years between retinal assessments,

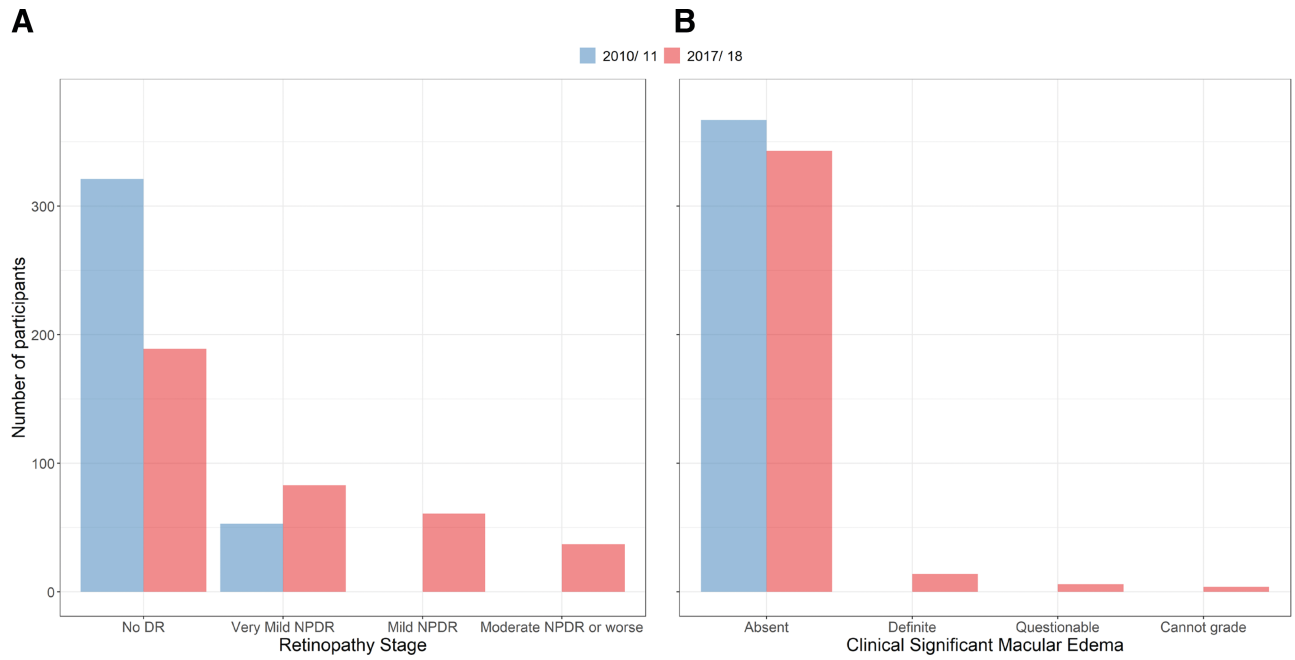

Figure 1—Results from the cohort ($N = 367$) with standard seven-field fundus exams during TODAY (2010–2011) and TODAY2 (2017–2018) for DR (*A*) and CSME (*B*).

participants progressed from at most very mild NPDR on initial assessment to more advanced stages of DR, including 5% of participants progressing to severe NPDR or PDR despite being, on average, only 25 years of age. CSME, not detected on the initial assessment, was present in 3.8% of participants on fundus photography 7 years later.

The prevalence rates of DR in younger patients with type 2 diabetes have been reported from other cross-sectional studies across various populations and have ranged from 4 to 37% (16–19). Notably, these studies included wide age ranges for diabetes diagnosis, spanned longer diabetes durations, and involved varied methods to detect DR. Our results rigorously confirm the presence of, and progression to, advanced retinal pathology over only 7–8 years in youth-onset type 2 diabetes. Of clinical concern, the prevalence of DR in our cohort is nearly twice the 28.5% prevalence reported for adults with type 2 diabetes aged 40 years and older with an average diabetes duration of 15 years as previously reported by National Health and Nutrition Examination Survey (NHANES) (20). Perhaps the elevated prevalence and accelerated progression of DR in youth-onset T2D or type 2 diabetes compared with adult-onset type 2 diabetes reflect the challenge of attaining and maintaining euglycemia in youth. The high rates of early treatment failure (i.e., defined as HbA_{1c} ≥8% for 6 months or sustained metabolic decompensation requiring insulin) observed in the TODAY trial suggested that youth were less responsive to oral therapies used and experienced a more rapid loss of endogenous insulin production by β-cells compared with adults (21).

Indeed, even with an average diabetes duration of only approximately one decade, those who experienced a 3-step progression or more in DR grading had many of the well-recognized risk factors for DR from studies of adults with diabetes: higher HbA_{1c}, blood pressure, and triglycerides as well as the presence of diabetic kidney disease (4,22). Not surprisingly, as in adults with short-duration type 2 diabetes, multivariate analyses identified glycemic control as the predominant risk factor for the development and progression of DR (23). Unlike in studies of adult-onset type 2 diabetes, however, males in our cohort were not more likely than females to experience progression of DR (19). As this cohort ages, one might hypothesize that hypertension and hyperlipidemia will play more significant roles, heralding concern for the proposed association of early retinal vascular changes with later cardiovascular disease risk (24). Future studies might include more detailed retinal vascular imaging to investigate the retina-heart connection in patients with youth-onset type 2 diabetes (25,26).

This is the first comprehensive report on the risk factors for progression of DR in youth-onset type 2 diabetes. The study strengths include the longitudinal study design and the systematic analysis of fundus photos performed by masked graders using the ETDRS scale in the TODAY/TODAY2 study. Although not all TODAY participants completed the two retinal assessments, the participants studied are a representative cohort, with no significant differences in clinical characteristics at TODAY baseline between those with repeat fundus examinations and the full TODAY cohort (Supplementary Table 1). Although the initial retinal assessment was performed early in the course of youth-onset type 2 diabetes, it is not a true baseline retinal assessment at the time of diabetes diagnosis. Yet, because only a minority of participants (13.9%) had developed retinopathy no more severe than very mild NPDR at the time of the initial assessment, this is a convincing baseline for analysis of further disease development and progression.

Table 2—Participant characteristics at follow-up fundus exam (2017–2018) by status of 3-step progression of retinopathy (*N* = 367)

	<3 steps progression*	≥3 steps progression*	*P*†
N	274	93	
Female sex	183 (66.7)	53 (56.9)	0.10
Race/ethnicity			0.17
Hispanic	107 (39.1)	39 (41.9)	
Non-Hispanic Black	89 (32.5)	37 (39.8)	
Non-Hispanic White	60 (21.9)	11 (11.8)	
Other	18 (6.5)	6 (6.5)	
Age (years)			
At baseline	13.7 ± 2.0	13.9 ± 2.1	0.31
At exam	25.3 ± 2.4	25.7 ± 2.6	0.18
Diabetes duration (years)	11.9 ± 1.5	12.1 ± 1.5	0.25
BMI (kg/m^2)	36.8 ± 8	34.6 ± 6.7	0.01
HbA_{1c} (%)	7.7 ± 1.9	10.3 ± 1.4	<0.0001
Blood pressure			
Systolic (mmHg)	116.5 ± 8.6	119.5 ± 9.9	0.01
Diastolic (mmHg)	70.4 ± 6.6	74.6 ± 7.4	<0.0001
Cholesterol			
HDL (mg/dL)	42.5 ± 9.3	42 ± 9.2	0.60
LDL (mg/dL)	94.6 ± 24.1	94.4 ± 21.4	0.93
Triglycerides (mg/dL)§	102.2 [38.3, 771.6]	128.5 [41.3, 1,211.2]	0.001
Fasting C-peptide (ng/mL)§	3 [0.5, 11.0]	2.5 [0.5, 6.8]	0.0004
Fasting glucose (mg/dL)§	129.7 [79.3, 286.7]	189.8 [87.2, 340.2]	<0.0001
Comorbidities			
Hypertension	154 (56.2)	70 (75.3)	0.001
ACR ≥30 mg/g	103 (37.6)	63 (67.7)	<0.0001
ACR ≥300 mg/g	21 (7.7)	27 (29.0)	<0.0001
Medications			
History of any hypertensive medication	151 (55.1)	65 (69.9)	0.01
History of any lipid-lowering medication	84 (30.7)	34 (36.5)	0.30
Ever smoked	39 (14.2)	9 (9.7)	0.72

Data are mean ± SD, median [IQR], or *n* (%) unless otherwise indicated. BP, blood pressure. †*P* values from Fisher exact test for categorical variables and Student *t* test for continuous variables. §Log-transformed for testing. *Based on original ETDRS scale on patient level (18 steps).

Given the accelerated decline of β-cell function documented among patients with youth-onset type 2 diabetes and the predominant role of glycemia in the progression of DR (19), screening and identification of at-risk youth with obesity who belong to historically marginalized populations for type 2 diabetes must occur routinely in clinical care and investigations to identify additional treatment options must continue. For youth with type 2 diabetes, aggressive management of glycemia from the time of diagnosis accompanied by the recommended annual screening exams for the development and progression of DR, with additional, more intensive monitoring as warranted by disease state, is critical to preserve vision into adulthood.

APPENDIX

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Table 3—Predictors of ≥3 steps progression of retinopathy based on logistic regression models ($N = 367$)

	Univariate analysis		Multivariate analysis	
Predictor	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Sex (male vs. female)	1.52 (0.94, 2.46)	0.09		
Race/ethnicity				
Non-Hispanic Black vs. Hispanic	1.14 (0.67, 1.94)	0.63		
Non-Hispanic White vs. Hispanic	0.50 (0.24, 1.05)	0.069		
Age (years)				
At baseline	1.06 (0.95, 1.20)	0.30		
At exam	1.07 (0.97, 1.18)	0.17	1.10 (0.96, 1.25)	0.17
Diabetes duration (per year)	1.10 (0.94,1.29)	0.24		
BMI (per 5 kg/m^2 increase)*	0.82 (0.69, 0.97)	0.02	0.83 (0.64, 1.07)	0.15
HbA_{1c} (per %)*	2.30 (1.90, 2.78)	<0.0001	1.93 (1.49, 2.50)	<0.0001
Blood pressure				
Diastolic (per 10 mmHg increase)*	2.31 (1.63, 3.27)	<0.0001	1.62 (0.78, 3.38)	0.20
Systolic (per 10 mmHg increase)*	1.44 (1.11, 1.87)	0.006	0.94 (0.52, 1.73)	0.85
Cholesterol				
Mean HDL (per 10 mg/dL increase)*	0.93 (0.72, 1.21)	0.60		
Mean LDL (per 10 mg/dL increase)*	1.00 (0.90, 1.10)	0.93		
Mean triglycerides (per 10 mg/dL increase)*	1.03 (1.01, 1.05)	0.0006	1.01 (0.99, 1.04)	0.20
Fasting C-peptide (ng/mL) *	0.69 (0.56, 0.85)	0.0004	0.92 (0.68, 1.25)	0.60
Fasting glucose (per 10 mg/dL increase) *	1.28 (1.21, 1.37)	<0.0001	1.06 (0.97, 1.15)	0.20
Comorbidities (%)				
Hypertension	1.89 (1.14, 3.13)	0.01		
ACR ≥30 mg/g	3.49 (2.12, 5.74)	<0.0001	1.09 (0.52, 2.30)	0.82
ACR ≥300 mg/g	4.93 (2.62, 9.27)	<0.0001	2.00 (0.80, 4.97)	0.14
Medications (%)				
History of any hypertensive medication	2.37 (1.40, 4.02)	0.001	0.75 (0.35, 1.64)	0.48
History of any lipid-lowering medication	1.30 (0.80, 2.14)	0.29		
Smoking (ever vs. never)*	0.90 (1.08, 1.85)	0.66		

*Based on cumulative exposure until follow-up Fundus exam.

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Author Contributions. R.G.K. wrote the manuscript. D.U. conducted the statistical analyses and wrote sections of the manuscript. I.L., K.L.D., B.A.B., L.L., L.L.L., M.M., S.M.W., N.H.W., and P.Z. wrote sections of the manuscript and reviewed and edited the manuscript. D.U. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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