Mortality in Type 1 Diabetes in the DCCT/EDIC Versus the General Population

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Historically, mortality in type 1 diabetes has exceeded that in the general population. We compared mortality in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study cohort to that of the current general U.S. population.

RESEARCH DESIGN AND METHODS

The DCCT (1983–1993) compared intensive versus conventional therapy, with HbA_{1c} levels of ~7 vs. 9%, respectively, over an average of 6.5 years of treatment. EDIC is the observational follow-up study of the DCCT (1994 to the present). Vital status was ascertained for 97.5% of the original DCCT cohort (*n* = 1,441) after a mean of 27 years follow-up. Expected mortality during DCCT/EDIC was estimated using the current age-, sex-, and race-specific risks in the general U.S. population, and the observed versus expected mortality compared using standardized mortality ratios (SMRs) and Poisson regression models.

RESULTS

Mortality in the DCCT intensive therapy group was nonsignificantly lower than that in the general U.S. population (SMR = 0.88 [95% CI 0.67, 1.16]), whereas mortality in the DCCT conventional therapy group was significantly greater than that in the general population (SMR = 1.31 [95% CI 1.05, 1.65]). The SMR increased with increasing mean HbA_{1c}, and above an HbA_{1c} of 9%, the rate of increase in SMR among females was greater than that among males.

CONCLUSIONS

Overall mortality in the combined DCCT/EDIC cohort was similar to that of the general population but was higher in the DCCT conventional therapy group. Mortality increased significantly with increasing mean HbA_{1c}, more so among females than males, especially for HbA_{1c} >9%.

In the preintensive treatment era, relative mortality in type 1 diabetes (T1D) exceeded that in the population without diabetes (1,2). Although substantial declines in mortality rates have been reported with improvements in glycemic control and better treatment of cardiovascular disease (CVD) risk factors (3–11), recent reports from Scotland (12) and Sweden (13) describe a greater excess mortality in T1D, even among those with a mean HbA_{1c} <7% (13).

Recently, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study demonstrated that intensive diabetes therapy in T1D during the DCCT yielded a 33% reduction in the risk of

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**A complete list of participants in the DCCT/EDIC Research Group is presented in the Supplementary Material published online for the article in N Engl J Med 2015;372:1722–1733. Members of the DCCT/EDIC Writing Group are presented in the APPENDIX.*

See accompanying article, p. 1309.

mortality, versus conventional diabetes therapy, over a 27-year period of follow-up (14). Herein we compare mortality during the DCCT/EDIC in the entire cohort to that in the general U.S. population using current (2013) U.S. age-, sex-, and race-specific mortality rates and assess relative mortality as a function of the level of HbA_{1c} and sex.

RESEARCH DESIGN AND METHODS

During 1983–1989, the DCCT enrolled 1,441 patients with T1D between the ages of 13 and 39 years who were randomly assigned to receive either intensive or conventional therapy. The primary objective of the DCCT was to assess the effects of intensive versus conventional therapy on the onset of retinopathy in a primary prevention cohort who entered with no retinopathy, and on the progression of retinopathy in a secondary intervention cohort who entered with preexisting mild to moderate nonproliferative retinopathy, each cohort comprising ~700 subjects. The primary prevention cohort also had 1–5 years diabetes duration and <40 mg albuminuria per 24 h. The secondary intervention cohort had 1–15 years duration and <200 mg albuminuria per 24 h.

In both cohorts, the mean age was 27 years with ~53% male. At baseline, those with a history of CVD, hypertension, or hypercholesterolemia were excluded (15).

The DCCT intensive therapy group was treated with insulin pumps or at least three daily insulin injections for an average of 6.5 years during which they maintained a mean HbA_{1c} of ~7%. Conversely, the DCCT conventional therapy group received then-standard care with a mean of HbA_{1c} of ~9% over the 6.5 years (15). The DCCT ended in 1993, at which time all patients were referred to their private health care providers with the recommendation that they follow an intensive regimen (16). Thereafter, 1,394 participants (representing 97% of the entire cohort) joined the EDIC observational study (1994 to present), with ongoing diabetes care provided by their local providers (16). Over the 21 years of follow-up in EDIC, the cohort maintained a mean HbA_{1c} of ~8%, with little difference between the DCCT intensive versus conventional therapy groups (17). The DCCT and EDIC protocols were approved by institutional review boards at all participating centers.

HbA_{1c} was measured quarterly during DCCT and annually in EDIC. The time-weighted mean HbA_{1c} represented the total glycemic exposure during DCCT/EDIC with weights of 0.25 and 1 for quarterly DCCT and annual EDIC values, respectively, up to the time immediately preceding the event or censoring for those without an event. The updated mean HbA_{1c} was then used as a time-dependent covariate in the regression model.

Analyses herein are based on 125 deaths that occurred up to 31 October 2014. Deaths, with documentation if available, were reported to the Data Coordinating Center and were adjudicated by a within-study Mortality and Morbidity Review Committee (14). There were 1,316 survivors, 1,241 of whom were under active follow-up whose observation time was right censored at 31 October 2014 and 75 of whom were inactive whose observation time was right censored at the date last known to be alive. Details of the ascertainment of outcomes and the verification of vital status were recently described (14).

The 2013 population life tables from the National Center for Health Statistics presented sex- and race-specific mortality risks in the general population for each year of age (18). The expected number of deaths in the DCCT cohort assuming these general population risks was calculated using the indirect method (19). For each subject of a given sex and race, the population probability of death over each year of age during DCCT/EDIC follow-up was applied. The sum of these probabilities for all subjects is the number of deaths in the DCCT/EDIC cohort that were expected had the current age-, sex-, and race-specific population risks been applied. The standardized mortality ratio (SMR) was computed as the ratio of the observed to expected number of deaths. All SMRs presented herein were computed in this manner.

Death rates per 100,000 person-years (PY) and 95% CIs were computed from robust Poisson regression models (20). Additional robust Poisson models using the PY method (21) assessed the effect of covariates, including the time-dependent updated mean HbA_{1c}, on the relative mortality rate (RMR) for DCCT/EDIC versus the general population, with offset terms that account for the expected mortality based on age, sex, and race. The RMR can be viewed as a covariate-adjusted estimate of the ratio of SMRs for two groups, or as the increase in the SMR per unit increase in a quantitative covariate. Semiparametric mortality risk gradients with respect to the time-dependent mean HbA_{1c} values are presented using plots from Poisson additive models with smoothing splines (df = 4) (22). Similar analyses were used to investigate whether the age- and sex-specific mortality rates in this cohort of participants with T1D differed from the general population.

All analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC) and the R package. Two-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

Characteristics of the DCCT/EDIC cohort used for these analyses were recently described (14). In brief, on entry, subjects had a mean age of 27 years (now 55 years) with 6 years duration of diabetes (now 34 years) and 48% were female. Those who subsequently died were older, had an older age at diabetes onset, and were more likely to be male, be smokers, and to have higher baseline blood pressure, triglycerides, and HbA_{1c} levels (13). Among 125 observed deaths, the primary underlying causes were CVD (n = 29, 23.2%) and cancer (n = 25, 20%), followed by T1D (n = 14, 11.2%), accident (n = 11, 8.8%), suicide (n = 8, 6.4%), renal disease (n = 7, 5.6%), and other (25, 20%), plus 2 pending adjudication and 4 nonadjudicable.

SMRs

Table 1 presents the SMRs comparing the mortality experience in the DCCT/EDIC cohort by treatment group, cohort, and sex, individually and jointly. The observed number of deaths, and the number expected when the population risks are applied to the cohort, the observed rate per 100,000 PY, and the SMR with its 95% CI are shown. During a total of 39,082 patient-years of follow-up in the DCCT/EDIC cohort, all-cause mortality was 320/100,000 PY (95% CI 269, 380). This overall mortality did not exceed that expected in the current U.S. population (SMR = 1.09 [95% CI 0.92, 1.30]) (Table 1).

Table 1 also shows that the mortality rate was lower in the DCCT intensive than

Table 1—DCCT/EDIC deaths and death rates by DCCT intensive versus conventional therapy group, primary versus secondary cohort, and sex, with SMRs relative to the U.S. population, along with RMRs comparing two SMRs

	Observed/expected*	Rate (95% CI)†	SMR (95% CI)‡	RMR (95% CI)§	*P*
Total (*n* = 1,441)	125/114	320 (269, 380)	1.09 (0.92, 1.30)		
Intensive (*n* = 711)	51/58	263 (200, 345)	0.88 (0.67, 1.16)	1.49 (1.04, 2.14)	0.028
Conventional (*n* = 730)	74/56	376 (301, 470)	1.31 (1.05, 1.65)		
Primary (*n* = 726)	61/54	315 (247, 404)	1.13 (0.88, 1.45)	0.95 (0.67, 1.35)	0.76
Secondary (*n* = 715)	64/60	324 (255, 412)	1.07 (0.83, 1.36)		
Females (*n* = 680)	47/39	252 (190, 333)	1.19 (0.90, 1.59)	0.87 (0.61, 1.26)	0.464
Males (*n* = 761)	78/75	382 (307, 475)	1.04 (0.83, 1.30)		
Treatment group by sex				Conventional vs. Intensive	
Females					
Intensive	21/21	220 (145, 335)	0.99 (0.64, 1.51)	1.46 (0.82, 2.59)	0.201
Conventional	26/18	284 (195, 415)	1.44 (0.98, 2.11)		
Males					
Intensive	30/37	304 (213, 434)	0.82 (0.57, 1.18)	1.54 (0.97, 2.43)	0.066
Conventional	48/38	456 (346, 600)	1.26 (0.95, 1.66)		
Treatment group by study cohort				Conventional vs. Intensive	
Primary					
Intensive	27/26	291 (200,422)	1.03 (0.70, 1.51)	1.17 (0.71, 1.95)	0.538
Conventional	34/28	338 (244,470)	1.21 (0.87, 1.69)		
Secondary					
Intensive	24/32	237 (160,353)	0.75 (0.50, 1.13)	1.88 (1.13, 3.12)	0.015
Conventional	40/28	415 (307,562)	1.42 (1.04, 1.93)		

*Number of deaths. †Rate per 100,000 PY with 95% CI from a Poisson regression model with robust information sandwich standard errors. ‡Expected number of deaths from the 2013 U.S. population life table for every year of age in the cohort and the SMR. §RMR obtained from an unadjusted Poisson model, each with 95% CI and *P* value (two sided).

conventional therapy group (263 vs. 376 per 100,000 PY). The SMR in the DCCT conventional therapy group was 49% higher than that in the intensive therapy group (RMR = 1.49, $P = 0.028$). Mortality in the DCCT intensive therapy group was lower than that in the general U.S. population, although not significantly so (SMR = 0.88 [95% CI 0.67, 1.16]), whereas mortality in the DCCT conventional therapy group was significantly greater than that in the general population (SMR = 1.31 [95% CI 1.05, 1.65], $P = 0.018$).

The RMR comparing the SMR of the secondary versus primary cohorts (1.07 vs. 1.13) was not significant (RMR = 0.95). Even though DCCT/EDIC males had a higher risk of mortality than females in a Cox proportional hazards model (HR = 1.61, $P = 0.02$) (see Orchard et al. [14]), the SMR for males was slightly less than that for females (1.04 vs. 1.19) and the RMR for males versus females was not significant (RMR = 0.87).

Among females alone, the SMRs in the DCCT conventional and intensive therapy groups (1.44 and 0.99, respectively) were similar to those in the overall cohort, as was the RMR (RMR = 1.46, $P = 0.201$). Among males, likewise, the SMRs in the two groups (1.26 and 0.82) were similar to those in the overall cohort, as was the RMR (RMR = 1.54, $P = 0.066$) (Table 1).

Within the primary cohort, the RMR comparing the SMRs in the DCCT conventional versus intensive therapy groups (1.21 vs. 1.03) was not significant (RMR = 1.17). Within the secondary cohort, the DCCT conventional therapy group SMR was nominally significant (SMR = 1.42 [95% CI 1.04, 1.93], $P = 0.027$) and was significantly higher than that in the DCCT intensive therapy group (SMR = 0.75), with an RMR = 1.88 ($P = 0.015$).

Role of HbA_{1c} and Sex

Glycemic exposure measured as the updated mean HbA_{1c} (time dependent) was significantly associated with mortality ($P < 0.0001$), with each 1% increase in the mean HbA_{1c} corresponding to a 74% increase (95% CI 53, 98) in the mortality rate relative to the age-, sex-, and race-specific rates in the general population. Figure 1 further describes this relationship by providing the mortality rates relative to the U.S. population over a range of HbA_{1c} values. The model assumes that the log of the RMR is a linear function of the HbA_{1c} that was largely verified by examining a spline-smoothed estimate of the relationship.

Figure 1 shows a largely flat relationship with a RMR <1 for periods of time with HbA_{1c} values $\leq 8\%$ but an exponential rise in the SMR for periods with HbA_{1c} values $>9\%$. Although only 7.8% of the mean HbA_{1c} values were $>10\%$ over the entire study period, 31 deaths (24.8%) occurred in subjects whose updated mean HbA_{1c} value was then $>10\%$.

In additional models adjusting for the time-dependent mean HbA_{1c} values, there was a significant interaction between sex and HbA_{1c} ($P = 0.016$), such that as the HbA_{1c} increased, the relative mortality among females was increasingly greater than that among males. RMRs compared with the age-, sex-, and race-specific rates are presented in Fig. 2 separately by sex over a range of HbA_{1c} values. For both males and females, the RMR is ≤ 1 for periods where the mean HbA_{1c} is $<9\%$, but the relative rate increases exponentially for values of HbA_{1c} $>9\%$, significantly more so among females. Age was not associated with the relative mortality of this cohort ($P = 0.42$), i.e., as mortality increased with increasing age, the SMR did not.

CONCLUSIONS

Relative to the age-, sex-, and race-specific mortality rates for the current general U.S. population, overall mortality in the DCCT/EDIC cohort was not significantly increased (SMR = 1.09 [95% CI 0.92, 1.3]). However, the relative

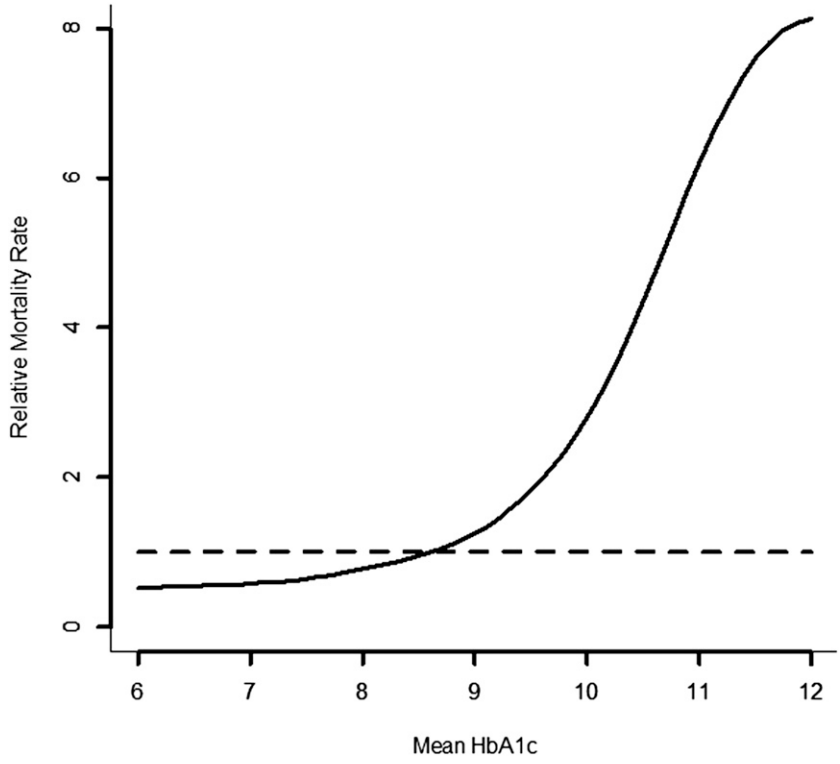

Figure 1—The RMR for the mortality in the combined DCCT/EDIC cohort relative to the age-, sex-, and race-specific risk in the general population as a function of the updated time-dependent mean HbA_{1c} during the DCCT and EDIC from a Poisson regression model. The horizontal dashed line at an RMR of 1.0 represents no difference in risk relative to the general population.

mortality in the DCCT intensive therapy group (SMR = 0.88) was nonsignificantly lower (i.e., neutral), whereas that in the DCCT conventional therapy group was significantly higher (SMR = 1.31 [95% CI 1.05, 1.65]) than in the general population. The RMR comparing the SMRs in the DCCT conventional versus intensive therapy groups was also significant (RMR = 1.49 [95% CI 1.04, 2.14], P = 0.028). The lower relative mortality in the DCCT intensive therapy compared with conventional therapy group is probably due to residual effects of the differential HbA_{1c} levels during the DCCT, also known as metabolic memory (14,17).

The increased relative mortality in the DCCT conventional versus intensive therapy group was also observed in the secondary intervention cohort (RMR = 1.88 [95% CI 1.13, 3.12], P = 0.0149). Within the primary prevention cohort, the SMR within either group was not significantly different from 1, and the groups did not differ (RMR = 1.17, P = 0.54).

Further, whereas mortality in the DCCT/EDIC was significantly higher in males than females, the SMR was similar for both sexes, reflecting the greater mortality among males than females in the general population.

Thus, in the DCCT/EDIC cohort with T1D, the excess mortality historically experienced in T1D appears to largely have been erased by intensive therapy. These findings may reflect the reduced occurrence of albuminuria (23). These findings are also consistent with the recent findings from the FinnDiane (24) and Pittsburgh Epidemiology of Diabetes Complications (EDC) (25) studies in which there was no excess mortality compared with the general population in the absence of micro- or greater albuminuria.

A recent report from Sweden (13), however, reported that an increased mortality risk still persists in T1D, even with glycemic levels at or near those recommended. However, the study collected limited data over only the most recent 8 years of diabetes duration, whereas the cohort had a mean diabetes duration over 20 years at baseline. Every patient had at least one HbA_{1c} measurement, but data on the density or completeness of the HbA_{1c} measurements that comprised their "time updated mean" HbA_{1c} were not provided. Considering the importance of early glycemic control, the conclusion that mortality was two- to threefold higher in patients with diabetes with an HbA_{1c} <7%, compared with the population without diabetes, merits qualification when viewed in a more complete historical perspective.

In contrast to the Swedish findings, the overall mortality rates in the DCCT/EDIC cohort were largely similar to the general population. However, increasing levels of HbA_{1c} were strongly associated with increasing mortality risk relative to the general U.S. population, and this was more so among females than males. In the full DCCT/EDIC cohort, a 10% higher HbA_{1c} (e.g., 8.8 vs. 8%) was associated with a 56% higher risk of mortality (14).

This relationship between the HbA_{1c} and mortality may represent confounding with other factors or an unhealthy nonadherer effect whereby patients with a very poor HbA_{1c} in both groups may be less adherent to other therapeutic suggestions such as nutrition, physical activity, smoking, and lipid and blood pressure medication adherence. Such confounding could be addressed in a multivariate model to assess the effect of HbA_{1c} on risk when adjusted for markers of adherence. However, EDIC has established a policy that such models will be embargoed until at least 100 subjects from the DCCT conventional therapy group have died, a number that provides adequate power to reliably detect risk factor effects in multivariate models.

There are a number of limitations to the current study. Our calculations used the 2013 SMR for the general U.S. population and likely underestimate the rates in the general population in prior years for the relevant follow-up period of 1983–2013. Although these results are consistent with the recent estimate that the life expectancy of childhood-onset diabetes now approaches that of the general population (11), they may not be applicable to the general population or directly comparable to other cohorts with T1D. For example, the DCCT/EDIC cohort has a relatively high socioeconomic status (26), with 55% being professionals on entry (Hollingshead index categories 1 and 2) (27), which might be expected to result in a relatively

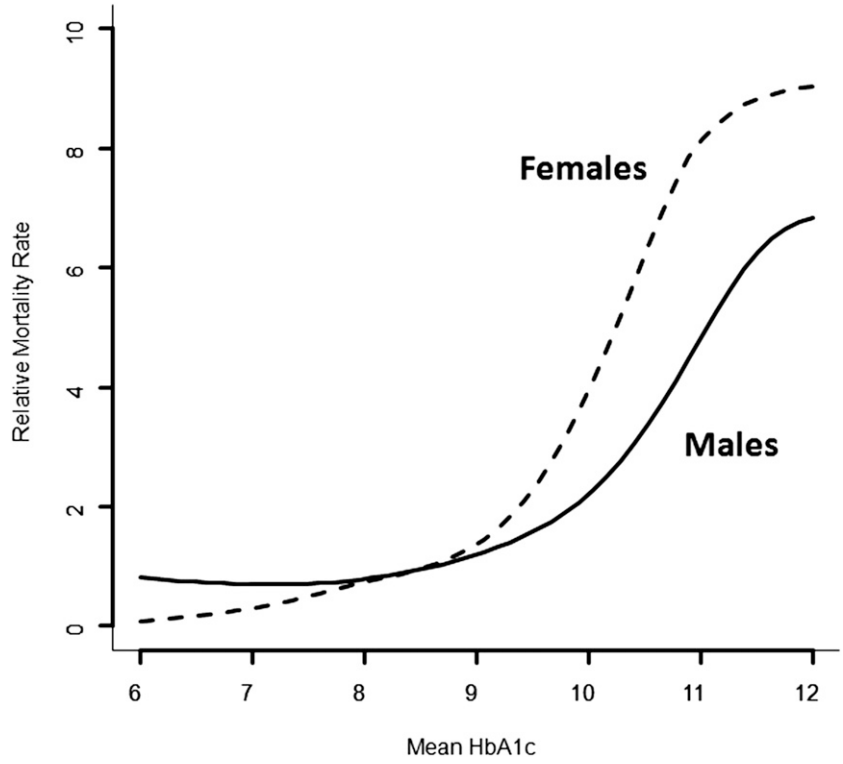

Figure 2—The RMR for the mortality in the combined DCCT/EDIC cohort relative to the age-, sex-, and race-specific risk in the general population as a function of the updated time-dependent mean HbA_{1c} during the DCCT and EDIC separately for males and females.

lower mortality than in the general population of people with T1D.

There are other important demographic differences between the DCCT/EDIC cohort and populations reported in past studies (4,9,28–30), such as the Allegheny County Registry study that followed children from the time of diabetes onset (9). On entry, DCCT subjects were 13–39 years of age with duration of diabetes 1–15 years. The mean age at the time of diagnosis (21 years) in this cohort is older than the usual mean age of onset and did not include the early mortality related to acute complications, such as hypoglycemia and diabetic ketoacidosis, during childhood (15). Additionally, the Allegheny Registry follow-up began in 1965, whereas the DCCT started in 1983. Furthermore, the DCCT selected participants with a high likelihood of compliance to the treatment protocol and excluded those with hypertension, severe dyslipidemia (15), or other serious comorbidities, thus reducing mortality risk. Interestingly, however, the DCCT conventional therapy group had a similar risk of diabetes complications to that of the Allegheny study (31), which indicates that the low mortality in DCCT/EDIC is not likely to be solely a reflection of the DCCT selection criteria.

In conclusion, the long-term follow-up of the DCCT/EDIC T1D cohort shows that the overall mortality in T1D is similar to that of the general population. However, mortality in the DCCT conventional therapy group is somewhat higher than that in the general population. Further, in the overall cohort, relative mortality increases with increasing HbA_{1c}, more prominently among females than males.

Appendix

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Author Contributions. J.M.L. conceived of and designed the study; acquired, analyzed, or interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; performed statistical analysis; and obtained funding. I.B. acquired, analyzed, or interpreted data and performed statistical analysis. D.M.N. conceived of and designed the study; acquired, analyzed, or interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; obtained funding; and supervised the study. B.Z. conceived of and designed the study; acquired, analyzed, or interpreted data; critically revised the manuscript for important intellectual content; obtained funding; provided administrative, technical, or material support; and supervised the study. D.B. conceived of and designed the study; acquired, analyzed, or interpreted data; drafted the manuscript; and critically revised the manuscript for important intellectual content. J.-Y.C.B. acquired, analyzed, or interpreted data; drafted the manuscript; performed statistical analysis; and provided administrative, technical, or material support. P.C. acquired, analyzed, or interpreted data; drafted the manuscript; performed statistical analysis; provided administrative, technical, or material support; and supervised the study. T.J.O. conceived of and designed the study; acquired, analyzed, or interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; performed statistical analysis; obtained funding; provided administrative, technical, or material support; and supervised the study. J.M.L. 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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