Physical Function in Middle-aged and Older Adults With Type 1 Diabetes: Long-term Follow-up of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

*Catherine L. Martin,[1] Victoria R. Trapani,[2] Jye-Yu C. Backlund,[2] Pearl Lee,[1] Barbara H. Braffett,[2] Ionut Bebu,[2] John M. Lachin,[2] Alan M. Jacobson,[3] Rose Gubitosi-Klug,[4] William H. Herman,[1,5] and the DCCT/EDIC Research Group**

Diabetes Care 2022;45:2037–2045 | https://doi.org/10.2337/dc21-2119

OBJECTIVE

To describe the prevalence and clinical correlates of functional limitations in middle-aged and older adults with long-standing type 1 diabetes.

RESEARCH DESIGN AND METHODS

Functional limitations were assessed for 1,094 participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a multicenter, longitudinal, observational follow-up of participants with type 1 diabetes randomly assigned to intensive or conventional diabetes therapy during the Diabetes Control and Complications Trial (DCCT). The primary outcome measure was a score <10 on the Short Physical Performance Battery (SPPB). The secondary outcome, self-reported functional limitation, was assessed by written questionnaire. Logistic regression models were used to assess associations of both outcomes with demographic and clinical factors (glycemic and nonglycemic factors, micro- and macrovascular complications, DCCT cohort, and treatment assignment).

RESULTS

Participants were 53% male, with mean ± SD age 59.5 ± 6.8 years and diabetes duration 37.9 ± 4.9 years. The prevalence of SPPB score <10 was 21%. The prevalence of self-reported functional limitations was 48%. While DCCT treatment assignment was not associated with physical function outcomes measured ∼25 years after the end of the DCCT, the time-weighted mean DCCT/EDIC HbA_{1c} was associated with both outcomes. Other clinical factors associated with both outcomes in multivariable analyses were BMI, general psychological distress, and cardiac autonomic neuropathy.

CONCLUSIONS

Almost half of the middle-aged and older adults with long-standing type 1 diabetes reported functional limitations, which were associated with higher HbA_{1c} and BMI, general psychological distress, and cardiac autonomic neuropathy. Future research is needed to determine whether these findings are generalizable.

[1]Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[2]Biostatistics Center, The George Washington University, Rockville, MD
[3]NYU Long Island School of Medicine, NYU Langone Hospital–Long Island, Mineola, NY
[4]Case Western Reserve University, Rainbow Babies and Children's Hospital, Cleveland, OH
[5]Department of Epidemiology, University of Michigan, Ann Arbor, MI

Corresponding author: Barbara H. Braffett, braffett@bsc.gwu.edu

Received 11 October 2021 and accepted 13 June 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.20198807.

**A complete list of members in the DCCT/EDIC Research Group is presented in the supplementary material.*

Functional limitations and disabilities associated with aging are more prevalent, occur earlier, and progress more rapidly in individuals with diabetes compared with those without diabetes (1–5). However, little is known about the burden of functional limitations in older adults with type 1 diabetes. While this knowledge gap is due in part to the shortened life span historically associated with type 1 diabetes (6), life expectancy for individuals with type 1 diabetes has increased and was recently shown to be only slightly shorter than that of the U.S. general population (7–9). As more people with type 1 diabetes survive to advanced ages, it is important to understand how type 1 diabetes may impact physical function.

The Diabetes Control and Complications Trial (DCCT) established the benefit of intensive therapy to delay the onset and slow the progression of microvascular and neuropathic complications in type 1 diabetes (10). In the long-term observational follow-up of the DCCT cohort, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, rates of diabetic retinopathy, kidney disease, neuropathy, cardiovascular disease (CVD), and mortality were lower in EDIC participants assigned to intensive therapy compared with those assigned to conventional therapy during DCCT, despite convergence of levels of glycemia during EDIC. This phenomenon is known as "metabolic memory" (11,12). The aims of this study were to *1*) examine the prevalence of functional limitations in the EDIC cohort, *2*) identify demographic and clinical factors associated with functional limitations, and *3*) determine whether the benefits of prior DCCT intensive therapy extend to measures of functional limitations. We hypothesized that hyperglycemia and the presence of diabetes-related complications would be associated with a greater prevalence of functional limitations.

RESEARCH DESIGN AND METHODS

Study Population

The DCCT and EDIC have previously been described (10,13–15). Briefly, between 1983 and 1987, the DCCT enrolled 1,441 individuals 13–39 years of age with type 1 diabetes and randomly assigned them to either intensive (N = 711) or conventional (N = 730) diabetes therapy. Intensive therapy was intended to achieve glucose levels as close to the nondiabetic range as safely possible using frequent self-monitoring of blood glucose to guide insulin doses administered via multiple daily injections or insulin infusion pumps. With conventional therapy the goal was to maintain clinical well-being using one to two daily injections of insulin without routine glucose monitoring. The primary prevention cohort (N = 726) had a diabetes duration of 1–5 years, no diabetic retinopathy, and urine albumin excretion rate (AER) $<$40 mg/24 h at baseline. The secondary intervention cohort (N = 715) had diabetes duration of 1–15 years, minimal to moderate nonproliferative diabetic retinopathy, and albumin excretion rate $<$200 mg/24 h at baseline. In 1993, the DCCT concluded, having demonstrated beneficial effects of intensive therapy on the development and progression of microvascular complications (10). Conventional therapy participants were taught intensive therapy, and diabetes clinical care was transitioned to community providers. In 1994, all surviving DCCT participants were invited to enroll in EDIC for assessment of the development and progression of and risk factors for more advanced diabetes complications including CVD, age-related morbidities, and survival (13).

The current study included 1,094 of 1,185 active EDIC participants (mean ± SD age 59.5 ± 6.8 years, diabetes duration 37.9 ± 4.9 years) and was conducted during the 25th through 26th years of EDIC follow-up (2018–2019) (14–16) (Supplementary Fig. 1). Institutional review boards at all 27 EDIC clinical centers approved the protocol. Written informed consent was obtained from all EDIC participants. EDIC staff were centrally trained and certified to conduct the assessments.

Assessment of Functional Limitations

The primary outcome was a Short Physical Performance Battery (SPPB) score $<$10 (16). The SPPB is an objective measure of lower-extremity mobility, and the SPPB score, ranging from 0 (worst) to 12 (best score), represents the sum of scores for each SPPB component (balance, gait speed, and repeated chair stands) (16). Lower SPPB scores are associated with worse physical function in older adults and SPPB scores $<$10, or reductions in scores over time, have been shown to predict falls, disability, and mortality (16–19). SPPB scores were excluded from the analysis for 56 EDIC participants from one clinical center due to incorrect administration of the 4-meter gait speed test.

The SPPB assessment and scoring were developed in a community-based cohort of nondisabled adults over the age of 70 years (16,17). In anticipation of possible ceiling effects in EDIC (78.1% of EDIC participants were $<$65 years of age), participants who successfully completed the SPPB balance measures were asked to attempt a more challenging 30-s unipedal stand test of balance (20). Up to three attempts to stand unaided on one foot for 30 s were permitted, and the test was scored as successful (held stance for 30 s) or not (held stance for $<$30 s).

The secondary outcome, presence of self-reported functional limitations, was assessed by written questionnaire with use of items from the National Health and Nutrition Examination Survey (NHANES) (21). Self-reported functional limitations were classified across five functional domains: activities of daily living (ADLs), instrumental activities of daily living (IADLs), leisure and social activities, lower-extremity mobility, and general physical function (21–24). A domain-specific functional limitation was considered present if a question for at least one item within the domain was answered as "some difficulty," "much difficulty," or "unable to do" and absent if the questions for all items in the domain were answered as "no difficulty". Responses of "do not do this activity," "prefer not to answer," and "don't know" were treated as missing.

Demographic and Clinical Factors Influencing Functional Limitations

Demographic and clinical factors expected to influence functional limitations among EDIC participants were selected a priori based on a literature review. Demographic factors were current age, sex, and level of formal education. Clinical factors (glycemic characteristics, nonglycemic characteristics, micro- and macrovascular complications, and study design characteristics) were measured using methods that have been previously described (10,13–15). Glycemic characteristics included diabetes duration, history of severe hypoglycemia (coma or seizure), and three measures of glycemia: the time-weighted mean DCCT/EDIC HbA_{1c} (weighted mean HbA_{1c} from DCCT baseline to EDIC year 25/26), mean EDIC HbA_{1c} (mean annual HbA_{1c} from the start of EDIC to follow-up year 25/26), and current HbA_{1c} level (EDIC year 25/26).

Nonglycemic characteristics were measured concurrently with functional limitation assessment and included heavy alcohol use (≥27 g/day), smoking status, BMI (kg/m^2, continuous and categorical), cognitive function, and psychological distress. Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) (25). Psychological distress (including depression) was defined according to Symptom Checklist-90-Revised Global Severity Index (GSI) score ≥63 (26). Micro- and macrovascular complications were assessed with standardized methods throughout DCCT and EDIC (10,13–15). Proliferative diabetic retinopathy was defined by neovascularization observed on centrally graded fundus photographs or self-reported and/or confirmed scatter photocoagulation at any time during DCCT/EDIC. Reduced estimated glomerular filtration rate (eGFR) was defined as a sustained eGFR <60 mL/min/1.73 m^2 (estimated with the Chronic Kidney Disease Epidemiology Collaboration equation) or chronic renal dialysis or transplant at any time during DCCT/EDIC. Diabetic peripheral neuropathy was defined as the presence of confirmed clinical neuropathy at the most recent full neurological assessment in EDIC year 13/14 (2006–2007). Cardiovascular autonomic neuropathy was defined according to R-R variation <15, R-R variation 15–19 plus Valsalva ratio ≤1.5, or a postural drop ≥10 mmHg in diastolic blood pressure at the most recent full autonomic neuropathy assessment in EDIC year 16/17 (2009–2010). Any nonfatal CVD included nonfatal myocardial infarction, stroke, angina, coronary revascularization, or congestive heart failure as reported by participants and supported by medical records and silent myocardial infarction identified on centrally evaluated electrocardiograms (obtained every other year during DCCT and annually during EDIC). All cardiovascular events were adjudicated and classified by the Mortality and Morbidity Review Committee (27). Study design characteristics, including DCCT treatment group (intensive vs. conventional) and DCCT study cohort (primary prevention vs. secondary intervention), were assessed to explore whether the effect of metabolic memory, observed for a number of outcomes during EDIC, might extend to measures of functional limitations (12).

Statistical Methods

Descriptive analyses were stratified by sex, as women typically bear a greater burden of functional limitations and disability and perform worse on objective measures of physical function than men (2,4,16,28,29). The Wilcoxon rank sum test (with continuity correction) was used to assess differences between women and men in quantitative measurements, and the χ^2 test (with Yates' continuity correction) was used to assess sex differences in categorical measurements.

The associations between clinical factors (glycemic, nonglycemic, micro- and macrovascular complications, and study design) and functional limitation outcomes were assessed with logistic regression models minimally adjusted for age, sex, and education level (graduate school, college graduate, some college or trade school, or secondary school graduate or less). A separate multivariable logistic regression model was developed for SPPB <10 and for self-reported functional limitations with use of a backward elimination procedure. Each model was subsequently tested with use of forward selection (30). The final multivariable model retained the selected covariates significant at $P < 0.05$. The odds ratios (ORs) and 95% CIs are presented.

In a sensitivity analysis we investigated the robustness of the results with respect to the 91 (7.7%) otherwise active EDIC participants with incomplete or absent functional limitation outcome measures (Supplementary Fig. 1). Individuals missing both the SPPB and questionnaire data for reasons given as "unwillingness to participate," "completion of tests unsafe," or "physical/clinical condition makes completion of test not possible" were assigned SPPB score <10 and self-reported functional limitations as "present." Those missing both SPPB and questionnaire data for any other reason were assigned SPPB score ≥10 and self-reported functional limitations as "absent." Individuals with partial data (either the SPPB or questionnaire was completed, but not both) were categorized according to their available (nonmissing) data. Specifically, if the SPPB was completed but not the questionnaire, those with SPPB score <10 were assigned "present" self-reported functional limitations, while those with SPPB score ≥10 were assigned "absent" self-reported functional limitations. Conversely, if the questionnaire but not the SPPB was completed, those with "present" self-reported functional limitation were assigned SPPB <10 and those with "absent" self-reported functional limitations were assigned SPPB ≥10.

Both *z* and *P* values are reported for logistic regression models to further clarify the relative strengths of the associations. The absolute value of the *z* test, which is the regression coefficient divided by its SE, indicates the strength of the association of each exposure with the outcome. Larger absolute *z* values indicate stronger associations resulting in smaller *P* values. Results nominally significant at $P < 0.05$ (two sided) are reported. All analyses were performed with SAS 9.4 and R statistical software.

Data and Resource Availability

Data collected for the DCCT/EDIC study through 30 June 2017 are available to the public through the NIDDK Central Repository (https://repository.niddk.nih.gov/studies/edic/). Data collected in the current cycle (July 2017–June 2022) will be available within 2 years after the end of the funding cycle.

RESULTS

Demographic and Clinical Characteristics

Characteristics of the 1,094 EDIC participants with stratification by sex are shown in Table 1. Men were slightly older than women (mean ± SD age 60.0 ± 6.4 vs. 59.0 ± 7.1 years, $P = 0.018$), but the proportions of men and women aged ≥65 years were similar. Sex differences were observed for heavy alcohol use, BMI categories, MoCA scores, current HbA_{1c}, and prevalence of peripheral neuropathy.

Prevalence of SPPB Score <10 and Unipedal Stand Test Results

Functional limitations as assessed based on SPPB score <10 were present in 217 (21.2%) of EDIC participants (Table 2). Unipedal balance was assessed in the 867 participants (84.6%) who successfully completed the SPPB balance measures, and of these, ∼30% were unable to successfully hold the unipedal stand for 30 s. No sex differences were observed for the prevalence of SPPB score <10, for any component of the SPPB (balance, gait speed, repeated chair stands), or for the unipedal stand test (Table 2).

Table 1—EDIC participant characteristics at the time of the physical function assessment (2018–2019)

	All	Women	Men	*P**
N	1,094	522	572	
Study design				
DCCT conventional treatment group	518 (47.3)	243 (46.6)	275 (48.1)	0.657
DCCT secondary intervention cohort	545 (49.8)	256 (49.0)	289 (50.5)	0.668
Demographics				
Age (years)	59.5 ± 6.8	59.0 ± 7.1	60.0 ± 6.4	0.018
Age <65 years	854 (78.1)	410 (78.5)	444 (77.6)	0.768
Education				0.450
Graduate school	276 (25.3)	130 (25.0)	146 (25.6)	
College graduate	415 (38.0)	190 (36.5)	225 (39.4)	
Some college or trade school	304 (27.8)	148 (28.4)	156 (27.3)	
Secondary school graduate or less	97 (8.9)	53 (10.2)	44 (7.7)	
Employment				0.088
Employed	760 (69.9)	353 (67.6)	407 (72.0)	
Retired	232 (21.3)	119 (22.8)	113 (20.0)	
Unemployed	44 (4.0)	28 (5.4)	16 (2.8)	
Disabled	51 (4.7)	22 (4.2)	29 (5.1)	
Nonglycemic characteristics				
Current smoker	91 (8.3)	35 (6.7)	56 (9.8)	0.083
Heavy alcohol use (≥27 g/day)	60 (5.5)	14 (2.7)	46 (8.1)	<0.001
BMI (kg/m^2)	29.2 ± 5.8	29.1 ± 6.4	29.4 ± 5.3	0.057
BMI category				0.001
Underweight	5 (0.5)	5 (1.0)	0 (0.0)	
Normal	263 (24.0)	147 (28.2)	116 (20.3)	
Overweight	403 (36.8)	173 (33.1)	230 (40.2)	
Obese	423 (38.7)	197 (37.7)	226 (39.5)	
Total MoCA score†	26.2 ± 2.6	26.5 ± 2.6	25.9 ± 2.6	<0.001
Psychological distress (GSI ≥63)	86 (8.1)	41 (8.2)	45 (8.0)	0.989
Glycemic characteristics				
Duration of type 1 diabetes (years)	37.9 ± 4.9	38.1 ± 5.0	37.8 ± 4.8	0.574
Time-weighted mean DCCT/EDIC HbA_{1c} (%)	7.9 ± 0.9	7.9 ± 0.9	7.9 ± 0.9	0.095
Time-weighted mean DCCT/EDIC HbA_{1c} (mmol/mol)	62.8 ± 9.8	63.3 ± 9.7	62.4 ± 9.8	0.095
EDIC HbA_{1c} (%)	7.9 ± 0.9	7.9 ± 0.9	7.8 ± 0.9	0.102
EDIC HbA_{1c} (mmol/mol)	62.6 ± 10.3	63.1 ± 10.4	62.1 ± 10.3	0.102
Current HbA_{1c} (%)	7.8 ± 1.2	7.9 ± 1.2	7.6 ± 1.1	<0.001
Current HbA_{1c} (mmol/mol)	61.2 ± 12.8	62.5 ± 12.9	60.0 ± 12.6	<0.001
Any severe hypoglycemia (≥1 vs. 0 cumulative events)‡	546 (50.5)	255 (49.3)	291 (51.6)	0.456
Micro- and macrovascular complications				
Any nonfatal CVD§	172 (15.7)	73 (14.0)	99 (17.3)	0.154
Any PDR	284 (26.0)	126 (24.1)	158 (27.6)	0.214
Any reduced eGFR	88 (8.1)	33 (6.3)	55 (9.6)	0.058
Diabetic peripheral neuropathy‖	277 (26.9)	102 (20.9)	175 (32.2)	<0.001
Cardiac autonomic neuropathy¶	374 (35.5)	182 (36.6)	192 (34.4)	0.493

Data are means ± SD or *n* (%). PDR, proliferative diabetic retinopathy. **P* values evaluate difference at $\alpha = 0.05$ level between the *N* = 522 female and *N* = 572 male participants. Pearson χ^2 test with Yates' continuity correction is used for binary and categorical variables, and Wilcoxon rank sum test with continuity correction is used for continuous variables. †MoCA was assessed in *N* = 1,049 active participants (*n* = 495 female, *n* = 554 male), and mild cognitive impairment was defined as a MoCA score ≤21. *n* = 58 participants scored ≤21. ‡Severe hypoglycemia was defined as events leading to coma or seizure documented by self-report for the 3-month period prior to each annual study visit. Cumulative refers to the running sum of all events. §CVD events were considered only if the event occurred before the physical function assessment. ‖Diabetic peripheral neuropathy was assessed in *N* = 1,031 participants (*n* = 487 female and *n* = 544 male). ¶Cardiac autonomic neuropathy was assessed in *N* = 1,055 participants (*n* = 497 female and *n* = 558 male).

Prevalence of Self-reported Functional Limitations

Self-reported functional limitations were reported by nearly half of participants (*N* = 522 [48.0%]). While the prevalence was higher among women than men, the difference was not significant (Table 2). General physical function domain limitations were reported by nearly all (*N* = 506 [96.9%]) participants with any self-reported functional limitations. Lower-extremity mobility limitations were reported by 218 participants (41.8%), IADL limitations by 190 (36.4%), ADL limitations by 176 (33.7%), and leisure and social limitations by 149 (28.5%). No sex differences were observed for the prevalence of self-reported functional limitations overall or for any domain.

Association of Demographic and Clinical Factors With SPPB Score <10 and Self-reported Functional Limitations

Table 3 presents two separate logistic regression models, minimally adjusted for age, sex, and education, evaluating the associations of clinical factors (study design, glycemic, and nonglycemic and micro- and macrovascular complications)

Table 2—Physical function outcomes by sex in EDIC participants

	All	Women	Men	*P*
N	1,025	492	533	
SPPB				
SPPB score (median [interquartile range])	11 [10, 12]	11 [10, 12]	11 [10, 12]	0.525
SPPB score <10	217 (21.2)	107 (21.7)	110 (20.6)	0.720
SPPB balance points earned (0–4)*				0.967
0	13 (1.3)	7 (1.4)	6 (1.1)	
1	26 (2.5)	13 (2.6)	13 (2.4)	
2	30 (2.9)	13 (2.6)	17 (3.2)	
3	89 (8.7)	44 (8.9)	45 (8.4)	
4	867 (84.6)	415 (84.3)	452 (84.8)	
SPPB gait speed points earned (0–4)*				0.053
0	8 (0.8)	4 (0.8)	4 (0.8)	
1	5 (0.5)	4 (0.8)	1 (0.2)	
2	24 (2.3)	14 (2.8)	10 (1.9)	
3	53 (5.2)	34 (6.9)	19 (3.6)	
4	935 (91.2)	436 (88.6)	499 (93.6)	
SPPB repeated chair stand points earned (0–4)*				0.488
0	48 (4.7)	27 (5.5)	21 (4.0)	
1	101 (9.9)	48 (9.9)	53 (10.0)	
2	190 (18.7)	83 (17.0)	107 (20.2)	
3	286 (28.1)	134 (27.5)	152 (28.7)	
4	391 (38.5)	195 (40.0)	196 (37.1)	
Held unipedal stand for 30 s*†	622 (71.7)	300 (72.3)	322 (70.2)	0.740
N	1,087	518	569	
Self-reported functional limitations				
Any self-reported functional limitation	522 (48.0)	264 (51.0)	258 (45.3)	0.064
Functional limitation domains‡				
IADLs	190 (36.4)	98 (37.1)	92 (35.7)	0.234
ADLs	176 (33.7)	86 (32.6)	90 (34.9)	0.726
Leisure and social limitation	149 (28.5)	76 (28.8)	73 (28.3)	0.378
General physical limitation	506 (96.9)	256 (97.0)	250 (96.9)	0.070
Lower-extremity mobility limitation	218 (41.8)	116 (43.9)	102 (39.5)	0.066

Data are *n* (%) unless otherwise indicated. **P* values compare point earned = 4 vs. <4 or unipedal stand held for 30 s vs. not held. †Percentages shown for unipedal stand are based on 867 participants (415 women, 452 men) with score of 4 on the SPPB balance measures. Unipedal stand was not performed for participants with SPPB balance score <4. ‡*n* = 522 of 1,087 EDIC participants reported at least one functional limitation in any domain. Domain-specific percentages are based on 522 participants (264 women, 258 men) reporting any functional limitation.

and SPPB score <10 (yes vs. no) and self-reported functional limitations (present vs. absent). Higher time-weighted mean DCCT/EDIC HbA_{1c} was most strongly associated with SPPB score <10 (*z* value = 5.73, OR 1.69 [95% CI 1.41, 2.02]; *P* value <0.001). All historical measures of severe hypoglycemia (≥1 vs. 0 cumulative events, 1–5 events vs. none, and >5 vs. none) were associated only with SPPB score <10. Cardiac autonomic neuropathy had the strongest association with self-reported functional limitations, (*z* value = 6.06, OR 2.43 [95% CI 1.82, 3.24]; *P* value <0.001). There was no significant association between DCCT treatment group and either outcome. DCCT cohort (secondary intervention vs. primary prevention) was associated with SPPB <10 (OR 1.83 [95% CI 1.34, 2.51]; *P* value <0.001) but not with self-reported functional limitations (OR 1.28 [95% CI 0.98, 1.66]; *P* value = 0.067).

Table 4 presents multivariable models predicting SPPB score <10 and self-reported functional limitations. Clinical factors associated with both outcomes were higher time-weighted mean DCCT/EDIC HbA_{1c}, higher BMI, psychological distress (GSI ≥63), and presence of cardiac autonomic neuropathy. Higher BMI was most strongly associated with SPPB score <10 (*z* value = 4.34), with each additional kg/m^2 unit of BMI associated with a 7% increased odds of SPPB score <10 (OR 1.07 [95% CI 1.04, 1.10]; *P* value <0.001). Psychological distress (GSI ≥63) had the strongest association with any self-reported functional limitations, with more than a fourfold increased odds of self-reported functional limitations (*z* value = 5.44, OR 5.57 [95% CI 3.00, 10.34]; *P* value <0.001). The odds of SPPB score <10 remained greater for the DCCT secondary intervention cohort than the primary prevention cohort in the multivariable model (OR 1.75 [95% CI 1.21, 2.52]; *P* value = 0.003).

Sensitivity Analysis

Supplementary Table 1 compares the characteristics of the 1,094 EDIC participants who completed the outcome assessments with those of the 91 EDIC participants who did not. Those who did not complete the assessments were more likely to have been assigned to DCCT conventional therapy and have higher mean HbA_{1c} levels during DCCT and EDIC, lower BMI, a greater prevalence of microvascular and cardiovascular complications and were more likely to report being unemployed due to disability. The prevalence of SPPB score <10 as imputed for those with missing or incomplete outcome data was proportionately similar to the prevalence among those who completed both measures, and the prevalence of self-reported functional limitations as imputed for those with missing or incomplete outcome data was higher among those who completed both measures. Incorporating the imputed values for the participants with incomplete or missing outcome data into the multivariable model did not affect the results of the multivariable analysis (data not shown).

CONCLUSIONS

In this cross-sectional study we examined the prevalence of and identified demographic and clinical factors associated with functional limitations in >1,000 middle-aged and older adults with long-standing type 1 diabetes. The primary functional limitation outcome was SPPB score <10, while any self-reported functional limitation was the secondary outcome. With logistic regression analyses we evaluated the association of clinical factors, assessed across 30 years of DCCT and EDIC evaluations, with SPPB score <10 and self-reported functional limitations.

SPPB score <10, indicating lower-extremity functional limitations, was present in approximately one-fifth of EDIC participants, with no difference by sex. A considerably higher prevalence of SPPB score <10 (43% of nondisabled 70-year-old men and nearly 60% of nondisabled 70 year old women) was reported in the

Table 3—Associations between clinical factors and SPPB score <10 and self-reported functional limitations, in separate logistic regression models adjusted for sex, age, and education

	SPPB score <10 (yes vs. no)				Self-reported functional limitation (present vs. absent)			
Clinical factors	OR	95% CI	*z*	*P*	OR	95% CI	*z*	*P*
Study design								
DCCT treatment group (conventional vs. intensive)	0.84	0.61, 1.14	–1.14	0.254	1.10	0.85, 1.43	0.72	0.472
DCCT cohort (secondary intervention vs. primary prevention)	1.83	1.34, 2.51	3.77	<0.001	1.28	0.98, 1.66	1.83	0.067
Glycemic characteristics								
Time-weighted mean DCCT/EDIC HbA_{1c} (per 1%)	1.69	1.41, 2.02	5.73	<0.001	1.47	1.26, 1.71	4.87	<0.001
Mean EDIC HbA_{1c} (per 1%)	1.63	1.38, 1.93	5.69	<0.001	1.41	1.22, 1.63	4.63	<0.001
Current HbA_{1c} (per 1%)	1.27	1.11, 1.44	3.53	<0.001	1.14	1.02, 1.28	2.26	0.024
Duration of type 1 diabetes (per 1 year)	1.05	1.01, 1.08	2.84	0.005	1.04	1.01, 1.06	2.53	0.011
Any severe hypoglycemia (≥1 vs. 0 cumulative events)*	1.80	1.31, 2.47	3.65	<0.001	1.24	0.96, 1.62	1.62	0.105
1–5 events vs. none	1.57	1.12, 2.20	2.64	0.0082	1.23	0.93, 1.62	1.45	0.148
>5 events vs. none	3.06	1.86, 5.03	4.39	<0.001	1.32	0.82, 2.10	1.14	0.253
Nonglycemic characteristics								
BMI (per 1 kg/m^2)	1.08	1.05, 1.1	5.53	<0.001	1.05	1.03, 1.08	4.34	<0.001
Total MoCA score (per 1 unit)†	0.89	0.84, 0.95	–3.69	<0.001	0.95	0.90, 1.00	–1.84	0.065
Psychological distress (GSI ≥63, yes vs. no)	3.93	2.4, 6.43	5.44	<0.001	6.07	3.36, 10.97	5.97	<0.001
Micro- and macrovascular complications								
Any nonfatal CVD (yes vs. no)‡	2.25	1.54, 3.28	4.19	<0.001	1.59	1.10, 2.29	2.46	0.014
Any PDR (yes vs. no)	2.40	1.73, 3.33	5.23	<0.001	1.63	1.21, 2.21	3.17	0.002
Any reduced eGFR (yes vs. no)	2.86	1.75, 4.66	4.20	<0.001	1.75	1.06, 2.88	2.18	0.029
Diabetic peripheral neuropathy (yes vs. no)§	2.65	1.89, 3.71	5.63	<0.001	2.17	1.59, 2.97	4.85	<0.001
Cardiac autonomic neuropathy (yes vs. no)‖	2.33	1.69, 3.21	5.15	<0.001	2.43	1.82, 3.24	6.06	<0.001

PDR, proliferative diabetic retinopathy. *Severe hypoglycemia was defined according to the cumulative number of events leading to coma or seizure documented by self-report for the 3-month period prior to each study visit. †MoCA was assessed in *N* = 1,049 active participants (*n* = 495 female, *n* = 554 male), and mild cognitive impairment was defined as a MoCA score ≤21. *n* = 58 participants scored ≤21. ‡CVD events were considered only if the event occurred before the physical function assessment. §Diabetic peripheral neuropathy was assessed in *N* = 1,031 participants (*n* = 487 female and *n* = 544 male). ‖Cardiac autonomic neuropathy was assessed in *N* = 1,055 participants (*n* = 497 female and *n* = 558 male).

Established Populations for Epidemiologic Studies of the Elderly (EPESE) study (16). More age-appropriate comparison groups were reported from a population-based study in Norway, where investigators found SPPB score <10 in 1% of men and 2% of women aged 40–59 years, 4% of men and 5% of women aged 60–69 years, and 7% of men and 15% of women aged 70–74 years. These rates are considerably lower than those observed in EDIC. In that study, it was further noted that while SPPB scores were generally lower in women than in men across all age groups, SPPB score <12 was uncommon in women younger than 65 years of age and in men younger than 70 years of age (28). Only 22% of EDIC participants were >65 years of age at the time of the study, suggesting the EDIC cohort is still too young for observation of a sex disparity for SPPB score <10.

Participants who successfully completed the SPPB balance tests attempted a more challenging 30-s unipedal stand test. Nearly 30% of participants attempting the unipedal stand test were unsuccessful. An inability to balance, unaided, on one leg for 30 s has been described as abnormal and shown to be a powerful predictor of falls in adults in their mid-60s (20).

The prevalence of self-reported functional limitations in EDIC was 48%. As with the SPPB, no difference was observed by sex. While this prevalence is lower than the 50%–77% prevalence reported by others using NHANES physical function data, those populations were nearly a decade older than the EDIC cohort (22–24). The prevalence of self-reported functional limitations among women (51.0%) and men (45.3%) in EDIC is similar to those reported in slightly older populations of non-Hispanic White women (54.2%, mean ± SD age 64.6 ± 0.1 years) and men (42.1%, age 63.0 ± 0.1 years) without diabetes and substantially lower than those reported for non-Hispanic White women (79.3%, age 67.0 ± 0.2 years) and non-Hispanic White men (66.9%, age 66.0 ± 0.1 years) with diabetes (31). The prevalence of domain-specific functional limitations appears higher in EDIC as compared with older adults without diabetes but lower when compared with older adults in the general population with diabetes (23). The hierarchy of self-reported functional limitations in EDIC (highest prevalence observed in the domain of general physical function, followed by lower-extremity mobility, IADL, and ADL, and lowest in the leisure and social activity domain) mirrors what has been reported by others (22,23).

Concurrent and longitudinal measures of HbA_{1c} and diabetes duration were associated with both functional limitation outcomes in separate logistic regression models. History of severe hypoglycemia was associated only with SPPB score <10. Higher time-weighted mean DCCT/EDIC HbA_{1c} was associated with SPPB score <10 and self-reported functional limitations, and longer diabetes duration was associated with self-reported functional limitations only. These findings support our hypothesis of an association between long-term poor glycemic control and functional limitations and are consistent with the

Table 4—Final multivariable models* for SPPB score <10 and self-reported functional limitations

	SPPB score <10 (yes vs. no)				Self-reported functional limitation (present vs. absent)			
Clinical factors	OR	95% CI	*z*	*P*	OR	95% CI	*z*	*P*
DCCT cohort (secondary intervention vs. primary prevention)	1.75	1.21, 2.52	2.99	0.003				
Time-weighted mean DCCT/EDIC HbA_{1c} (per 1%)	1.41	1.13, 1.77	3.07	0.002	1.28	1.07, 1.52	2.77	0.006
Duration of type 1 diabetes (per 1 year)					1.03	1.00, 1.07	2.20	0.028
Any severe hypoglycemia (≥1 vs. 0 cumulative events)†	1.79	1.25, 2.57	3.15	0.002				
BMI (per 1 kg/m^2)	1.07	1.04, 1.10	4.34	<0.001	1.05	1.02, 1.07	3.52	<0.001
Psychological distress (GSI ≥63, yes vs. no)	3.28	1.88, 5.71	4.19	<0.001	5.57	3.00, 10.34	5.44	<0.001
Total MoCA score (per 1 unit)‡	0.90	0.84, 0.97	–2.86	0.004				
Any nonfatal CVD (yes vs. no)§	1.67	1.07, 2.63	2.24	0.025				
Diabetic peripheral neuropathy (yes vs. no)‖	1.63	1.09, 2.45	2.36	0.018				
Cardiac autonomic neuropathy (yes vs. no)¶	1.67	1.15, 2.43	2.70	0.007	2.13	1.56, 2.91	4.78	<0.001

*Two separate multivariable models were obtained using a backward elimination and further adjusted for age, sex, and education. †Severe hypoglycemia was defined as the cumulative number of events leading to coma or seizure documented by self-report for the 3-month period prior to each study visit. ‡MoCA was assessed in *N* = 1,049 active participants (*n* = 495 female, *n* = 554 male), and mild cognitive impairment was defined as a MoCA score ≤21. *n* = 58 participants scored ≤21. §CVD events were considered only if the event occurred before the physical function assessment. ‖Diabetic peripheral neuropathy was assessed in *N* = 1,031 participants (*n* = 487 female and *n* = 544 male). ¶Cardiac autonomic neuropathy was assessed in *N* = 1,055 participants (*n* = 497 female and *n* = 558 male).

results of others who have noted associations between higher HbA_{1c} levels and/or longer duration of diabetes with functional limitations (1,4,5,23,32). To our knowledge, this is the first report of an association of a history of severe hypoglycemia with an objective measure of physical function.

Higher BMI, psychological distress as assessed by GSI ≥63, and lower total MoCA score were associated with both outcomes in separate logistic models. In multivariable analyses, higher BMI and GSI ≥63 were significantly associated with both SPPB score <10 and self-reported functional limitations, while lower MoCA scores were significantly associated with SPPB score <10. Obesity (BMI >30 kg/m^2), which was present in 38.7% of EDIC participants, is consistently recognized as a risk factor for functional limitations and has been shown to partially account for the excess risk of functional limitations associated with diabetes (4). Furthermore, obesity may promote or exacerbate other comorbidities, such as hypertension, heart disease, kidney disease, and arthritis, all of which may impact physical function (1,22,29,33,34). Our findings align with those of others who have reported associations of depression, anxiety, and cognitive impairment with functional outcomes (1,35–37).

The presence of micro- and macrovascular complications was associated with both outcomes in separate logistic regression models. In multivariable models, a history of nonfatal CVD, diabetic peripheral neuropathy, and cardiac autonomic neuropathy was associated with SPPB score <10. Cardiac autonomic neuropathy was also associated with self-reported functional limitations. Peripheral neuropathy has been identified by others as a risk factor for reduced physical performance, especially lower-extremity function, and for disability (1,38). This relationship is not surprising as diminished sensation, impaired proprioception, altered weight bearing, muscle wasting, and weakness may all adversely affect lower-extremity strength and balance. The association of cardiac autonomic neuropathy with the measured outcomes may reflect aberrant heart rate and blood pressure responses to postural changes and exercise. The association of severe hypoglycemia with SPPB score <10 may be further evidence of an association between autonomic dysfunction (hypoglycemia unawareness) and reduced physical function. The association of measures of autonomic dysfunction and functional limitations is a novel finding requiring confirmation.

DCCT cohort (secondary intervention vs. primary prevention) was associated with SPPB score <10 but not with self-reported functional limitations. The DCCT secondary intervention cohort was distinguished by their longer diabetes duration and observable (vs. absent) microvascular complications at DCCT randomization (10). DCCT cohort therefore may be a surrogate, albeit less robust, measure of diabetes duration. DCCT treatment group (intensive vs. conventional) was not associated with either outcome, suggesting that the effect of the 2% separation in HbA_{1c} between the intensive and conventional treatment groups during the DCCT has been overshadowed by essentially equivalent glucose control during 26 years of EDIC follow-up, consistent with the waning of metabolic memory over time (12). Indeed, within a few years of EDIC follow-up, the glycemic separation observed between the former intensive and conventional groups had vanished, and nearly equivalent levels of glycemia have been observed since (39).

The main strengths of this study are the well-characterized population of middle-aged and older adults with long-standing type 1 diabetes, the precise measures of diabetes duration and glucose control, excellent retention, and careful characterization of micro- and macrovascular complications over ~30 years of DCCT and EDIC follow-up. The potential

bias introduced by the 91 EDIC participants who did not complete the outcome assessments was addressed through sensitivity analysis. When we used imputed outcomes for these 91 participants, the results were unchanged (data not shown).

There are several limitations to this study, including the lack of an appropriate comparator population without diabetes. The EDIC cohort is still young relative to individuals usually included in studies of functional limitations. Further, the EDIC cohort is composed entirely of people with type 1 diabetes, thus limiting comparisons of differences in age, diabetes type, and diabetes duration to published reports of functional limitations. The EDIC cohort is racially and ethnically homogeneous (~95% non-Hispanic White) and is well educated (64% with college or advanced degrees) and thus not typical of the average population with type 1 diabetes, which limits the generalizability of our findings. As such, results from EDIC participants may reflect higher physical functioning than the average population with type 1 diabetes. Additional studies should be conducted in other populations with type 1 diabetes to validate these findings. The primary outcome measure, SPPB <10, may not be sufficiently sensitive given the relatively young age of the EDIC cohort. The questionnaire used includes questions about limitations due to "any long-term physical, mental or emotional problem or illness" and is not specific with regard to diabetes and its complications. We did not consider the effect of nondiabetes-related comorbidities or the number of comorbidities, as has been done by others (22,23). For these reasons, our findings must be interpreted cautiously. Still, this study provides an important foundation for longitudinal assessments addressing the interactions of aging and type 1 diabetes.

Conclusion

In this cross-sectional study we leveraged phenotypic data collected over >30 years of follow-up from the DCCT/EDIC study to identify factors associated with functional limitations in >1,000 middle-aged and older adults with long-standing type 1 diabetes. While many of the clinical factors associated with functional limitations are consistent with findings from other studies, including glycemia, BMI, psychological and cognitive function, peripheral neuropathy, and CVD, novel findings from this study include an association of severe hypoglycemia and cardiac autonomic neuropathy with measures of functional limitations. These findings suggest that glucose control, body weight, and mental health could all be targets for risk reduction strategies.

To our knowledge, this is the first study to examine functional limitations in an exclusively type 1 diabetes cohort, providing the necessary foundation for ongoing and planned longitudinal studies of risk factors and predictors of incident disability, frailty, falls, and fractures. This work should guide future studies in evaluating older subjects in different contexts and with varying life histories to fully understand how type 1 diabetes affects physical functioning. The findings from this and future studies may inform strategies aimed at reducing the burden and consequences of functional limitations in individuals aging with type 1 diabetes.

Funding. DCCT/EDIC (clinical trial reg. nos. NCT00360815 and NCT00360893, ClinicalTrials.gov) has been supported by cooperative agreement grants (1982–1993, 2012–2017, 2017–2022) and contracts (1982–2012) with the Division of Diabetes Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (current grant nos. U01 DK094176 and U01 DK094157) and by the National Eye Institute, the National Institute of Neurologic Disorders and Stroke, the General Clinical Research Centers program (1993–2007), and Clinical and Translational Science Center program (2006–present), Bethesda, MD. Industry contributors have provided free or discounted supplies or equipment to support participants' adherence to the study: Abbott Diabetes Care (Alameda, CA), Animas (Westchester, PA), Bayer Diabetes Care (North America Headquarters, Tarrytown, NY), Becton, Dickinson and Company (Franklin Lakes, NJ), Eli Lilly (Indianapolis, IN), Extend Nutrition (St. Louis, MO), Insulet Corporation (Bedford, MA), LifeScan (Milpitas, CA), Medtronic Diabetes (Minneapolis, MN), Nipro Home Diagnostics (Ft. Lauderdale, FL), Nova Diabetes Care (Billerica, MA), OMRON (Shelton, CT), Perrigo Diabetes Care (Allegan, MI), Roche Diabetes Care (Indianapolis, IN), and Sanofi (Bridgewater, NJ).

The sponsor of this study is represented by the NIDDK Project Scientist who serves as part of the DCCT/EDIC Research Group and plays a part in the study design and conduct as well as the review and approval of manuscripts. The NIDDK Project Scientist was not a member of the writing group of this paper. The opinions expressed are those of the investigators and do not necessarily reflect the views of the funding agencies.

Industry contributors have had no role in the DCCT/EDIC study.

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

Author Contributions. C.L.M., V.R.T., and J.-Y.C.B. wrote the manuscript. V.R.T. and J.-Y.C.B. conducted the statistical analyses. C.L.M., V.R.T., J.-Y.C.B., P.L., B.H.B., I.B., J.M.L., A.M.J., R.G.-K., and W.H.H. wrote sections of the manuscript and reviewed and edited the manuscript. B.H.B. 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.

References

1. de Rekeneire N, Volpato S. Physical function and disability in older adults with diabetes. Clin Geriatr Med 2015;31:51–65, viii [viii]
2. Ryerson B, Tierney EF, Thompson TJ, et al. Excess physical limitations among adults with diabetes in the U.S. population, 1997-1999. Diabetes Care 2003;26:206–210
3. Wong E, Backholer K, Gearon E, et al. Diabetes and risk of physical disability in adults: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2013;1:106–114
4. Gregg EW, Beckles GL, Williamson DF, et al. Diabetes and physical disability among older U.S. adults. Diabetes Care 2000;23:1272–1277
5. Volpato S, Ferrucci L, Blaum C, et al. Progression of lower-extremity disability in older women with diabetes: the Women's Health and Aging Study. Diabetes Care 2003;26:70–75
6. Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one. I. Survival, causes of death, and complications. Diabetologia 1978;14:363–370
7. Orchard TJ, Nathan DM, Zinman B, et al.; Writing Group for the DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. JAMA 2015;313:45–53
8. Lung TW, Hayes AJ, Herman WH, Si L, Palmer AJ, Clarke PM. A meta-analysis of the relative risk of mortality for type 1 diabetes patients compared to the general population: exploring temporal changes in relative mortality. PLoS One 2014;9:e113635
9. Orchard TJ, Secrest AM, Miller RG, Costacou T. In the absence of renal disease, 20 year mortality risk in type 1 diabetes is comparable to that of the general population: a report from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetologia 2010;53:2312–2319
10. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
11. Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and

Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med 2009;169:1307–1316
12. Lachin JM; DCCT/EDIC Research Group. Understanding metabolic memory: the prolonged influence of glycemia during the Diabetes Control and Complications Trial (DCCT) on future risks of complications during the study of the Epidemiology of Diabetes Interventions and Complications (EDIC). Diabetes Care 2021;44:2216–2224
13. Epidemiology of Diabetes Interventions and Complications Study Research Group. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care 1999;22:99–111
14. DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: summary and future directions. Diabetes Care 2014;37:44–49
15. DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: overview. Diabetes Care 2014;37:9–16
16. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 2000;55:M221–M231
17. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–M94
18. Vasunilashorn S, Coppin AK, Patel KV, et al. Use of the Short Physical Performance Battery Score to predict loss of ability to walk 400 meters: analysis from the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2009;64:223–229
19. Veronese N, Bolzetta F, Toffanello ED, et al. Association between Short Physical Performance Battery and falls in older people: the Progetto Veneto Anziani Study. Rejuvenation Res 2014;17:276–284
20. Hurvitz EA, Richardson JK, Werner RA, Ruhl AM, Dixon MR. Unipedal stance testing as an indicator of fall risk among older outpatients. Arch Phys Med Rehabil 2000;81:587–591
21. National Health and Nutrition Survey 2013-2014 Questionnaire Variable List. Centers for Disease Control and Prevention, 2013-2014. Accessed 18 March 2016. Available from https://wwwn.cdc.gov/nchs/nhanes/Search/variablelist.aspx?Component=Questionnaire&CycleBeginYear=2013
22. Jindai K, Nielson CM, Vorderstrasse BA, Quiñones AR. Multimorbidity and functional limitations among adults 65 or older, NHANES 2005-2012. Prev Chronic Dis 2016;13:E151
23. Kalyani RR, Saudek CD, Brancati FL, Selvin E. Association of diabetes, comorbidities, and A1C with functional disability in older adults: results from the National Health and Nutrition Examination Survey (NHANES), 1999–2006. Diabetes Care 2010;33:1055–1060
24. McGrath RP, Ottenbacher KJ, Vincent BM, Kraemer WJ, Peterson MD. Muscle weakness and functional limitations in an ethnically diverse sample of older adults. Ethn Health 2020;25:342–353
25. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695–699
26. Derogatis L. *SCL-90-R: Administration, Scoring and Procedures. Manual II for the R (evised) Version and Other Instruments of the Psychopathology Rating Scale Series*. Towson, MD, Clinical Psychometric Research, 1983
27. Lachin JM, Orchard TJ, Nathan DM; DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:39–43
28. Bergland A, Strand BH. Norwegian reference values for the Short Physical Performance Battery (SPPB): the Tromsø Study. BMC Geriatr 2019;19:216
29. Ferrucci L, Penninx BW, Leveille SG, et al. Characteristics of nondisabled older persons who perform poorly in objective tests of lower extremity function. J Am Geriatr Soc 2000;48:1102–1110
30. Neter J, Kutner MH, Nachtsheim CJ, Wasserman W. *Applied Linear Statistical Methods.* 4th ed. Chicago, Irwin, 1996
31. Kalyani RR, Rodriguez DC, Yeh HC, Golden SH, Thorpe RJ Jr. Diabetes, race, and functional limitations in older U.S. men and women. Diabetes Res Clin Pract 2015;108:390–397
32. De Rekeneire N, Resnick HE, Schwartz AV, et al.; Health, Aging, and Body Composition study. Diabetes is associated with subclinical functional limitation in nondisabled older individuals: the Health, Aging, and Body Composition study. Diabetes Care 2003;26:3257–3263
33. Holmes J, Powell-Griner E, Lethbridge-Cejku M, Heyman K. Aging differently: physical limitations among adults aged 50 years and over: United States, 2001-2007. NCHS Data Brief 2009 (20):1–8
34. Reese PP, Cappola AR, Shults J, et al.; CRIC Study Investigators. Physical performance and frailty in chronic kidney disease. Am J Nephrol 2013;38:307–315
35. Bruce-Keller AJ, Brouillette RM, Tudor-Locke C, et al. Relationship between cognitive domains, physical performance, and gait in elderly and demented subjects. J Alzheimers Dis 2012;30:899–908
36. Geerlings SW, Beekman AT, Deeg DJ, Twisk JW, Van Tilburg W. The longitudinal effect of depression on functional limitations and disability in older adults: an eight-wave prospective community-based study. Psychol Med 2001;31:1361–1371
37. Simning A, Seplaki CL. Association of the cumulative burden of late-life anxiety and depressive symptoms with functional impairment. Int J Geriatr Psychiatry 2020;35:80–90
38. Strotmeyer ES, de Rekeneire N, Schwartz AV, et al. The relationship of reduced peripheral nerve function and diabetes with physical performance in older white and black adults: the Health, Aging, and Body Composition (Health ABC) study. Diabetes Care 2008;31:1767–1772
39. Writing Group for the DCCT/EDIC Research Group. Coprogression of cardiovascular risk factors in type 1 diabetes during 30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2016;39:1621–1630