Longitudinal Association of Depressive Symptoms, Binge Eating, and Quality of Life With Cardiovascular Risk Factors in Young Adults With Youth-Onset Type 2 Diabetes: The TODAY2 Study

TODAY Study Group*

Diabetes Care 2022;45:1073–1081 | https://doi.org/10.2337/dc21-1995

OBJECTIVE

To report the prevalence of depression, eating disorder symptoms, and impaired health-related quality of life (HRQOL) and examine their longitudinal associations with glycemia and diabetes complications in young adults with youth-onset type 2 diabetes.

RESEARCH DESIGN AND METHODS

Participants recruited over a 4-year period were enrolled at 15 clinical diabetes centers in the follow-up observational Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY2) study. From 2014–2020, prevalence of symptoms of depression, eating disorders, and HRQOL by sex, race/ethnicity, and baseline family income were assessed annually. Longitudinal relationships between assessments of glycemia and complications with psychiatric symptoms and HRQOL were evaluated in adjusted models.

RESULTS

Participants (n = 514) were 21.7 ± 2.5 years old with a diabetes duration of 8.6 ± 1.5 years in year 1 of TODAY 2 (2014). Symptoms of depression and impaired HRQOL were common and increased significantly over 6 years (14.0% to 19.2%, P = 0.003; and 13.1% to 16.7%, P = 0.009, respectively). Depression and impaired HRQOL were more common in women and those with lower baseline family income but did not differ by race/ethnicity. Rates of binge eating were stable over time; self-reported purging increased. Over time, symptoms of depression were associated with higher HbA_{1c}, hypertension, and retinopathy progression; impaired HRQOL was associated with higher BMI, systolic blood pressure, hypertension, and retinopathy progression; and symptoms of eating disorders were associated with higher BMI.

CONCLUSIONS

Significant psychiatric symptoms and impaired HRQOL are common among emerging adults with youth-onset type 2 diabetes and are positively associated with glycemia, hypertension, and retinopathy progression in this group that is at ongoing risk for medical morbidity.

Corresponding author: Laure El ghormli, elghorml@bsc.gwu.edu

Received 24 September 2021 and accepted 16 February 2022

Clinical trial reg. no. NCT00081328, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.19196663.

**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.*

This article is part of a special article collection available at diabetesjournals.org/journals/collection/268/Serious-Later-Risks-Associated.

See accompanying articles pp. 1038, 1046, 1049, 1056, and 1065.

Rates of pediatric type 2 diabetes have increased significantly. A recent investigation reported an estimated prevalence of 0.34 per 1,000 youths in 2017, which represented a relative increase of 95.3% since 2001 (1). A growing body of literature has shown that pediatric type 2 diabetes is associated with high rates of comorbidities and complications in young adulthood (2,3) and led to the characterization of youth-onset type 2 diabetes as a severe phenotype (4). Symptoms of depression and eating disorders (particularly, regular binge eating [BE]) are common comorbidities among adults with type 2 diabetes that are negatively associated with health outcomes (5–7) and health-related quality of life (HRQOL) (8). Available evidence suggests that these symptoms and impairments in HRQOL also are common among youth with type 2 diabetes (9,10), but longitudinal studies that examine these over time and evaluate the relationship between these factors and other diabetes-related comorbidities or complications are lacking.

In the Treatment Options for Type 2 Diabetes in Adolescent and Youth (TODAY) study, a randomized controlled trial of treatments for recent-onset pediatric type 2 diabetes (mean age 14.0 years at study entry), 14.8% of participants self-reported clinically significant symptoms of depression, a rate similar to that observed in youth without diabetes (11). Although symptoms of depression were common in the TODAY cohort over the 2- to 6-year period of randomized intervention, there was no observed relationship between elevated symptoms and higher levels of glycemia, but depressive symptoms were associated with poorer HRQOL (12). BE was also common in the TODAY cohort, with 26% of participants self-reporting BE at baseline. BE was positively associated with obesity severity and depressive symptoms and impaired HRQOL (10).

The TODAY randomized treatment trial was followed by a 9-year-long observational follow-up period (TODAY2), during which participants no longer received randomized treatment but were seen by study staff from 2014–2020 for annual assessments, which included self-report evaluations of psychiatric symptoms and HRQOL. Protocolized assessments of comorbidities and complications were also conducted.

Thus, the carefully phenotyped TODAY cohort of youth-onset type 2 diabetes provided a unique opportunity to determine the association between depressive symptoms, indicators of eating disorders, and HRQOL with diabetes complications in emerging adults with type 2 diabetes. The primary aims for this study were to *1*) evaluate the prevalence of depressive and eating disorder symptoms and HRQOL overall, and within subgroups of sex, race/ethnicity, and baseline socioeconomic status over time, and *2*) examine the association between depressive symptoms, eating disorders, and HRQOL with glycemia and diabetes-related complications. Further, we explored whether any of the observed relationships differed by sex or race/ethnicity.

RESEARCH DESIGN AND METHODS

Study Design

The TODAY protocol (ClinicalTrials.gov NCT00081328) and primary outcome results have been published (2,13,14). In brief, 699 participants with type 2 diabetes diagnosed before the age of 18 years, with duration of diabetes <2 years, BMI >85th percentile for age and sex, negative islet cell antibodies, and C-peptide >0.6 ng/mL were randomized at 15 participating diabetes centers to receive metformin alone, metformin plus rosiglitazone, or metformin plus an intensive lifestyle intervention program. Exclusion criteria also included the presence of another significant condition, such as a major psychiatric or developmental disorder. The primary goal of TODAY (2004–2011) was to evaluate the effects of the three treatment arms on time to treatment failure, defined as loss of glycemia above the target range (HbA_{1c} $\geq$8% for 6 consecutive months or failure to wean from temporary insulin after acute metabolic decompensation).

In 2011, 572 TODAY participants (82%) enrolled in the TODAY2 postintervention follow-up study. Between 2011 and 2014, participants no longer received randomized treatment but continued to receive protocolized diabetes-related care from the TODAY study with visits at 3-month intervals. From 2014 to 2020, 518 TODAY participants (74% of original cohort) transitioned to community care and continued to be followed by the TODAY study group for annual observational visits.

Depression, eating disorders, and HRQOL questionnaires were completed annually during the TODAY2 period, from 2014 to 2020 (end of study). Owing to the staggered enrollment of participants in the TODAY randomized trial (2004–2009), the length of follow-up at the beginning of TODAY2 varied for each participant. For purposes of this study, data are presented by calendar year (year 1 to 6) for those participants who completed annual visits between 2014 and 2020. Data from 514 of the 518 TODAY participants were examined. Four consented TODAY2 participants who did not complete the assessment questionnaires were excluded.

The TODAY and TODAY2 studies met the Declaration of Helsinki guidelines and were approved by Institutional Review Boards at all 15 centers. All participants and guardians provided written informed assent and/or consent as appropriate for age and local guidelines.

Study Evaluations and Assessments

Demographic factors including sex, race/ethnicity, education, and household level of income ($\geq$\$50,000 per year or $<$\$50,000 per year) were collected at baseline of the TODAY randomized clinical trial (15). Baseline household income was selected as a proxy for financial strain over time; a significant number of participants reported no income at the end of TODAY2, so end-of-study average income was not included in the current analysis. Participants were seen annually during the last 6 years of the study in TODAY2 for physical examinations and other assessments. Height and weight were measured, and blood pressure was measured using a CAS 740 monitor with standardized oscillometric cuff sizes. Fasting laboratory data were collected at each study visit, as previously described (13). Measurements of fasting lipids and HbA_{1c} were processed centrally at the TODAY Central Biochemistry Laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, WA) (13). Standardized definitions were used for phenotyping throughout, with longitudinal assessments of hypertension, dyslipidemia, microalbuminuria, and neuropathy evaluated, as previously described (2). Fundus photography

was performed twice (2010–2011 and 2017–2018) and graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol by masked assessors at a centralized reading center (2). Retinopathy was defined as ETDRS grade ≥20 in either eye or clinically significant macular edema. A progression of three or more steps on the ETDRS scale was defined as retinopathy progression.

Beck Depression Inventory II

The Beck Depression Inventory II (BDI-II), a self-report measure with documented validity and reliability for adolescents and adults (16), was completed annually by participants to assess the severity of depressive symptoms. Responses to each of the 21 items on the inventory are rated on a 4-point scale ranging from 0 to 3 based on severity. Missing/incomplete responses were not scored and set to missing in the analyses (<3% of questionnaires). Individual items scores were combined to yield a total symptom score (maximum score: 63), with a higher score indicating more severe depressive symptoms. A cutoff score ≥14 on the BDI-II was used to indicate clinically significant levels of depressive symptoms (17).

Eating Disorder Diagnostic Scale

The Eating Disorder Diagnostic Scale (EDDS) is a self-report scale consisting of 23 items for assessing symptoms (e.g., recurrent BE or severe dietary restriction) and establishing diagnoses of anorexia nervosa, bulimia nervosa, and BE disorder (BED) based on the *Diagnostic and Statistical Manual*, Fifth Edition (American Psychiatric Association, 2013) criteria (18). The first three items of the scale assess the attitudinal symptoms of anorexia nervosa and bulimia nervosa over the past 3-month period (e.g., fear of fatness and overvaluation of weight and shape measured) on a 7-point scale, ranging from 0 (not at all) to 6 (extremely). The next three items measure the frequency of uncontrollable consumption of a large amount of food, with a focus on the number of times per month on average over the past 3 months. BE is defined as recurrent episodes (more than one per month) of overeating over the past 3 months with an associated loss of control. The subsequent items assess the frequency of compensatory behaviors during the past 3 months. Endorsements of self-induced vomiting and misuse of laxative or diuretic medications were included in the present analysis. Missing/incomplete responses were not scored and set to missing in the analyses (<5% of questionnaires). An overall eating disorder symptom composite score was computed by summing up the raw scores across all items. The presence of *Diagnostic and Statistical Manual*, Fifth Edition eating disorders (anorexia nervosa, bulimia nervosa, and BED) was determined by scoring algorithms for the EDDS (19).

HRQOL

Self-reported HRQOL was measured by total score on the 23-item Pediatric Quality of Life Inventory (Generic Core Scales Version 4.0) (20). Age-specific versions for teen (13–18 years), young adult (19–25 years), and adults (≥26 years) were used. The Pediatric Quality of Life Inventory can be grouped into four scales assessing participant: *1*) physical functioning (eight items), *2*) emotional functioning (five items), *3*) social functioning (five items), and *4*) school/work functioning (five items). A 5-point Likert response scale is used to assess problem severity during the past month (0 = never a problem, 4 = almost always a problem). Items were reverse-scored and linearly transformed to a 0–100 scale, so that higher scores indicated better HRQOL. The mean total score of a scale is calculated as the sum of all the items divided over the number of items answered (21). If >50% of the items in the scale were missing, scale scores were not computed (<1% of questionnaires had ≥50% missing responses). Clinically significant impairment in HRQOL was defined as a total score at least 1 SD below the mean score (<71.8) for the sample (11,21).

Statistical Analyses

Generalized estimating equations models were used to evaluate the effect of covariates on the odds of each binary outcome (e.g., BDI-II score ≥14), and linear mixed models were used to evaluate the effect of covariates on the mean of each quantitative outcome (e.g., BDI-II total score) over repeated time points. The original TODAY intervention condition was evaluated in the initial analysis but not retained in the models due to lack of effect.

Multivariable models evaluating the longitudinal associations between glycemia, blood pressure, and diabetes-related complications with the psychiatric symptoms and HRQOL outcomes were adjusted for age, duration diabetes duration, sex, race/ethnicity, BMI (except for the model involving BMI itself), and highest household level of income at TODAY baseline. Factors were entered in the models as fixed (e.g., sex, race/ethnicity, retinopathy) or as time-varying covariates (e.g., HbA_{1c}, systolic blood pressure [SBP], diastolic blood pressure [DBP]) as indicated). Time-weighted mean values for HbA_{1c}, SBP, DBP, and LDL cholesterol were used, representing the running means up to each study visit starting with TODAY baseline.

Interaction terms between the factors and complications with sex (e.g., HbA_{1c} by sex interaction) and race/ethnicity were added to the models to examine the potential modifying effects of sex or race/ethnicity. Descriptive analyses (using *t* test or χ^2) examined differences in the factors and complications by psychiatric symptoms and HRQOL outcome status (e.g., BDI-II ≥14 vs. BDI-II <14) at TODAY2 year 1 and 6. Analyses were done using SAS for Windows 9.4 software (SAS Institute, Cary, NC). All analyses were considered exploratory, and statistical significance was defined as $P < 0.05$.

RESULTS

Participants ($n = 514$) were racially/ethnically diverse, 65.2% were women, and there was a significant level of socioeconomic challenge (44.5% at TODAY baseline had annual household income <$50,000) (Table 1). At year 1 (2014), the average (± SD) participant age was 21.7 ± 2.5 years, diabetes duration was 8.6 ± 1.5 years, BMI was 36.5 ± 8.3 kg/m^2, and HbA_{1c} was 9.2% ± 3.1%.

Prevalence of Psychiatric Symptoms and HRQOL During TODAY2

Over the last 6 years of TODAY2, the prevalence of symptoms of depression (BDI-II score ≥14) increased significantly (12.6% at year 1 and 17.6% at year 6, $P = 0.01$) (Table 2). Reports of recurrent BE episodes (more than one per month over the past 3 months) did not significantly change over time (10.4% at year 1 and 12.8% at year 6, $P = 0.44$). Less than 2% (1.1% at year 1 and 1.9% at year 6) of participants met the criteria for bulimia nervosa or BED on the

Table 1—Participant characteristics at TODAY baseline and TODAY2 year 1 (2014)

Participant characteristics	Values (N = 514)
TODAY baseline/randomization	
Age (years)	13.8 ± 2.0
Type 2 diabetes duration (years)	0.7 ± 0.5
Female	65.2
Race/ethnicity	
Non-Hispanic Black	34.4
Hispanic	37.7
Non-Hispanic White	20.4
Other	7.4
Highest household level of education	
Less than high school	25.5
High school/GED	27.3
Some college, no degree	30.8
Graduate degree	16.4
Highest household level of income	
<$25,000	44.5
$25,000–$49,999	34.7
≥$50,000	20.8
TODAY2 year 1 (2014)	
Time in study since randomization (years)	7.9 ± 1.3 (6–10)
Age (years)	21.7 ± 2.5 (16–28)
Type 2 diabetes duration (years)	8.6 ± 1.5 (6–12)
BMI (kg/m^2)	36.5 ± 8.3
HbA_{1c} (%)	9.2 ± 3.1
SBP (mmHg)	118.5 ± 11.9
DBP (mmHg)	74.0 ± 10.1
LDL cholesterol (mg/dL)	97.0 ± 30.8

Data presented are mean ± SD (minimum–maximum) or percent.

EDDS at any TODAY2 study visit (there were no self-reported cases of anorexia nervosa at any assessment point). Reports of specific purging behaviors (self-induced vomiting and misuse of laxatives or diuretics) increased over time (3.6% at year 1 and 6.9% at year 6, $P = 0.02$). Although insulin underdosing or omission are not specified as compensatory behaviors on the EDDS, eating disorder symptoms did not vary as a function of the use of insulin as a diabetes medication. Self-reported impairments in HRQOL (score <71.8) increased significantly over the period of observation ($P = 0.009$), with prevalence increasing from 13.1% in year 1 to 16.7% in year 6. Similar findings were obtained when the continuous total and subscale scores were examined (vs. the binary cutoffs). The continuous total scores from all three instruments were significantly associated with each other during TODAY2 over all of the 6 years combined. Specifically, BDI-II total score was moderately positively correlated with the EDDS symptom composite score ($r = 0.49$, $P < 0.0001$) and strongly negatively correlated with the HRQOL total score ($r = -0.68$, $P < 0.0001$). The EDDS symptom composite score moderately negatively correlated with the HRQOL total score ($r = -0.49$, $P < 0.0001$).

Differences by Sex, Race/Ethnicity, and Family Socioeconomic Status

Higher prevalence of depressive symptoms and impaired HRQOL were found in women compared with men over time (all significant $P \leq 0.01$) (Fig. 1*A* and *C*). No race/ethnicity difference was observed for any of the psychiatric symptoms and HRQOL outcomes (data not shown). However, on average across the TODAY2 visits, lower prevalence of symptoms of depression and impaired HRQOL were reported among participants with the highest annual household income levels at TODAY (baseline ≥$50,000; $P = 0.002$) compared with those with lower annual income levels (<$50,000; $P = 0.003$) (Supplementary Fig. 1*A* and *C*) . Prevalence of BE did not differ by sex, or baseline household income (Fig. 1*B* and Supplementary Fig. 1*B*) and did not differ by baseline household level of education for any of the psychiatric symptoms and HRQOL outcomes (data not shown).

Longitudinal Associations With Glycemia, Blood Pressure, and Diabetes-Related Complications

Table 3 presents multivariable associations over time during TODAY2 in longitudinal models adjusted for age, duration of diabetes, sex, race/ethnicity, time-varying BMI, and highest household level of income at TODAY baseline. Supplementary Table 2 presents means and prevalence of the diabetes complications and related risk factors at year 1 (2014) and year 6 (2020), stratified by presence of symptoms of depression, BE, or impaired HRQOL. Higher HbA_{1c}, hypertension, and retinopathy progression were associated with clinically elevated symptoms of depression (BDI-II score ≥14) (Table 3) in multivariable longitudinal models. The odds of having symptoms of depression were increased by 9% (odds ratio [OR] 1.09, 95% CI 1.00–1.18) per 1% increase in HbA_{1c}, on average, from year 1 to year 6. The odds of having symptoms of depression increased by 46% in participants with hypertension versus those without (OR 1.46, 95% CI 1.02–2.08) and by 75% between participants with retinopathy progression versus those without (OR 1.75, 95% CI 1.16–2.64).

A 5-kg/m^2 increase in BMI was associated with 18% higher odds of BE after multivariable adjustment (OR 1.18, 95% CI 1.05–1.33) (Table 3). At year 6, participants with a higher mean BMI were more likely to report BE than those with a lower mean BMI (38.6 vs. 35.3 kg/m^2, $P = 0.01$).

On average during the last 6 years of TODAY2, higher BMI and SBP were respectively associated with 12% (OR 1.12, 95% CI 1.00–1.26 per 5 kg/m^2) and 28% (OR 1.28, 95% CI 1.02–1.60 per 10 mmHg) increases in the odds of having impaired HRQOL after multivariable adjustment, respectively (Table 3). At year 1, participants with a higher mean BMI were more likely to report impaired HRQOL than participants with a lower mean BMI (38.7 vs. 36.2 kg/m^2, $P = 0.03$). The odds of having impaired quality of life increased by 65% between participants with and without hypertension (OR 1.65, 95% CI 1.09–2.50) and by 80% between participants with and without retinopathy progression (OR 1.80, 95% CI 1.14–2.84) over time. A

Table 2—Psychiatric symptoms (symptoms of depression and eating disorder) and HRQOL measures by year of data collection in TODAY2

	TODAY2 Year (2014–2020)						
	Year 1 (*n* = 478)**	Year 2 (*n* = 472)	Year 3 (*n* = 467)	Year 4 (*n* = 465)	Year 5 (*n* = 450)	Year 6 (*n* = 452)	*P* value
A. BDI-II							
Total score	5.7 ± 7.4	5.8 ± 7.7	6.4 ± 8.4	6.0 ± 7.9	6.7 ± 8.7	6.8 ± 8.3	0.0003
Total score ≥14	12.6	12.9	16.6	15.2	17.4	17.6	0.01
B. EDDS†							
Symptom composite score	10.7 ± 11.6	11.0 ± 12.1	10.1 ± 12.1	9.8 ± 11.6	9.6 ± 10.8	10.8 ± 11.6	0.15
BE	10.4	11.5	12.3	11.8	11.0	12.8	0.44
Purging behavior	3.6	4.8	3.9	5.4	5.1	6.9	0.02
Diagnosable eating disorder (e.g., BED)	1.4	1.1	1.9	1.5	1.1	1.4	n/a
C. HRQOL							
Total score	87.3 ± 12.8	86.8 ± 13.4	86.3 ± 12.6	85.1 ± 12.2	84.2 ± 13.9	84.2 ± 12.7	<0.0001
Total score <71.8	13.1	12.3	14.6	15.2	17.6	16.7	0.009
Physical score	88.6 ± 14.7	87.3 ± 16.3	87.0 ± 15.0	85.7 ± 15.5	84.1 ± 17.1	83.9 ± 15.9	<0.0001
Psychosocial score‡	86.6 ± 13.9	86.5 ± 13.7	85.9 ± 13.5	84.9 ± 12.4	84.3 ± 14.2	84.3 ± 13.1	<0.0001

Data presented are mean ± SD or percent. n/a, not applicable (numbers too small for testing). **A total of 514 participants participated in TODAY2 and attended at least one of their yearly scheduled visit; however, not all participants attended their year 1 (*n* = 36) or year 2 (*n* = 42) visit, etc. †BE was defined as recurrent episodes (one or more per month) of overeating over the past 3 months with an associated loss of control; purging behavior includes self-induced vomiting and misuse of laxatives or diuretics. Diagnosable eating disorders on the EDDS include anorexia nervosa, bulimia nervosa, and BED. ‡Psychosocial score includes items from the emotional, social, and school/work scales. *P* value derived from linear mixed models for continuous outcomes or from generalized estimating equations models for binomial outcomes adjusted for age and duration of diabetes.

greater proportion of participants with hypertension at year 1 reported impaired quality of life compared with those without hypertension (69.3% vs. 53.3%, $P = 0.02$).

The observed relationships remained significant when analyzed within each subscale of the HRQOL (physical and psychosocial) instrument (data not shown). Randomized treatment group (data not shown), and LDL cholesterol, dyslipidemia, microalbuminuria, neuropathy, and retinopathy (Table 3) did not relate to any of the psychiatric symptoms and HRQOL outcomes. Finally, we examined whether the observed relationships varied by sex or race/ethnicity. We found that the relationship between BMI and BE significantly differed by sex (borderline interaction term $P = 0.05$), with the association observed in men (OR 1.40, $P = 0.003$) but not in women (OR 1.08, $P = 0.24$). None of the other relationships differed by sex or race/ethnicity.

CONCLUSIONS

This study adds to the literature on youth-onset type 2 diabetes by confirming that elevated rates of psychiatric symptoms and impaired HRQOL are common over an observation period of 6 years. Rates of elevated depressive symptoms and impaired quality of life increased over time, and rates of BE remained stable, but purging behaviors increased. Importantly, the current findings provide the strongest evidence to date that depressive symptoms are associated with higher HbA_{1c} over time. Moreover, depressive symptoms and HRQOL impairments were associated with hypertension and retinopathy progression. Although elucidation of the multifaceted array of factors associated with these findings is needed, the current results suggest that interventions that address psychiatric symptoms are needed to minimize distress and the impact of symptoms on self-care and health outcomes.

There is a large literature documenting a relationship between diabetes and depression in adults with diabetes (22,23), and consequently, annual screening for depression and appropriate referrals for mental health care are recommended for adults (24) to mitigate the effects of depression on health and well-being. Less is known about depression in youth-onset diabetes, and longitudinal data are limited. In the TODAY2 cohort, 12.6% of participants reported BDI-II scores ≥14 at year 1 of follow-up; prevalence increased significantly over time, with 17.6% of young adults reporting elevated symptoms at year 6. Cross-study comparisons are difficult because of methodological variability (e.g., assessment tools, sample characteristics, study design), but the rates of depressive symptoms observed in the TODAY cohort are consistent with those observed in other studies focusing on adolescents with diabetes. In SEARCH for Diabetes in Youth (SEARCH) (25), 14% of the sample (average age of 15 years) with type 1 or type 2 diabetes reported mild symptoms of depression, and 8.6% reported moderate/severe symptoms of depression, and these rates remained stable over time (9). The rate of depressive symptoms among youth (aged 10–17 years) with type 2 diabetes who participated in a pediatric diabetes registry (26) was 22%. Data from these studies (9,26) also suggest that rates of depressive symptoms were higher among youth with type 2 diabetes than those with type 1 diabetes. Data from the current investigation, when participants were young adults, showed that clinically significant rates of depressive symptoms increased over

Table 3—Longitudinal associations between elevated symptoms of depression, BE, and impaired HRQOL with glycemia, blood pressure, and diabetes-related complications*

	Elevated symptoms of depression (BDI-II score ≥14)		BE		Impaired quality of life (HRQOL score <71.8)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
BMI (per 5 kg/m^2)†	1.03 (0.93, 1.15)	0.57	**1.18 (1.05, 1.33)**	**0.004**	**1.12 (1.00, 1.26)**	**0.04**
Mean HbA_{1c} (per 1%)†	**1.09 (1.00, 1.18)**	**0.04**	0.91 (0.81, 1.02)	0.09	1.05 (0.96, 1.16)	0.29
Mean SBP (per 10 mmHg)†	1.17 (0.96, 1.44)	0.12	0.90 (0.65, 1.26)	0.54	**1.28 (1.02, 1.60)**	**0.03**
Mean DBP (per 10 mmHg)†	1.25 (0.99, 1.57)	0.06	0.89 (0.63, 1.27)	0.55	1.24 (0.94, 1.65)	0.12
Hypertension†	**1.46 (1.02, 2.08)**	**0.04**	0.92 (0.57, 1.48)	0.73	**1.65 (1.09, 2.50)**	**0.02**
Mean LDL (per 10 mg/dL)†	0.99 (0.92, 1.05)	0.68	0.98 (0.89, 1.08)	0.74	1.00 (0.93, 1.08)	0.97
Dyslipidemia†	0.80 (0.56, 1.14)	0.22	0.98 (0.61, 1.57)	0.94	0.84 (0.56, 1.26)	0.40
Microalbuminuria†	1.11 (0.80, 1.55)	0.54	1.02 (0.64, 1.61)	0.94	1.03 (0.71, 1.48)	0.89
Neuropathy†	1.23 (0.82, 1.84)	0.31	0.91 (0.56, 1.48)	0.72	1.30 (0.84, 2.00)	0.24
Retinopathy‡	1.34 (0.95, 1.91)	0.10	1.07 (0.67, 1.71)	0.78	1.09 (0.73, 1.61)	0.68
Retinopathy progression‡	**1.75 (1.16, 2.64)**	**0.007**	1.30 (0.70, 2.38)	0.40	**1.80 (1.14, 2.84)**	**0.01**

Bolded data are statistically significant ($P < 0.05$). *ORs, 95% CIs, and *P* values from generalized estimating equations models examining the longitudinal relationship between the binary outcomes and factors and complications during TODAY2. The generalized estimating equations models are adjusted for age, duration of diabetes, sex, race/ethnicity, time-varying BMI (except in the BMI model), and highest household level of income at TODAY baseline. †Time-varying covariates. Time-weighted mean values for HbA_{1c}, SBP, DBP, and LDL are used, representing the running means up to each visit starting since TODAY baseline. ‡Fixed covariates.

time, with rates increasing nearing 18% by 2020, when the mean age of participants was 27 years. The observed rate of depressive symptoms is similar to that reported for young adults (aged 18–29 years) without diabetes in the National Health Interview Survey (23). Nevertheless, data from the current study confirm that regular depression screening and intervention is indicated for youth as well as adults with diabetes.

We also examined potential differences in race/ethnicity and sex among individuals in the TODAY2 sample. Differences in race/ethnicity were not identified, but women, compared with men, reported higher levels of depressive symptoms, as has been observed in other studies of youth-onset type 2 diabetes (25). These findings are consistent with work on sex differences in depression, in general, which has shown that women are likelier than men to experience mild, moderate, and severe depressive symptoms (23).

Symptoms of disordered eating are common in adults with type 2 diabetes (27,28) and are associated with negative metabolic and psychological outcomes and impaired quality of life (29). Recurrent BE, the primary symptom of BED, was reported by 10.4% of TODAY2 participants, with stable rates over the period of observation. The rates of BE observed in the TODAY2 cohort are roughly comparable to those reported for young adults with overweight or obesity and no diabetes, with 7.3% in one study (30) study reporting BE. At year 6 of TODAY2, participants with BE had a mean ± SD BMI of 38.6 ± 8.5 kg/m^2 in comparison with participants without BE, who had an average BMI of 35.3 ± 7.9 kg/m^2, confirming a relationship between BE and obesity even in this group of young adults with severe obesity.

Purging in the form of self-induced vomiting or misuse of drugs and laxatives were common in the TODAY cohort and increased over time, with 3.2% of the cohort reporting self-induced vomiting and 4.2% reporting use of laxatives or prescribed medications to avoid weight gain at year 6. These rates are higher than the rate of 1% reported in a younger sample of college freshmen (31) who endorsed purging behaviors on a self-report questionnaire. Insulin misuse (underdosing or dose omission) is routinely assessed as a form of purging in youth with type 1 diabetes, but unfortunately, insulin misuse was not assessed in TODAY2. Future work is needed to examine the relation between insulin use and misuse with eating disorder symptoms in young adults with type 2 diabetes.

Prevalence of diagnosable eating disorders (e.g., BED) assessed by self-report ranged from 1.1 to 2% over the last 6 years of TODAY2. These rates are lower than those reported for youth with type 1 diabetes (7.0%) (32) or adults with type 2 diabetes (5.3–14%) (29,33). However, rates of diagnosable disorders observed in the TODAY2 cohort resemble those reported in a large group of young adults with overweight or obesity but without diabetes (2.1%) (30). Taken together, findings relating to symptoms of and diagnosable disorders in the TODAY2 cohort provide a strong argument that eating-disordered behaviors, including those that are specific to diabetes, should be assessed routinely and targeted for intervention in youth-onset type 2 diabetes.

Rates of impaired HRQOL increased over the course of TODAY2, with 16.7% of participants reporting impairments in physical and psychosocial subscale scores at year 6. Previous research, including the SEARCH study (34), has indicated that youth with type 2 diabetes have poorer HRQOL than those with type 1

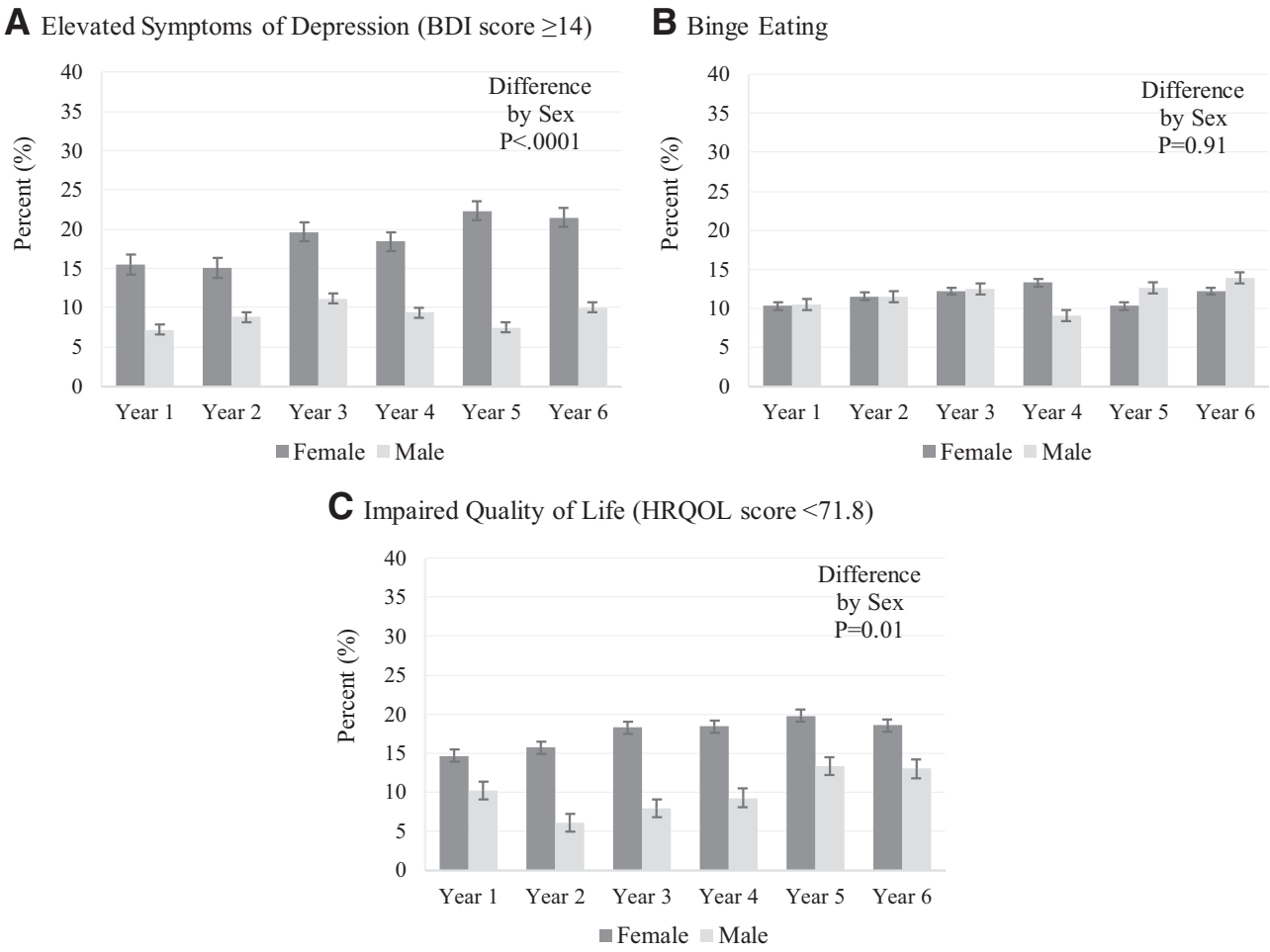

Figure 1—Percentage of participants with elevated symptoms of depression (*A*), BE (*B*), and impaired HRQOL (*C*) over time during TODAY2, by sex. *P* value from generalized estimating equations models testing for a sex difference over time, in models adjusted for age and duration of diabetes.

diabetes. Women, when compared with men, had poorer quality of life in SEARCH and TODAY2. The reasons women report poorer HRQOL are not known but may relate to psychosocial concerns (34).

Longitudinal analyses examining relations between psychiatric symptoms and quality of life with comorbidities and complications provided additional information. Specifically, the current study provides the strongest evidence to date that depressive symptoms are related to diabetes management. Previous evidence from adult studies has been inconsistent, with some studies (6,35,36), but not others (9,37–39), showing an association. Pediatric studies are limited, but like studies of adults, findings have been variable. The current findings document a relationship between HbA_{1c} and depressive symptoms in a carefully assessed cohort over a 6-year period of observation. Whether treatment of depression would improve levels of glycemia in this population, or conversely, whether achieving and maintaining target glycemic outcomes would be associated with decreases in depressive symptoms, is unknown.

Type 2 diabetes in youth represents a "severe phenotype" that is associated with the early onset of comorbidities and complications relative to adult-onset type 2 diabetes (4). In the TODAY2 cohort, participants had high rates of hypertension, dyslipidemia, and microalbuminuria, and by year 6, 60.1% of participants had developed at least one microvascular complication (2). Results of the current study indicated that depressive symptoms and impaired quality of life were associated only with hypertension and retinopathy progression. Complications such as neuropathy are more difficult to characterize over time, and the development of cardiovascular disease, the major cause of morbidity and mortality in diabetes, takes many years to become evident. Longer follow-up may be needed to understand the relationship of psychosocial factors and the development of complications among those youth-onset type 2 diabetes.

Other factors, such as poverty, environment, poor diet, and lower levels of physical activity, that were not assessed in TODAY2 have been implicated in the etiopathogenesis of depression, as well as glycemia levels outside the target range, and the development of complications in type 2 diabetes (22,40). The TODAY study group previously reported an association between lacking health care coverage and having higher HbA_{1c} (41). Although social determinants of health were not examined comprehensively in TODAY2, the findings suggesting a relationship between a proxy of financial strain and health in the current sample indicate that future work to

understand health inequities is of critical importance.

The strengths of the current study include the diverse longitudinal sample and the standardized assessment of cardiovascular risk factors and complications over time. It should be noted that the TODAY2 cohort may not be representative of the population of youth with type 2 diabetes. The lack of interview assessments to ascertain psychiatric symptoms and diagnosable disorders also is a limitation. Standardized self-report assessments were used to evaluate depressive and eating disorder symptoms and HRQOL, but misuse of insulin as a symptom of disordered eating was not included. Although physical activity and diet were collected in the parent TODAY study, the information was not obtained during TODAY2. For those reasons, we were unable to account for the effect of physical activity and diet in the analyses over time. Similarly, the use of TODAY baseline income as a proxy for financial strain and insufficient assessment of social determinants of health are significant drawbacks.

Taken together, the TODAY randomized trial (10,11) and the TODAY2 study have documented that elevated rates of depressive and eating disorder symptoms and impaired HRQOL are common, emerge early in the course of illness, and continue through young adulthood among individuals with youth-onset type 2 diabetes. Clinically significant psychiatric symptoms and impaired HRQOL among emerging adults with youth-onset type 2 diabetes are related to glycemia, hypertension, and retinopathy progression in this group that is at ongoing risk for medical morbidity.

APPENDIX

TODAY Study Group Writing Committee. Marsha D. Marcus (University of Pittsburgh School of Medicine, Pittsburgh, PA), Rachelle Gandica (Columbia University Irving Medical Center, New York, NY), Laure El ghormli (George Washington University Biostatistics Center, Rockville, MD), Janine Higgins (University of Colorado Anschutz Medical Campus, Aurora, CO), Bereket Tesfaldet (George Washington University Biostatistics Center, Rockville, MD), Dorit Koren (Massachusetts General Hospital, Boston, MA), Sarah Macleish (Case Western Reserve University, Cleveland, OH), Elia Nila Escaname (UT Health San Antonio, San Antonio, TX), and Ruth S. Weinstock (University of New York Upstate Model University, Syracuse, NY).

Acknowledgments. The authors gratefully acknowledge the participation and guidance of the American Indian partners associated with the clinical center located at the University of Oklahoma Health Sciences Center, including members of the Absentee Shawnee Tribe, Cherokee Nation, Chickasaw Nation, Choctaw Nation of Oklahoma, and Oklahoma City Area Indian Health Service.

The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the respective Tribes and the Indian Health Service.

Funding. This work was completed with funding from National Institute of Diabetes and Digestive and Kidney Diseases and the National Institutes of Health Office of the Director through grants U01-DK61212, U01-DK61230, U01-DK61239, U01-DK61242, and U01-DK61254.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The National Institute of Diabetes and Digestive and Kidney Diseases project office was involved in all aspects of the study, including design and conduct, collection, management, analysis, and interpretation of the data, review and approval of the manuscript, and decision to submit the manuscript for publication.

Duality of Interest. The TODAY Study Group thanks the following companies for donations in support of the study's efforts: Becton, Dickinson and Company, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, LifeScan, Inc., Pfizer, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. M.D.M. designed the study and wrote the manuscript. R.G. designed the study and contributed to data interpretation and writing. L.E. conducted the statistical analyses and contributed to data interpretation and writing. J.H., D.K., S.M., E.N.E., and R.S.W. contributed to study and manuscript design, data interpretation, and manuscript edits. B.T. conducted part of the analyses. L.E. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Lawrence JM, Divers J, Isom S, et al.; SEARCH for Diabetes in Youth Study Group. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001-2017. JAMA 2021;326:717–727

2. TODAY Study Group; Bjornstad P, Drews KL, Caprio S, et al. Long-term complications in youth-onset type 2 diabetes. N Engl J Med 2021;385:416–426

3. Jensen ET, Dabelea D. Type 2 diabetes in youth: new lessons from the SEARCH Study. Curr Diab Rep 2018;18:36

4. Viner R, White B, Christie D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. Lancet 2017;389:2252–2260

5. de Groot M, Golden SH, Wagner J. Psychological conditions in adults with diabetes. Am Psychol 2016;71:552–562

6. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000;23:934–942

7. Crow S, Kendall D, Praus B, Thuras P. Binge eating and other psychopathology in patients with type II diabetes mellitus. Int J Eat Disord 2001;30:222–226

8. Hart LM, Gordon AR, Sarda V, et al. The association of disordered eating with health-related quality of life in U.S. young adults and effect modification by gender. Qual Life Res 2020;29:1203–1215

9. Hood KK, Beavers DP, Yi-Frazier J, et al. Psychosocial burden and glycemic control during the first 6 years of diabetes: results from the SEARCH for Diabetes in Youth study. J Adolesc Health 2014;55:498–504

10. TODAY Study Group; Wilfley D, Berkowitz R, Goebel-Fabbri A, et al. Binge eating, mood, and quality of life in youth with type 2 diabetes: baseline data from the today study. Diabetes Care 2011;34:858–860

11. Anderson BJ, Edelstein S, Abramson NW, et al. Depressive symptoms and quality of life in adolescents with type 2 diabetes: baseline data from the TODAY study. Diabetes Care 2011;34:2205–2207

12. Van Buren DJ, Wilfley DE, Marcus MD, et al.; TODAY Study Group. Depressive symptoms and glycemic control in youth with type 2 diabetes participating in the TODAY clinical trial. Diabetes Res Clin Pract 2018;135:85–87

13. TODAY Study Group; Zeitler P, Epstein L, Grey M, et al. Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes. Pediatr Diabetes 2007;8:74–87

14. TODAY Study Group; Zeitler P, Hirst K, Pyle L, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012;366:2247–2256

15. Copeland KC, Zeitler P, Geffner M, et al.; TODAY Study Group. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. J Clin Endocrinol Metab 2011;96:159–167

16. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory-II*. San Antonio, TX, Psychological Corporation, 1996

17. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: twenty-five years of evaluation. Clin Psychol Rev 1988;8:77–100

18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, American Psychiatric Association, 2013

19. Stice E, Telch CF, Rizvi SL. Development and validation of the Eating Disorder Diagnostic Scale: a brief self-report measure of anorexia, bulimia, and binge-eating disorder. Psychol Assess 2000;12:123–131

20. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001; 39:800–812
21. Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. Health Qual Life Outcomes 2005;3:34
22. Holt RI, de Groot M, Lucki I, Hunter CM, Sartorius N, Golden SH. NIDDK international conference report on diabetes and depression: current understanding and future directions. Diabetes Care 2014;37:2067–2077
23. Villarroel MA, Terlizzi EP. Symptoms of depression among adults: United States, 2019. NCHS Data Brief 2020:1–8
24. Young-Hyman D, de Groot M, Hill-Briggs F, Gonzalez JS, Hood K, Peyrot M. Psychosocial care for people with diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2126–2140
25. Lawrence JM, Standiford DA, Loots B, et al.; SEARCH for Diabetes in Youth Study. Prevalence and correlates of depressed mood among youth with diabetes: the SEARCH for Diabetes in Youth study. Pediatrics 2006;117:1348–1358
26. Silverstein J, Cheng P, Ruedy KJ, et al.; Pediatric Diabetes Consortium. Depressive symptoms in youth with type 1 or type 2 diabetes: results of the Pediatric Diabetes Consortium Screening Assessment of Depression in Diabetes Study. Diabetes Care 2015;38:2341–2343
27. Meneghini LF, Spadola J, Florez H. Prevalence and associations of binge eating disorder in a multiethnic population with type 2 diabetes. Diabetes Care 2006;29:2760
28. Chevinsky JD, Wadden TA, Chao AM. Binge eating disorder in patients with type 2 diabetes: diagnostic and management challenges. Diabetes Metab Syndr Obes 2020;13:1117–1131
29. Nicolau J, Simó R, Sanchís P, et al. Eating disorders are frequent among type 2 diabetic patients and are associated with worse metabolic and psychological outcomes: results from a cross-sectional study in primary and secondary care settings. Acta Diabetol 2015; 52:1037–1044
30. Nagata JM, Garber AK, Tabler JL, Murray SB, Bibbins-Domingo K. Prevalence and correlates of disordered eating behaviors among young adults with overweight or obesity. J Gen Intern Med 2018;33:1337–1343
31. Serra R, Kiekens G, Vanderlinden J, et al. Binge eating and purging in first-year college students: prevalence, psychiatric comorbidity, and academic performance. Int J Eat Disord 2020;53:339–348
32. Young V, Eiser C, Johnson B, et al. Eating problems in adolescents with Type 1 diabetes: a systematic review with meta-analysis. Diabet Med 2013;30:189–198
33. Çelik S, Kayar Y, Önem Akçakaya R, et al. Correlation of binge eating disorder with level of depression and glycemic control in type 2 diabetes mellitus patients. Gen Hosp Psychiatry 2015;37:116–119
34. Naughton MJ, Yi-Frazier JP, Morgan TM, et al.; SEARCH for Diabetes in Youth Study Group. Longitudinal associations between sex, diabetes self-care, and health-related quality of life among youth with type 1 or type 2 diabetes mellitus. J Pediatr 2014;164:1376–83.e1
35. Lustman PJ, Griffith LS, Freedland KE, Kissel SS, Clouse RE. Cognitive behavior therapy for depression in type 2 diabetes mellitus: a randomized, controlled trial. Ann Intern Med 1998;129:613–621
36. Whitworth SR, Bruce DG, Starkstein SE, Davis WA, Davis TM, Bucks RS. Lifetime depression and anxiety increase prevalent psychological symptoms and worsen glycemic control in type 2 diabetes: the Fremantle Diabetes Study Phase II. Diabetes Res Clin Pract 2016;122:190–197
37. Indelicato L, Dauriz M, Santi L, et al. Psychological distress, self-efficacy and glycemic control in type 2 diabetes. Nutr Metab Cardiovasc Dis 2017;27:300–306
38. Pibernik-Okanović M, Roglić G, Prasek M, Metelko Z. War-induced prolonged stress and metabolic control in type 2 diabetic patients. Psychol Med 1993;23:645–651
39. Geringer ES, Perlmuter LC, Stern TA, Nathan DM. Depression and diabetic neuropathy: a complex relationship. J Geriatr Psychiatry Neurol 1988;1:11–15
40. Hill-Briggs F, Adler NE, Berkowitz SA, et al. Social Determinants of Health and Diabetes: A Scientific Review. Diabetes Care 2020;44: 258–279
41. TODAY Study Group. Health care coverage and glycemic control in young adults with youth-onset type 2 diabetes: results from the TODAY2 Study. Diabetes Care 2020;43:2469–2477