Not Only Diabetes but Also Prediabetes Leads to Functional Decline and Disability in Older Adults

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OBJECTIVE

Diabetes is linked to functional decline, but the impact of prediabetes on physical function is unknown. We aimed to examine and compare the impact of prediabetes and diabetes on physical function and disability progression and to explore whether cardiovascular diseases (CVDs) mediate these associations.

RESEARCH DESIGN AND METHODS

A cohort of 2,013 participants aged ≥60 from the Swedish National Study on Aging and Care in Kungsholmen, an ongoing population-based longitudinal study, was monitored for up to 12 years. Physical function was measured with chair stand (s) and walking speed (m/s) tests, and disability was measured by summing the numbers of impaired basic and instrumental activities of daily living. Diabetes was identified through medical examinations or clinical records, medication use, or glycated hemoglobin (HbA_{1c}) ≥6.5%. Prediabetes was defined as HbA_{1c} ≥5.7–6.4% in participants free of diabetes. CVDs were ascertained through clinical examinations and the National Patient Register. Data were analyzed using mixed-effect models and mediation models.

RESULTS

At baseline, 650 (32.3%) had prediabetes and 151 had diabetes (7.5%). In multi-adjusted mixed-effect models, prediabetes was associated with an increased chair stand time (β 0.33, 95% CI 0.05–0.61), a decreased walking speed (β −0.006, 95% CI −0.010 to −0.002), and an accelerated disability progression (β 0.05, 95% CI 0.01–0.08), even after controlling for the future development of diabetes. Diabetes led to faster functional decline than prediabetes. In mediation analyses, CVDs mediated 7.1%, 7.8%, and 20.9% of the associations between prediabetes and chair stand, walking speed, and disability progression, respectively.

CONCLUSIONS

Prediabetes, in addition to diabetes, is associated with faster functional decline and disability, independent of the future development of diabetes. This association may be in part mediated by CVDs.

Type 2 diabetes (hereafter diabetes) and prediabetes are major public health challenges affecting ∼463 million and 374 million adults worldwide, respectively (1). Diabetes is associated with a higher risk of limitations in physical function and disability (2), which may lead to institutionalization (3) and premature death (4),

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imposing a tremendous burden on the health and social care systems. Because limitations in physical function are regarded as a predisability phase (5), individuals with physical function decline represent an ideal target population for interventions to prevent disability.

Several cross-sectional studies assessing the association between diabetes and physical function have shown a high prevalence of physical limitation in individuals with diabetes (6,7). Only a few studies have examined the association between diabetes and incident physical impairment (8,9). Because prediabetes has been related to various disorders (e.g., vascular diseases and renal disease) (10,11), functional decline and disability might occur in individuals with prediabetes before the onset of full-blown diabetes (12). However, most studies addressing the association between functionality and diabetes have classified individuals with prediabetes into the normoglycemia group. Moreover, of the studies that have addressed prediabetes and physical function, most are cross-sectional (12–16), and only two have shown a positive association between prediabetes and impaired physical function (12,14). To date, no population-based cohort studies have specifically investigated the association of prediabetes with physical function decline and the development of disability.

One potential, and perhaps most relevant, pathophysiological pathway from diabetes to impaired physical function could involve the development of cardiovascular diseases (CVDs) (2). Although CVDs have been associated with walking speed decline over time (17), whether and to what extent CVDs may explain the pre/diabetes-physical function association remains unknown. In the current study, we aimed to *1*) examine the longitudinal association of prediabetes and diabetes with physical function decline and disability, *2*) compare the impact of prediabetes and diabetes on the functional capacity of older adults, and *3*) assess the possible mediating role of cardiovascular burden in these associations.

RESEARCH DESIGN AND METHODS

Study Population

Participants were derived from an ongoing population-based cohort study, the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K), in which 4,590 residents aged ≥60 years living at home or in institutions in central Stockholm were randomly sampled from 11 age cohorts (18). After the baseline examination (March 2001–June 2004), the younger cohorts (60, 66, and 72 years) have been reexamined every 6 years, and the older cohorts (78, 81, 84, 87, 90, 93, 96 and ≥99 years) have been reexamined every 3 years due to high attrition rates and more rapid changes in health status.

Among those who were alive and eligible, 3,363 individuals (participation rate 73.3%) participated in the baseline examination. Of them, we excluded 21 with type 1 diabetes or with missing information on glycemic status at baseline, 373 who refused to take part in the first follow-up examination, 587 who died between the baseline and first follow-up examinations, and 369 who were evaluated less than twice in chair stand, walking speed, and impaired activities of daily living (ADL) or instrumental activities of daily living (IADL). Finally, 2,013 participants were included in the analysis (Supplementary Fig. 1).

SNAC-K was approved by the Karolinska Institutet Ethics Committee (Stockholm, Sweden) and by the Regional Ethical Review Board in Stockholm. Written informed consent was obtained from all participants or from a proxy in the case of cognitive impairment.

Data Collection

In SNAC-K, data were collected through a standard protocol consisting of structured interviews and comprehensive clinical and physical function examinations by trained nurses, physicians, and psychologists (https://www.snac-k.se). Peripheral blood samples were taken for laboratory tests based on standard procedures. Information on medical conditions was obtained through the linkage to the Swedish National Patient Register (NPR), and vital status was confirmed by the Swedish Cause of Death Register.

Assessment of Prediabetes and Diabetes

Glycated hemoglobin A_{1c} (HbA_{1c}) was assessed with Swedish Mono-S filament high-performance liquid chromatography, and 1.1% was added to the measured HbA_{1c} values to equalize them with international values based on the NGSP (HbA_{1c} in %) (19).

Diabetes was identified according to medical examinations, antidiabetic drug use, diagnoses from the NPR (*International Classification of Diseases*, Ninth Revision: code 250; ICD-10: code E11), or HbA_{1c} ≥6.5% (48 mmol/mol) (20). In participants free of diabetes, prediabetes was defined as HbA_{1c} of ≥5.7–6.4% (39–46 mmol/mol), and normoglycemia was defined as HbA_{1c} <5.7% (39 mmol/mol) (16). Diabetes status was further categorized into controlled diabetes (HbA_{1c} <7.5%, 58 mmol/mol) and uncontrolled diabetes (HbA_{1c} ≥7.5%) according to the recommended glycemic targets for older adults (21).

Physical Function and Disability Assessment

Physical function was assessed with chair stand and walking speed tests, which are considered highly reliable and are able to discriminate physical function even in relatively high-functioning older adults (22). Chair stand was timed when the participants moved as quickly as possible from a sitting to a standing position five times consecutively, with their arms folded across their chests. To assess walking speed, participants were asked to walk 6 m at self-selected speed, or 2.4 m if they reported slow walking or if the assessment was performed in a limited space (such as at home or in an institution). Participants who were unable to perform the tests due to severe physical limitations received the worst score—that is, a chair stand time of 75 s or a walking speed of 0 m/s—both of which were defined as chair stand limitation or walking speed limitation (23).

Disability was assessed by the nurses as the inability to independently perform ADL (dressing, bathing, eating, continence, toileting, and transferring) and IADL (meal preparing, grocery shopping, housekeeping, laundry, handling money, using the telephone, taking transportation, and managing medications). The level of disability accumulation was measured by summing the numbers of ADL and IADL limitations. This was considered an extension of a solely ADL or IADL scale that would therefore be more sensitive to discriminate functional disability (24). The physical function tests and ADL/IADL were both assessed at baseline and at each follow-up for up to 12 years.

CVDs

Information on diagnosis of CVDs was collected through clinical examinations

by physicians, medical history, medical records, laboratory tests, medications, and inpatient and outpatient data from the NPR. All diagnoses were coded with ICD-10 codes and further classified into the following seven CVD categories based on the clinically driven methodology proposed by our group (25): ischemic heart disease, heart failure, atrial fibrillation, cardiac valve diseases, bradycardias and conduction disorders, peripheral artery diseases, and other CVDs.

The total number of CVDs was calculated as a measurement of CVD burden at baseline and at each follow-up (every 6 years for younger cohorts and every 3 years for older cohorts). When investigating the meditating role of CVD burden, we used CVD diagnoses from baseline until the 6-year follow-up to minimize potential reverse causality.

Covariates

Participants' demographics (i.e., age, sex, and education) were collected through a questionnaire administered by the nurse. Age was categorized into younger groups (60–72 years) versus older groups (≥78 years), according to the study design. Education was measured by the maximum years of formal schooling. This was dichotomized as elementary school (<8 years of schooling and/or vocational training) and high school or university (≥8 years) because individuals with education <8 vs. ≥8 years showed a significant difference in speed of disability trajectory in a previous study (26). Living arrangement was dichotomized as community or institution. Smoking status was categorized as never smoker, former smoker, and current smoker. Alcohol consumption was categorized as no/occasional, light to moderate, or heavy drinking (27). Physical activity was assessed based on two questions about activity intensity and frequency in a self-administered questionnaire (28): *1*) "Do you regularly engage in light exercise? (Walking on roads or in parks, walking in the woods, short bicycle rides, light aerobics, golf)" and *2*) "Do you regularly engage in more intense exercise? (Jogging, brisk long walks, heavy-duty gardening, long bicycle rides, high-intensity aerobics, long distance ice skating, skiing, swimming, ball sports or other similar activity)." For both questions, the answer alternatives were "In the last 12 months: every day, several times/week, two to three times/month, less, never." A dichotomous variable of physical activity (active vs. inactive) was created based on the answers from these two questions with reference to the World Health Organization recommendations on the frequency of physical activity for older adults (28). Individuals were considered physically active if they were engaged in light and/or intense exercise every day or several times per week and inactive if they chose the other response options.

Weight and height were measured when the participants were standing in light clothes without shoes, and BMI was calculated as weight (kg) divided by the square of height (m). Arterial blood pressure, including systolic and diastolic blood pressure (SBP and DBP), was measured twice at a minimum 5-min interval on the left arm, with the participant sitting, using a sphygmomanometer, and the average of the two readings of SBP/DBP was used. Hypertension was defined as having SBP ≥140 or DBP ≥90 mmHg or current use of antihypertensive medication. High cholesterol was defined as having a nonfasting total cholesterol of ≥6.22 mmol/L or use of cholesterol-lowering drugs. Estimated glomerular filtration rate (eGFR) (in mL/min/1.73 m^2) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equations based on serum creatinine (29).

The Mini-Mental State Examination (MMSE) was used to evaluate global cognitive function (30). We collected diagnoses for diabetes-related chronic conditions, including depression and mood disorders, cerebrovascular disease, and peripheral neuropathy, as described elsewhere (25), and dichotomized presence versus absence of the disease.

Statistical Analysis

Between-group differences in baseline characteristics of the study population were analyzed using the χ^2 test (or the Fisher exact test) for categorical variables and one-way ANOVA with pairwise mean comparisons with the Bonferroni correction for continuous variables.

We used multiple linear mixed-effect models to estimate the β coefficients (β) with 95% CIs of annual changes in physical function and disability score over the follow-up as a function of pre/diabetes at baseline. Participants with normoglycemia were treated as the reference group. The model included the baseline glycemic status, follow-up time (in years), and time-by-glycemic status interactions. Functional measures (walking speed and chair stand time) and disability scores at each follow-up were included as dependent variables separately. The estimates for glycemic groups reflect the difference in functional measures or disability score at baseline. The estimate for the time reflects annual changes in the functional test score or disability score. The glycemic group-by-time interaction indicates the additional annual change in the functional test or disability score for participants with prediabetes or diabetes, relative to those with normoglycemia. Because prediabetes may progress to diabetes during the follow-up (22), we adjusted the analysis for incident diabetes over the 12-year follow-up. This is to assess whether prediabetes-related functional decline is independent of the future development of diabetes. Furthermore, the impact of prediabetes and diabetes on functional capacity was compared with linear mixed-effect models. We reported the results from the models adjusted for demographic factors (age, sex, and education) (model 1) and the models additionally adjusted for potential confounders associated with cardiovascular burden (BMI, physical inactivity, alcohol consumption, smoking status, hypertension, and high cholesterol) and severity of dysglycemia (eGFR, depression and mood disorder, cerebrovascular disease, and peripheral neuropathy) (model 2). Possible interactions were tested by incorporating the three-way product term (e.g., glycemic status × follow-up time × sex) in the model. *P* values <0.10 were considered indicative of a significant multiplicative interaction as a relaxation of type 1 error (31).

In mediation analysis, we used CVDs accumulation over the first 6 years of follow-up as the mediator to address temporality from the mediators to the outcomes. We first verified the association of glycemic status with the rate of accumulating CVDs over the 6-year follow-up using linear mixed-effect models. We then performed path analysis to assess the direct and indirect (i.e., through CVDs accumulation) associations of prediabetes and diabetes with the changes in physical function and disability, respectively (32). Because the ability to accumulate CVDs may differ in participants

with different numbers of CVDs at baseline, we estimated the person-specific slopes of change in CVDs as a function of time from univariate linear mixed-effect models. We then extracted the random slopes (interpreted as annual rate of CVDs accumulation accounting for the number of CVDs at baseline) as a potential mediator. The mediation models were adjusted for covariates, and the bootstrapping method was applied to estimate the 95% CI. *P* values <0.05 (two-tailed) were considered statistically significant. All analyses were performed using Stata 15.0 software (StataCorp LLC).

RESULTS

Among the 2,013 participants (mean age, 70 ± 9.3 years; 62.3% women), 650 (32.3%) had prediabetes and 151 (7.5%) had diabetes at baseline. Individuals with prediabetes or diabetes were older, more likely to have lower consumption of alcohol, a higher BMI, hypertension, more chronic diseases, a lower eGFR, and less physical activity than those with normoglycemia (Table 1). Participants with prediabetes or diabetes also had a longer chair stand time and slower walking speed than those with normoglycemia at baseline.

Compared with the participants included in the study, those who were excluded were older and more likely to be women, living in institutions, physically inactive, and to have chronic diseases. They were also more likely to have ADL or IADL disability and worse physical function than those included in the study (Supplementary Table 1).

Glycemic Status and Physical Function and Disability Progression

At baseline, compared with normoglycemia, prediabetes was associated with less time for the chair stand (−2.86, 95% CI −4.79 to −0.90) and lower disability score (−0.16, 95% CI −0.27 to −0.05), and diabetes was related to slower walking speed (−0.07, 95% CI −0.13 to −0.01). Over the follow-up, prediabetes was associated with a faster deterioration in chair stand, walking speed, and disability than normoglycemia in basic adjusted mixed-effect models (Table 2). A total of 110 individuals (17%) with prediabetes progressed to diabetes during 12-year follow-up. After further adjustment for potential confounders as well as future development of diabetes, we found significant associations

Table 1—Baseline characteristics of participants by glycemic status (*n* = 2,013)

Characteristics	Normoglycemia (*n* = 1,212)	Prediabetes (*n* = 650)	Diabetes (*n* = 151)	*P* value
Age (years)	69 ± 9.2	72 ± 9.5*	71 ± 8.5*	<0.001
60–78 years	876 (72.3)	390 (60.0)	96 (63.6)	<0.001
≥78 years	336 (27.7)	260 (40.0)	55 (36.4)	
Female sex	770 (63.5)	429 (66.0)	74 (49.0)	<0.001
Education ≥elementary	1,072 (88.7)	563 (86.6)	128 (84.8)	0.209
Living in institutions	13 (1.07)	4 (0.62)	2 (1.32)	0.549
BMI (kg/m^2)	25 ± 3.7	26 ± 3.8*	28 ± 3.9*	<0.001
Smoking status				0.082
Never smoker	575 (47.9)	286 (44.3)	63 (42.3)	
Former smoker	480 (39.9)	254 (39.4)	69 (46.3)	
Current smoker	147 (12.2)	105 (16.3)	17 (11.4)	
Alcohol consumption				<0.001
No or occasional	281 (23.4)	216 (33.3)	56 (37.3)	
Light to moderate	699 (58.1)	319 (49.2)	71 (47.3)	
Heavy	223 (18.5)	113 (17.4)	23 (15.3)	
Physically active	969 (80.0)	493 (75.6)	110 (72.9)	0.034
MMSE score	28.8 ± 2.6	28.6 ± 1.8	28.7 ± 1.7	0.868
SBP (mmHg)	142 ± 19.6	144 ± 18.8	147 ± 19.9	0.024
DBP (mmHg)	82 ± 10.4	81 ± 10.1	80 ± 11.5	0.014
Hypertension	849 (70.1)	483 (74.3)	133 (88.1)	<0.001
High total cholesterol	611 (52.5)	368 (56.8)	82 (55.0)	0.214
eGFR (mL/min/1.73 m^2)	68 ± 11.7	65 ± 12.9	65 ± 15.6	<0.001
Depression and mood disorders	98 (8.09)	43 (6.62)	17 (11.3)	0.143
Cerebrovascular disease	43 (3.55)	36 (5.54)	11 (7.28)	0.031
Peripheral neuropathy	19 (1.57)	6 (0.92)	4 (2.65)	0.211§
Number of CVDs				<0.001
0	1,038 (85.6)	516 (79.4)	90 (59.6)	
1	131 (10.8)	83 (12.8)	35 (23.2)	
≥2	43 (3.55)	51 (7.85)	26 (17.2)	
Chair stand (s)	20 ± 20.8	21 ± 21.4*	25 ± 24.8*	0.029
Walking speed (m/s)	1.2 ± 0.4	1.1 ± 0.4*	1.0 ± 0.4*	<0.001
ADL disability#	29 (2.4)	15 (2.3)	2 (1.3)	0.707
IADL disability¤	108 (9.1)	55 (8.6)	18 (12.2)	0.390

Data are *n* (%) or means ± SD. #At least one impairment in ADL. ¤At least one impairment in IADL. *Pairwise means comparison with Bonferroni correction: $P < 0.05$ (reference group, normoglycemia). §Fisher exact test.

between prediabetes and the chair stand time (0.33, 95% CI 0.05–0.16), walking speed (−0.006, 95% CI −0.010 to −0.002), and disability score (0.05, 95% CI 0.01–0.08) over time.

On average, diabetes was associated with a 1.08-s increase in chair stand time, a 0.008 m/s decrease in walking speed, and a 0.14 increase in the disability score per year relative to normoglycemia. These associations became stronger among individuals with uncontrolled diabetes. Furthermore, compared with prediabetes, diabetes was significantly associated with a 0.74-s annual increase in chair stand time (95% CI 0.14–1.34) and a 0.08 annual increase in the disability score (95% CI 0.01–0.14). Figure 1 describes the physical function and disability trajectories over 12 years by glycemic status, with normoglycemia or prediabetes as the reference.

A significant multiplicative interaction was detected between age-group (<78 vs. ≥78) and diabetes in association with functional decline and disability (*P* for interaction <0.05 for all three outcomes). After stratification by age-group, the associations between diabetes and physical function decline or disability progression were present only among the younger group (<78 years) (Supplementary Table 2). However, no significant interactions between pre/diabetes and sex were observed on the changes in physical function or disability progression.

Mediating Role of CVDs

Because prediabetes (0.01, 95% CI 0.001–0.027) and diabetes (0.03, 95% CI 0.011–0.057) were both significantly related to a faster rate of CVDs accumulation than normoglycemia in the multiadjusted mixed-effect models (Supplementary Table 3), we conducted mediation analysis to estimate direct and indirect associations of prediabetes and diabetes with the chair stand time increase, walking speed decline, and disability progression separately. Figure 2 shows the models with coefficients for prediabetes (Fig. 2*A*) and diabetes (Fig. 2*B*) and 95% CIs. For prediabetes, the development of CVDs over the first 6 years mediated 7.1%, 7.8%, and 20.9% of the association of prediabetes with the chair stand, walking speed, and disability progression, respectively. The corresponding mediation proportions of CVDs accumulation were 13.3%, 22.9%, and 14.4% for the diabetes-chair stand, walking speed, and disability associations, respectively.

Sensitivity Analysis

To test the robustness of our results, we conducted the following sensitivity analyses: *1*) excluding participants with physical limitations, ADL/IADL disability at baseline, or who were living in institutions for each outcome; *2*) excluding participants with cerebrovascular disease and peripheral neuropathy; *3*) excluding participants with an MMSE <24 at baseline and follow-up assessments; *4*) performing the analysis for only participants who completed all follow-up examinations (because death and dropout are not random); and *5*) performing the analysis with additional adjustment for serum albumin level. Results from these analyses were generally similar to those from the initial analyses (Supplementary Table 4).

CONCLUSIONS

In this population-based longitudinal study of older adults in Sweden, we found that *1*) in addition to diabetes, prediabetes was associated with faster physical function decline and disability progression in older adults, independent of the future development of diabetes; *2*) such associations were stronger for diabetes than for prediabetes; and *3*) faster development of CVDs—arguably interpretable as the development of diabetes complications—partly mediated the associations between pre/diabetes and functional decline/disability.

To the best of our knowledge, this study is the first to demonstrate that prediabetes is an independent risk factor for a steeper decline in physical function and for a faster disability progression. Only a few cross-sectional studies have investigated the association of prediabetes with poor physical function, and with inconsistent results (12–14,16). One study including people aged 60–70 years from the U.K. showed that impaired glucose tolerance was associated with a

Table 2—β coefficients and 95% CIs of the associations between glycemic status and physical function decline and disability progression over 12 years using mixed-effect models

		Chair stand		Walking speed		Disability score	
Glycemic status × time	No.	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 1 β (95% CI)	Model 2 β (95% CI)
Normoglycemia × time	1,212	Reference	Reference	Reference	Reference	Reference	Reference
Prediabetes × time	650	0.33** (0.06–0.60)	0.33[a]** (0.05–0.61)	−0.005** (−0.009 to −0.002)	−0.006[a]** (−0.010 to −0.002)	0.06* (0.02–0.09)	0.05[a]* (0.01–0.08)
Diabetes × time	151	1.05** (0.55–1.54)	1.08** (0.52–1.65)	−0.007* (−0.014 to −0.001)	−0.008* (−0.015 to −0.002)	0.13** (0.06–0.20)	0.14** (0.10–0.23)
Controlled × time	111	0.95** (0.39–1.50)	0.95** (0.30–1.62)	−0.005 (−0.008 to 0.002)	−0.006 (−0.014 to 0.001)	0.11** (0.04–0.19)	0.12** (0.04–0.21)
Uncontrolled × time	39	1.56** (0.57–2.53)	1.49** (0.42–2.56)	−0.016* (−0.029 to −0.003)	−0.014* (−0.028 to −0.001)	0.17** (0.04–0.30)	0.21** (0.01–0.41)
Diabetes × time vs. prediabetes × time		0.72** (0.20–1.24)	0.74* (0.14–1.34)	−0.002 (−0.009 to 0.005)	−0.002 (−0.009 to 0.004)	0.07* (0.01–0.14)	0.08* (0.01–0.14)

Model 1 adjusted for baseline age, sex, and education. Model 2 adjusted for model 1 + BMI, physical activity, alcohol consumption, smoking status, SBP, high total cholesterol, eGFR, depression and mood disorders, cerebrovascular disease, and peripheral neuropathy. [a]Model 2 additionally adjusted for incident diabetes. *$P < 0.05$, **$P < 0.01$.

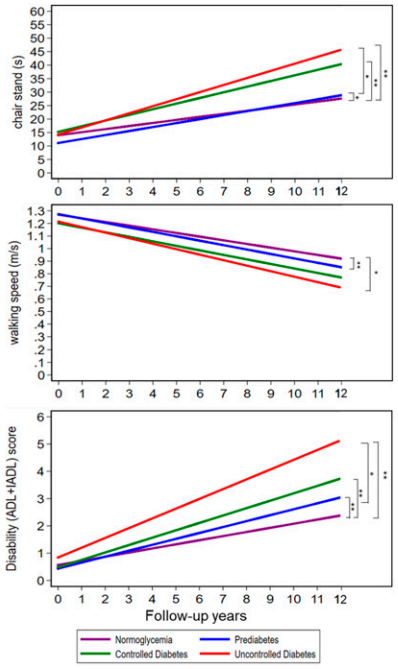

Figure 1—Predicted trajectories of chair stand, walking speed, and disability score (ADL + IADL) over 12-year follow-up by glycemic status. The lines represent β coefficients from the linear mixed-effects model adjusted for age, sex, education, BMI, physical activity, alcohol consumption, smoking status, SBP, eGFR, high total cholesterol, depression and mood disorders, cerebrovascular diseases, and peripheral neuropathy, with normoglycemia or prediabetes as the reference group. *$P < 0.05$, **$P < 0.01$.

60% higher likelihood of poor physical function (14), whereas a study of Japanese older adults (mean age, 71 years) indicated no association between prediabetes and walking speed, chair stand time, or performance in a balance test (16). This discrepancy might be due to different ascertainments of prediabetes (oral glucose tolerance test vs. HbA_{1c}) and different measurements of physical function (self-reported vs. objective measurements). Notably, we found that in addition to diabetes, prediabetes was also longitudinally associated with a faster deterioration in chair stand time and walking speed, independent of the future development of diabetes. This association was stronger in participants with diabetes, especially among those with uncontrolled diabetes, demonstrating the importance of maintaining adequate glycemic control even in old age.

Although many studies have addressed the association between diabetes and incident disability (2), we expand this knowledge by demonstrating that diabetes is related to an accelerated decline of physical function and progression of disability. Previous studies looking at elevated HbA_{1c} levels have yielded inconclusive results, possibly due to different HbA_{1c} cutoffs and age ranges in the different study populations (33–35). One study found that even an HbA_{1c} ≥9.0% was not associated with persistent functional decline using data from U.S. veterans (mean age, 76 years) (35). On the other hand, another study including adults aged ≥50 reported that people with elevated HbA_{1c} (≥6.5%) were at greater risk of being classified into the disability progressing group, and this risk was significantly modified by age, as was the case in our study, where we found a significantly faster functional deterioration only in younger individuals (34). This indicates that the detrimental impact of hyperglycemia on functional status may vary by age, with younger individuals benefitting more from the prevention of long-term complications, such as functional impairment and disability progression. We did not observe a significant association between diabetes and functional decline/disability progression in the older cohorts (≥78 years). This might be due to a survival bias, because those who survived at least to 78 years of age at baseline are otherwise relatively healthy. In addition, whether optimal glycemic control is associated with better functionality in the oldest old adults is still debated. Previous studies have shown that an HbA_{1c} of 8.0–8.9% is associated with better functional outcomes compared with an HbA_{1c} of 7.0–7.9% among older adults with mean age of 80 years (36). Older adults with diabetes might not benefit from strict glycemic control because severe complications (e.g., hypoglycemia) are often observed in this group (37). Therefore, glycemic targets should be tailored to the individual considering their comorbidities, cognitive and physical function status, treatment modality, and remaining life expectancy.

Accumulating evidence has shown that CVDs might explain the excess odds of functional disability observed in individuals with diabetes (2,38), but so far, no studies have estimated the extent to which CVDs might mediate these associations. As expected, we found that diabetes was related to a faster rate of CVD accumulation, which in turn was related to functional decline over time. Notably, our mediation analysis suggests that beyond diabetes, prediabetes was also associated with physical function decline/disability, in part through an association with faster CVD accumulation. Previous studies have reported the higher risk of CVDs in people with prediabetes (39), and hyperglycemia might exacerbate the decline in the cardiovascular system and in physical function. Indeed, a faster accumulation of CVDs reflects accelerated aging of the cardiovascular system, arguably fostered—as suggested by our analyses—by altered glucose metabolism, which is known to contribute to both micro- and macrovascular disorders (1,40). These eventually impact cardiovascular fitness and the oxygen supply to several tissues (e.g., muscle) (41). The maintenance of both adequate walking speed and chair stand performance requires the integrity of several organs and systems, which in turn might be affected by hyperglycemia directly and indirectly. However, our results indicate that CVDs explained only a small proportion of the associations, and a number of other contributors might lie on the pathway between hyperglycemia and functional decline. Conditions associated with hyperglycemia, such as cognitive impairment, neuropathy, and sarcopenia, may explain the greater burden of functional disability in people with diabetes (42). First, prediabetes and diabetes are associated with cognitive impairment (43), which may interfere with patients' routine glycemic self-management and, in turn, might have an impact on their day-to-day functioning and dependency (44). In addition, chronic hyperglycemia could accelerate cognitive decline resulting from microvascular lesions (e.g., white matter hyperintensities), which is associated with poor motor function (45). Indeed, in sensitivity analysis excluding individuals with cognitive impairment during the entire follow-up, we found a slightly attenuated association between prediabetes/diabetes and functionality/disability. Second, motor-neuropathic processes could affect intrinsic foot muscle strength, and a strong association has been reported between autonomic neuropathy and disability (46). Third, inflammation and insulin resistance can be induced by hyperglycemia involved in

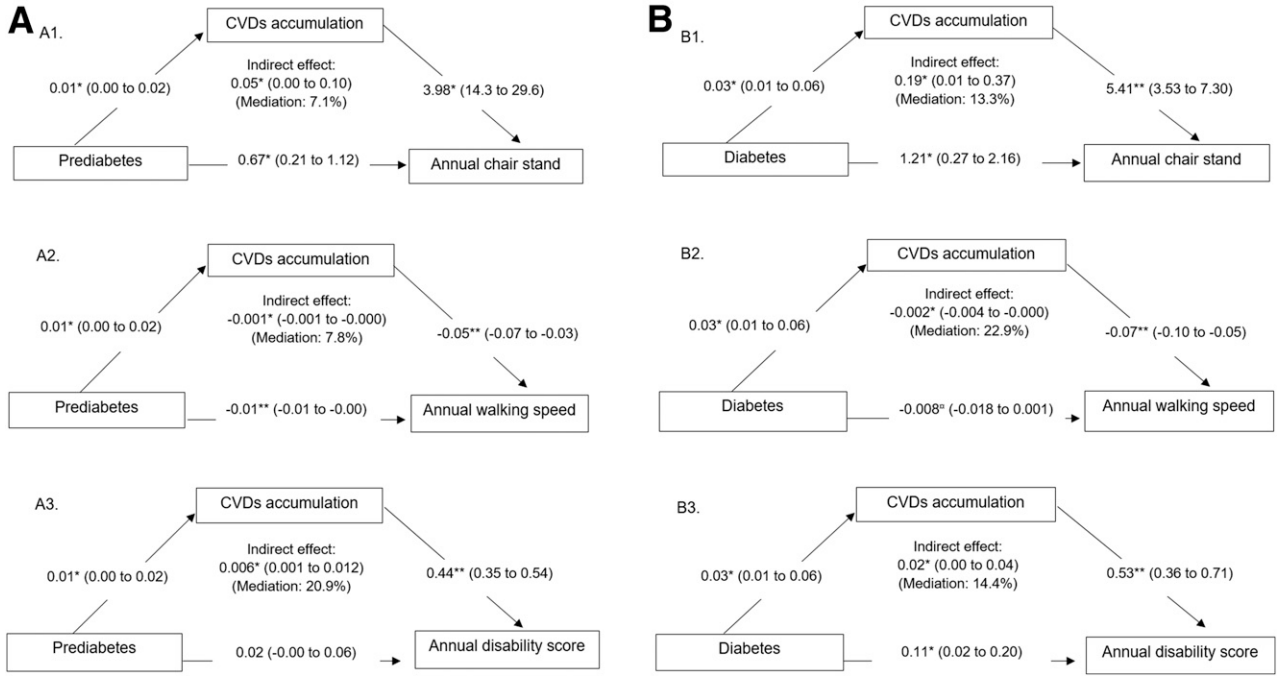

Figure 2—Mediation analysis of changes in CVDs during the follow-up on the associations of baseline prediabetes and diabetes with chair stand, walking speed, and disability scores. Prediabetes (*A*) and diabetes (*B*) constitute the dependent variables; CVDs accumulation is the mediator; and annual changes in chair stand time (*1*), walking speed (*2*), and disability scores (*3*) are the outcomes. The estimates are given as standardized coefficients, with *P* values and 95% CIs derived from bootstrapping in path analysis adjusted for baseline age, sex, education, BMI, physical activity, alcohol consumption, smoking status, SBP, eGFR, high total cholesterol, depression and mood disorders, cerebrovascular diseases, and peripheral neuropathy. The results also show the proportion mediated by the CVDs accumulation in each association. *$P < 0.05$, **$P < 0.01$, ¤$P = 0.09$.

the pathophysiology of sarcopenia (47). These two conditions could give rise to muscle damage and increase fat infiltration into muscle, leading to a decline in both muscle mass and strength (46). Nevertheless, it is worth noting that even after adjustment for these aforementioned conditions in the analysis, an association between hyperglycemia and excess deterioration in functionality still exists. Future studies are warranted to investigate other mechanisms.

A number of relevant clinical implications can be drawn from our findings. First, preventing or delaying the progression of CVDs appears to be crucial for implementing effective strategies to protect people with pre/diabetes from physical function decline and disability. In this regard, it is important to perform closer monitoring and screening of older individuals with pre/diabetes to diagnose and treat concomitant CVD risk factors in a timely manner. Moreover, health professionals should inform older adults with prediabetes of the risk for functional decline and start to evaluate their functionality early and often, because a steeper decline in physical function can already begin at the prediabetic stage. Lifestyle interventions, including promotion of healthy dietary intake and exercise training, might benefit older adults by improving glycemic control as well as delaying functional decline (48). Nevertheless, more clinical studies are needed to identify effective approaches for older adults with prediabetes to maintain physical function—a particularly important issue because older adults with prediabetes are not widely involved in relevant clinical trials.

A major strength of this study is the large, well-established population-based design with 12 years of meticulous follow-up. The repeated objective measurements of outcomes and mediating variables enabled us to investigate the impact of CVDs accumulation with respect to subtle changes in physical functionality before the clinical manifestation of impaired mobility.

However, several limitations need to be acknowledged. First, due to the low sensitivity of HbA_{1c} compared with fasting plasma glucose or oral glucose tolerance tests (49), the occurrence of pre/diabetes in our study might be underestimated, leading to an underestimation of the observed associations. Second, CVDs accumulation may take place at the same time as physical function decline and disability progression, so reverse causality cannot be ruled out. We addressed this by using 6-year follow-up data on the mediator and 12-year follow-up data on the outcomes. Furthermore, the results were not materially altered even after we excluded those with functional limitations and disability at baseline in the analysis. Third, other important factors, such as nutritional status and sarcopenia, might confound the observed association. Unfortunately, data on sarcopenia are not available in this study. Fourth, given a high attrition rate during the follow-up in our study, the association between pre/diabetes and physical function decline might have been underestimated. Results from the sensitivity analysis including only participants who completed all follow-up assessments still showed a faster decline in physical function among people with pre/diabetes. Finally, because the SNAC-K population consisted of older adults who were living in central Stockholm and had a higher level of education compared with other areas of Sweden, caution is required when generalizing our findings to other populations.

In conclusion, this study provides the first evidence of the impact of prediabetes on physical function decline and disability progression, independent of future development of diabetes. Accumulation of CVDs over time may partly account for the associations between pre/diabetes and functional decline. Our study highlights the importance of preventing CVDs among people with hyperglycemia and underscores the need to monitor functionality among older people even at the prediabetic stage. Further studies are warranted to identify and understand other contributors to the pre/diabetes-functional decline association.

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Author Contributions. Y.S. conducted the literature search, analyzed data, interpreted the findings, and wrote, reviewed, and edited the manuscript. Y.S. and W.X. conceptualized and designed the study. L.F. designed, initiated, and directed SNAC-K. Y.S., L.F., D.L.V., A.D., A.-K.W., and W.X. contributed to the data interpretation and revision of the manuscript and approved the final draft. Y.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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