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Role of Cardiorespiratory Fitness and Mitochondrial Oxidative Capacity in Reduced Walk Speed of Older Adults With Diabetes

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METABOLISM

Cardiorespiratory fitness and mitochondrial oxidative capacity are associated with reduced walking speed in older adults, but their impact on walking speed in older adults with diabetes has not been clearly defined. We examined differences in cardiorespiratory fitness and skeletal muscle mitochondrial oxidative capacity between older adults with and without diabetes, as well as determined their relative contribution to slower walking speed in older adults with diabetes. Participants with diabetes (*n* = 159) had lower cardiorespiratory fitness and mitochondrial respiration in permeabilized fiber bundles compared with those without diabetes (*n* = 717), following adjustments for covariates including BMI, chronic comorbid health conditions, and physical activity. Four-meter and 400-m walking speeds were slower in those with diabetes. Mitochondrial oxidative capacity alone or combined with cardiorespiratory fitness mediated ∼20–70% of the difference in walking speed between older adults with and without diabetes. Additional adjustments for BMI and comorbidities further explained the group differences in walking speed. Cardiorespiratory fitness and skeletal muscle mitochondrial oxidative capacity contribute to slower walking speeds in older adults with diabetes.

ARTICLE HIGHLIGHTS

- The contributors to slower walking speed in older adults with diabetes remain unclear.
- This study was conducted to answer the question of how mitochondrial oxidative capacity and cardiorespiratory fitness impact walking speed in older adults with diabetes.
- We found that mitochondrial oxidative capacity, cardiorespiratory fitness, and walking speed were lower in older adults with diabetes compared with those without diabetes.
- In addition, mitochondrial oxidative capacity and cardiorespiratory fitness contributed to slower walking speed in those with diabetes.

The U.S. population is rapidly aging, and in 2022, the percentage of Americans aged ≥65 years diagnosed with diabetes remained high at 30% (1). This represents a health care challenge as older adults with diabetes have a greater

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risk of cardiovascular disease and mobility disability (2,3). The contributors to impaired mobility in older individuals with diabetes include the presence of comorbidities, increased BMI (4), and lower muscle strength and quality (5–7). However, the relationship between diabetes and loss of mobility measured by 4-m and 400-m walking speeds remains only partially explained by muscle variables, such as quality and strength (5). Skeletal muscle mitochondrial oxidative capacity is an integral contributor to cardiorespiratory fitness, along with the ability of the cardiopulmonary system to supply oxygen to contracting muscles. Our group and others reported that cardiorespiratory fitness and skeletal muscle mitochondrial oxidative capacity are significantly associated and that each link to reduced walking speed in aging, which is a predictor of mobility disability (8–10). For example, mitochondrial oxidative capacity assessed using ^{31}P-magnetic resonance spectroscopy (MRS) is highly correlated with walking speed and partially explains age-related poorer performance in short (6-m) and long (400-m) walking tasks (10). Several studies have found a close relationship between cardiorespiratory fitness and walking speed in older adults (11), which suggests that the decline in aerobic capacity also contributes to slower walking speed and mobility disability with age.

Muscle biopsies from individuals with diabetes have been shown to have lower oxidative phosphorylation (OXPHOS) capacity compared with muscle from healthy control individuals (12–14). However, some studies (15,16), but not all (12,13,17), indicated no differences between patients with diabetes and BMI-matched control individuals, indicating that obesity per se may underlie the lower muscle oxidative capacity. Indeed, other studies in people without diabetes have shown that BMI is strongly related to muscle oxidative capacity (18). In addition, reports assessing mitochondrial oxidative capacity in older adults with diabetes tend to have small sample sizes (n = 8–12) and lack adjustment for critical confounding variables, including physical activity and adiposity (13,14,17), and there are few reports that focused on older adults with diabetes specifically. Whether the presence of diabetes in a population of older adults further exacerbates declines in mitochondrial oxidative capacity and cardiorespiratory fitness remains unclear. Lower fitness is a predictor of insulin resistance and diabetes (19), and prevalence of diabetes is greater in individuals with low fitness (20). Skeletal muscle mitochondrial oxidative capacity is an integral contributor to cardiorespiratory fitness, along with pulmonary function (ventilation and alveolar-capillary gas exchange), cardiac stroke volume, oxygen transport and delivery (hemoglobin concentration, arteries and arterioles, capillary density, and diffusion capacity system) to supply oxygen to contracting muscles. While each of these factors could contribute to walking speed, it is unknown whether diabetes-associated changes in cardiorespiratory fitness and/or muscle energetics explain slower walking speed seen in older adults with diabetes, independent of other covariates.

In this analysis, we leveraged data from the Study of Muscle, Mobility and Aging (SOMMA) (21) to investigate the association of diabetes with cardiorespiratory fitness and mitochondrial oxidative capacity in a cohort of 879 older adults who were well phenotyped in terms of the free-living physical activity behaviors and body composition. We assessed mitochondrial oxidative capacity using two approaches: ^{31}P-MRS to measure muscle in vivo (ATPmax) and high-resolution respirometry to measure mitochondrial respiration in muscle biopsies, a complementary approach that interrogates mitochondrial OXPHOS capacity at the myocellular level. Here, we tested the hypothesis that diabetes would be associated with lower cardiorespiratory fitness and muscle oxidative capacity in older adults independent of adiposity, physical activity levels, chronic comorbid health conditions, and oral hypoglycemic medication use. We also tested the extent to which cardiorespiratory fitness and mitochondrial respiration mediate slower walking speed of older adults with diabetes.

RESEARCH DESIGN AND METHODS

Participant Recruitment

SOMMA (https://sommaonline.ucsf.edu) is a prospective longitudinal cohort study of older adults designed to understand the biological basis of muscle aging (21). Men and women (≥70 years old) were recruited between April 2019 and December 2021. Participants were enrolled at the University of Pittsburgh and Wake Forest University School of Medicine if they were willing and able to complete a skeletal muscle biopsy and undergo MRI and MRS. Exclusion criteria included an inability to walk one quarter of a mile or climb a flight of stairs, having a BMI $>$40 kg/m^2, having an active malignancy or dementia, or having any medical contraindication to biopsy or magnetic resonance. Finally, participants must have been able to complete the 400-m walking test; those who appeared as they might not be able to complete the 400-m walk at the in-person screening visit completed a short-distance walk (4-m) to ensure their walking speed was ≥0.6 m/s. Individuals with diabetes were identified by self-report, use of prescribed hypoglycemic medication, or an HbA_{1c} ≥6.5%. The WIRB-Copernicus Group institutional review board (study no. 20180764) approved the study, and all participants provided written informed consent.

Baseline Assessments

Details on study design and methodology have been published elsewhere (21). The SOMMA baseline visit generally consisted of 3 days of assessments over several weeks. On "Day 1," the 400-m walk plus most other in-person assessments were performed. On "Day 2," cardiopulmonary exercise testing (CPET), MRI, and MRS were assessed. On "Day 3," a muscle biopsy specimen was collected. Age, sex, and race were collected by self-report. Self-reported medical conditions (heart disease, stroke, kidney disease/renal failure, and peripheral vascular disease) were assessed to determine whether participants had those conditions. Participants were asked to bring all prescription medications they had taken in the 30 days prior to their "Day 1" clinic visit. If a participant forgot to bring one or more medications, clinic staff obtained this information over the telephone or at the return visit. Prescription medication use was reviewed and updated at the additional baseline visit days where CPET and tissue sampling were done. Body weight, height, and physical function assessments were also measured, and accelerometry devices were provided. Most SOMMA participants completed CPET, MRS and provided a percutaneous biopsy of the vastus lateralis muscle, which was performed under fasted conditions. On the day of the muscle biopsy, participants prescribed oral hypoglycemic medication were asked to take their medications after tissue sampling.

Mobility Assessments

Mobility was assessed by 400-m and 4-m walking tests. For the 400-m walking test, participants were instructed to walk 10 complete laps around a set course at their usual pace and without overexerting themselves. The 4-m walking speed was measured in two trials, and the participant's best time was used to calculate walking speed in m/s.

Physical Activity Assessments

Two devices were used to assess activity: the thigh-worn activPal that recorded total daily step count and the wrist-worn ActiGraph GT9X. Devices were placed on the participants at the baseline "Day 1" visit with a data collection period of 7 full days. Data were included only if the device was worn over a 24-h period and had ≥17 h/day wear time. Activity levels collected from the ActiGraph device were determined by cut points described by Montoye et al. (22), and included total daily physical activity time and time spent in sedentary physical activity, light physical activity, and moderate to vigorous physical activity (MVPA).

CPET

Participants walked for 5 min at a preferred walking speed, and a progressive symptom-limited exercise protocol ensued with increases in speed (0.5 mph) and incline (2.5%) in 2-min increments using a modified Balke protocol or a manual protocol (23,24). Cardiorespiratory fitness was determined as VO_2peak (mL/min) which was identified as the highest 30-s average of VO_2 (mL/min) achieved.

MRS and MRI

^{31}P-MRS was used to assess in vivo mitochondrial adenosine triphosphate (ATP) generation in the quadriceps muscle during an acute bout of knee isometric extension exercise (21,24). A detailed description of the ^{31}P-MRS protocol can be found in Mau et al. (24). A 3-T magnetic resonance magnet (MAGNETOM Prisma [Pittsburgh] or MAGNETOM Skyra [Wake Forest]; Siemens Healthineers) with a 12-cm Ć^{31}P/^{1}H dual-tuned, surface radiofrequency coil (PulseTeq) was placed over the quadriceps with the shell of the coil consistently placed 10 cm superior to the patella over the distal vastus lateralis muscle. Dynamic quantification of phosphocreatine (PCr), inorganic phosphate, phosphodiesterase, and ATP peak areas were acquired using 100-μs block pulse targeting a pulse angle of 45° with 2,048 points and a sweep width of 5,000 Hz. Seventy-five dynamic spectra were acquired, averaging four acquisitions with a 1.5-s recycle time each for a spectral time resolution of 6-s throughout the rest, exercise, and recovery periods. Data were immediately processed to determine PCr breakdown and acidosis and then used to adjust exercise duration for a second or third trial to satisfy breakdown and acidosis criteria. Raw data were used to quantify peaks representing phosphorus metabolites using jMRUI version 6.0 software. Temporal response of PCr area was used to calculate ATPmax (aka, Qmax) from PCr recovery rates (25). PCr area time course was referenced to the last 10 spectra of a 76-spectrum series. ATPmax was calculated using the recovery time constant as the inverse of the rate constant as described in Meyerspeer et al. (26) and assuming a resting/recovered PCr concentration of 24.5 mmol/L. Inorganic phosphate chemical shifts were followed relative to PCr = −2.54 parts/million to calculate intracellular pH to monitor muscle acidosis. Quality control criteria for inclusion of dynamic ^{31}P-MRS data in analyses were *1*) PCr breakdown between 33 and 50%, *2*) pH throughout dynamic experiment >6.8, and *3*) monoexponential fit of PCr recovery data. Participant data not meeting all criteria were excluded from the analysis.

An AMRA scanning protocol with the Dixon water-fat imaging method was used to assess abdominal subcutaneous adipose tissue (ASAT), visceral adipose tissue (VAT), the VAT/ASAT ratio, and quadricep muscle fat infiltration (QFI). The entire body was scanned, and images were analyzed using AMRA Researcher (AMARA Medical AB, Linköping Sweden) (27).

Muscle Biopsy and Mitochondrial Respiration

Muscle biopsy was completed with a Bergström trocar (5 or 6 mm) as previously described (24). Approximately 10 mg of muscle tissue was allocated for respirometry assays and were immediately submerged in ice cold BIOPS buffer. Fiber bundles of ∼2–3 mg wet weight were gently teased apart and permeabilized as previously described (24), and weight was measured using an analytical balance (Mettler Toledo, Columbus, OH). Permeabilized fiber bundle (PmFB) oxygen consumption was measured using a high-resolution respirometer (Oxygraph-2k; Oroboros Instruments, Innsbruck, Austria). PmFBs were placed into chambers containing MiR05 buffer supplemented with 25 μmol/L blebbistatin in the absence of light. Two protocols were completed in duplicate measuring carbohydrate-supported (protocol 1: 5 mmol/L pyruvate and 2 mmol/L malate) and fatty acid oxidation (FAO)–supported (protocol 2: 25 μmol/L palmitoyl-carnitine and 2 mmol/L malate) respiration. For protocol 1, state 3 respiration was stimulated with the addition of 4.2 mmol/L ADP ($OXPHOS_{CHO}$)

followed by subsequent additions of 10 mmol/L glutamate and 10 mmol/L succinate sequentially ($maxOXPHOS_{CHO}$). Maximal uncoupled respiration was stimulated with consecutive 0.5 μmol/L titrations of 2-[2-[4-(trifluoromethoxy)phenyl]-hydrazinylidene]propanedinitrile until maximum electron transport system (ETS) capacity was attained ($maxETS_{CHO}$). For protocol 2, state 3 respiration was stimulated with the addition of 4 mmol/L ADP ($OXPHOS_{FAO}$) followed by subsequent additions of 10 mmol/L glutamate and 10 mmol/L succinate to further stimulate mitochondrial complexes I and II ($maxOXPHOS_{FAO}$). PmFBs eliciting an oxygen consumption response to cytochrome c oxidase >15% were not included in the final analysis. Respiratory control ratios for protocol 1 (7.11 ± 2.86) and protocol 2 (3.47 ± 1.74) were assessed for quality control. Respiration was analyzed using DatLab 7.4.0.4 software. In SOMMA, not all participants completed both protocols because of time constraints. Protocol 1 (carbohydrates) was prioritized over protocol 2 (fatty acids) when limited technician time was available, which left fewer participants with complete data for protocol 2.

Statistical Analysis

Differences in participant characteristics between older adults with and without diabetes were compared using the *t* test for continuous variables (or Kruskal-Wallis nonparametric test for skewed variables) and χ^2 test for dichotomized variables. Linear regressions without adjustment were performed to determine differences in cardiorespiratory fitness and mitochondrial oxidative capacity between those with and without diabetes, and additional adjustments were made for the following confounders: age, race, sex, site/technician, BMI, and chronic conditions (model 1). Model 1 was further adjusted for steps per day from activPal or volume of the adipose tissue depots ASAT, VAT, VAT/ASAT ratio, and QFI. Finally, to determine the impact of hypoglycemic medication use within the group of older adults with diabetes, multivariable linear regression was performed adjusting for age, race, and site/technician. Those analyses were completed using JMP version 16 software.

Linear regression was also used to determine the association of diabetes with walking speed. We evaluated the potential mediating influence of VO_2peak and/or mitochondrial respiration. We did this by comparing the β-coefficient for the association of diabetes status on walking speed from the 400-m and 4-m walking tests. The base model included the following confounding variables: sex, age, and race. Model 2 included the base model plus technician and $maxOXPHOS_{CHO}$; model 3 included the base model plus technician and $maxOXPHOS_{FAO}$; model 4 included the base model plus clinical site and VO_2 peak; model 5 included the base model plus technician, VO_2 peak, and $maxOXPHOS_{CHO}$; and model 6 included the base model plus technician, VO_2peak, and $maxOXPHOS_{FAO}$. Fully adjusted models also included the potential confounders/mediators BMI and chronic conditions. Finally, we compared the percent difference in the β-coefficient between the base model and subsequent models to understand how each adjustment impacted group differences in walking speed. Those analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC).

Data and Resource Availability

All SOMMA data are publicly available via a web portal. Updated data sets are released approximately every 6 months (https://sommaonline.ucsf.edu/).

RESULTS

Participant Characteristics

A total of 879 participants (59.2% women) with an average age of 76.5 ± 5.0 years were enrolled in SOMMA (21). A summary of participants with available data is included in Supplementary Fig. 1. Participant characteristics are summarized in Table 1. Eighteen percent of the SOMMA cohort was classified as having diabetes. The proportion of women to men was greater in the group without diabetes (P = 0.02). The proportion of White participants compared with non-White participants was greater in the group without diabetes ($P < 0.001$). Older adults with diabetes had a higher body weight, waist circumference, BMI, and HbA_{1c} (all $P < 0.001$). Participants with diabetes tended to have a higher prevalence of heart disease and hypertension, whereas those without diabetes more often had a history of cancer ($P < 0.001$). Approximately 75% of participants with diabetes reported use of a hypoglycemic agent, where 83% used metformin, 19% used insulin, and 2% used thiazolidinediones. Total daily steps and time in MVPA was significantly lower ($P < 0.001$ for both) and total sedentary time significantly higher in participants with diabetes ($P < 0.001$). QFI was higher in those with diabetes (P = 0.002). In addition, both ASAT and VAT volume and VAT/ASAT ratio were significantly higher in older adults with diabetes (P = 0.005 for ASAT and $P <$ 0.001 for both VAT and VAT/ASAT ratio) (Table 1).

Cardiorespiratory Fitness and Muscle Oxidative Capacity in Diabetes

In the adjusted model (Table 2, model 1 plus physical activity), VO_2peak was significantly lower in older adults with diabetes compared with those without diabetes (P = 0.004). $OXPHOS_{CHO}$ (P = 0.12) and $maxOXPHOS_{CHO}$ (P = 0.10) were similar between groups. $maxETS_{CHO}$ was significantly lower in participants with diabetes (P = 0.03) (Table 2). $OXPHOS_{FAO}$ was similar between participants with and without diabetes (P = 0.10), and $maxOXPHOS_{FAO}$ remained significantly lower in older adults with diabetes in model 1 plus physical activity (P = 0.006). Sensitivity analyses completed in participants with data for both protocol 1 and protocol 2 had similar results (data not shown) to ensure that differences between protocols were not due to differences in sample size.

Adjustment for levels of ASAT, VAT, VAT/ASAT ratio, and QFI did not impact group differences in mitochondrial respiration and VO_2peak measurements, with an exception

Table 1—Participant characteristics

	Without diabetes	With diabetes	*P*
Basic characteristics			
Participants, *n*	717	159	
Age (years)	76.47 ± 5.05	75.79 ± 4.84	0.12
Female	61 (438)	51 (81)	**0.02**
Race (White)	88 (631)	70 (111)	**<0.001**
Hispanic ethnicity	1 (7)	1 (2)	0.76
Weight (kg)	74.74 ± 14.75	82.41 ± 15.58	**<0.001**
Height (m)	1.66 ± 0.10	1.67 ± 0.10	0.16
Waist circumference (cm)	92.69 ± 12.98	100.90 ± 12.57	**<0.001**
BMI (kg/m^2)	27.17 ± 4.44	29.55 ± 4.63	**<0.001**
HbA_{1c} (%)	5.51 ± 0.31	6.73 ± 0.89	**<0.001**
Systolic blood pressure (mmHg)	129.71 ± 15.80	133.72 ± 16.08	**0.004**
Comorbidities			
Lung disease	13 (93)	14 (22)	0.77
Arthritis	57 (409)	52 (83)	0.25
Stroke	2 (16)	3 (5)	0.51
Heart disease	6 (42)	11 (18)	**0.02**
Cancer	43 (308)	24 (38)	**<0.001**
Hypertension	26 (187)	37 (59)	**0.006**
Kidney disease/renal failure	3 (24)	6 (9)	0.19
Peripheral vascular disease	1 (4)	1 (2)	0.37
Hypothyroidism	19 (133)	17 (27)	0.64
Glaucoma	9 (65)	11 (18)	0.39
Macular degeneration	9 (61)	5 (8)	0.12
Cataracts	66 (472)	62 (99)	0.37
Hypoglycemic medications*			
All	—	75 (118)	
Insulin	—	19 (23)	
Metformin	—	84 (99)	
Thiazolidinediones	—	3 (3)	
Physical activity			
Total daily steps	7,066.68 ± 3,233.95	5,848.70 ± 2,791.12	**<0.001**
Total sedentary time (min)	610.10 ± 112.28	659.40 ± 108.65	**<0.001**
Time in light physical activity (min)	98.20 ± 26.54	92.84 ± 29.16	**0.027**
Time in MVPA (min)	192.95 ± 86.40	155.66 ± 76.74	**<0.001**
Body adiposity			
ASAT (L)	7.50 ± 3.14	8.30 ± 3.31	**0.005**
VAT (L)	3.96 ± 2.21	5.36 ± 2.31	**<0.001**
VAT/ASAT	0.57 ± 0.34	0.72 ± 0.38	**<0.001**
QFI (%)	0.066 ± 0.022	0.072 ± 0.020	**0.002**

Data are mean ± SD or % (*n*). Boldface indicates significance accepted at $P < 0.05$. *Calculated only for participants taking medications.

for $OXPHOS_{CHO}$ (Table 2). Adjustment for VAT tended to explain some variance in $OXPHOS_{CHO}$ between participants with and without diabetes ($P = 0.06$) (Table 2). Within the diabetes group only, ATPmax was lower in older adults taking any hypoglycemic medication ($P = 0.05$) or metformin alone ($P = 0.01$) (Supplementary Table 1). These findings make it difficult to distinguish the impact of medications versus diabetes on ATPmax, and therefore, further analysis of mitochondrial oxidative capacity focused on respiration measurements. VO_2peak and mitochondrial oxidative capacity assessed by respiration were similar with the use of all hypoglycemic agents and metformin (Supplementary Table 1).

VO_2peak and Mitochondrial Oxidative Capacity Mediate the Relationship Between Diabetes and Walking Speed

To determine the extent to which cardiorespiratory fitness and mitochondrial oxidative capacity were linked to clinically meaningful outcomes in older adults with and without diabetes, we next evaluated their relationship with 400-m and 4-m walking speeds. Both were significantly lower in participants with diabetes compared with those without diabetes following adjustments for sex, age, and race (base model) (Table 3). To assess whether VO_2peak and mitochondrial respiration mediated the relationship between diabetes and walking speed, we compared the β-coefficient for mean

Table 2—Cardiorespiratory fitness and mitochondrial oxidative capacity in older adults with and without diabetes

Model	Diabetes status	VO_2peak (mL/min)	OXPHOS$_{CHO}$ (pmol/mg/ww)	maxOXPHOS$_{CHO}$ (pmol/mg/ww)	maxETS$_{CHO}$ (pmol/mg/ww)	OXPHOS$_{FAO}$ (pmol/mg/ww)	maxOXPHOS$_{FAO}$ (pmol/mg/ww)
Unadjusted	WOD	1,532.10 ± 16.67	**31.08 ± 0.45**	**60.63 ± 0.74**	**81.43 ± 0.97**	12.94 ± 0.22	**58.22 ± 0.84**
	WD	1,513.75 ± 36.19	**28.10 ± 0.97**	**55.11 ± 1.61**	**73.80 ± 2.11**	11.93 ± 0.47	**53.31 ± 1.78**
Model 1	WOD	**1,486.68 ± 19.07**	**30.14 ± 0.91**	**59.02 ± 1.45**	**77.53 ± 1.90**	**12.58 ± 0.47**	**59.25 ± 1.64**
	WD	**1,386.69 ± 25.66***	**27.88 ± 1.11**	**54.98 ± 1.80**	**71.25 ± 2.37**	**11.49 ± 0.55**	**54.12 ± 1.93**
Model 1 + PA (steps/day)	WOD	**1,487.30 ± 19.53**	30.15 ± 0.91	58.65 ± 1.47	**77.02 ± 1.98**	12.60 ± 0.50	**59.21 ± 1.61**
	WD	**1,412.11 ± 26.03**	28.51 ± 1.11	55.89 ± 1.78	**71.83 ± 2.44**	11.70 ± 0.59	**54.29 ± 1.92**
Model 1 + ASAT (L)	WOD	**1,492.37 ± 19.52**	**30.34 ± 0.94**	**59.50 ± 1.49**	**77.64 ± 1.95**	**12.67 ± 0.48**	**59.83 ± 1.67**
	WD	**1,376.07 ± 26.56***	**27.83 ± 1.15**	**55.07 ± 1.82**	**70.92 ± 2.45**	**11.37 ± 0.57**	**53.85 ± 1.98**
Model 1 + VAT (L)	WOD	**1,488.92 ± 19.56**	30.16 ± 0.94	**59.16 ± 1.49**	**77.33 ± 1.96**	**12.62 ± 0.49**	**59.57 ± 1.68**
	WD	**1,386.86 ± 26.60***	28.04 ± 1.15	**55.46 ± 1.81**	**71.29 ± 2.45**	**11.50 ± 0.57**	**54.66 ± 1.98**
Model 1 + VAT/ASAT	WOD	**1,491.43 ± 19.47**	**30.29 ± 0.94**	**59.39 ± 1.49**	**77.53 ± 1.95**	**12.67 ± 0.49**	**59.90 ± 1.68**
	WD	**1,391.58 ± 26.76***	**28.02 ± 1.16**	**55.44 ± 1.83**	**71.33 ± 2.46**	**11.44 ± 0.57**	**54.01 ± 2.00**
Model 1 + QFI (%)	WOD	**1,486.37 ± 19.00**	**30.28 ± 0.93**	**59.38 ± 1.48**	**77.78 ± 1.94**	**12.68 ± 0.48**	**59.74 ± 1.68**
	WD	**1,386.10 ± 25.75***	**27.97 ± 1.14**	**55.33 ± 1.81**	**71.06 ± 2.43**	**11.37 ± 0.57**	**54.22 ± 1.98**

Data are mean ± SE. Boldface indicates significance accepted at $P < 0.05$ and an asterisk indicates significance at 0.001. Model 1 is adjusted for age, race, sex, site/technician, BMI, and comorbidities. PA, physical activity; WD, with diabetes; WOD, without diabetes; ww, wet weight.

400-m and 4-m walking speed from the base linear regression model with the β-coefficient of models that included VO_2peak and/or mitochondrial respiration variables. Additional individual adjustments for maxOXPHOS$_{CHO}$ (400-m, P = 0.02; model 2), maxOXPHOS$_{FAO}$ (400-m, P = 0.02; model 3), and VO_2peak (400-m, P = 0.01; model 4) resulted in no significant change in group differences in 400-m walking speed between participants with and without diabetes (Table 3). Alternatively, for 4-m walking speed, further adjustments for maxOXPHOS$_{CHO}$ (4-m, P = 0.12; model 2) and maxOXPHOS$_{FAO}$ (4-m, P = 0.51; model 3) significantly mediated differences between groups, whereas VO_2peak (4-m, P = 0.04; model 4) did not. Examining the impact of combinations of VO_2peak and mitochondrial respiration revealed that VO_2peak with maxOXPHOS$_{CHO}$ (400-m, P = 0.07; 4-m, P = 0.27; model 5) or maxOXPHOS$_{FAO}$ (400-m, P = 0.20; 4-m, P = 0.99; model 6) mediated differences between those with and without diabetes. Full adjustments including potential confounders/mediators BMI and chronic conditions explained the remaining variance in walking speed between groups (Table 3). Comparing the β-coefficients for mean 400-m and 4-m walking speed from the base linear regression model with the those of models that included both VO_2peak and mitochondrial respiration variables revealed that VO_2peak and mitochondrial respiration explained an additional ∼46–100% of the variance in 400-m and 4-m walking speeds between groups (Fig. 1).

DISCUSSION

This study is the first to investigate whether cardiorespiratory fitness and skeletal muscle oxidative capacity contribute to slow walking speed in older adults with diabetes in a unique, well-phenotyped cohort of older adults that included 159 participants with diabetes. The main novel findings of the study are that *1*) the association of diabetes status with slow walking speed was mediated by VO_2peak and skeletal muscle mitochondrial respiration, *2*) VO_2peak and mitochondrial respiration were lower in older adults with diabetes while controlling for objectively assessed physical activity and adiposity, and *3*) older adults taking hypoglycemic medications (insulin, thiazolidinediones, and/or metformin) or metformin alone had significantly lower ATPmax compared with older adults with diabetes but not taking medications, an observation that aligns with reports in the literature that metformin can impair mitochondrial oxidative capacity. Slower walking speed is indicative of poor health and has been shown to associate with survival in older adults (28). Together, these findings are impactful as they are the first to link a biological quality of muscle (oxidative capacity) to explain slower walking speed in a particularly vulnerable patient population.

The well-phenotyped SOMMA cohort provided an opportunity to assess the impact of diabetes status on VO_2peak and mitochondrial oxidative capacity in older adults while controlling for objectively measured indices of physical activity, adiposity, and chronic conditions in addition to demographic variables. Many of the previous studies reporting lower muscle oxidative capacity measured in PmFBs from patients with diabetes have not rigorously assessed and controlled for the participants' physical activity (12–14,17). This is important because physical activity interventions (e.g., walking) can improve mitochondrial energetics in type 2 diabetes (29), during weight loss in obesity (30), and in older adults (31). Here, we report that lower levels of objectively assessed physical activity partially explain lower respiration in older adults with diabetes. Interestingly, comparing our

Table 3—Multivariable linear regression analysis for the association of diabetes with 400-m and 4-m walking speed

	Without diabetes	With diabetes	
Multivariable model	Mean ± SE	β ± SE	*P*
400-m walking speed (m/s)			
Base model: adjusted for sex, age and race	1.06 ± 0.01	−0.05 ± 0.01	**0.00**
Model 2: base model plus $maxOXPHOS_{CHO}$	1.06 ± 0.01	−0.04 ± 0.02	**0.02**
Model 3: base model plus $maxOXPHOS_{FAO}$	1.06 ± 0.01	−0.04 ± 0.02	**0.02**
Model 4: base model plus VO_2peak	1.07 ± 0.01	−0.04 ± 0.01	**0.01**
Model 5: base model plus VO_2peak and $maxOXPHOS_{CHO}$	1.07 ± 0.01	−0.03 ± 0.02	0.07
Model 6: base model plus VO_2peak and $maxOXPHOS_{FAO}$	1.07 ± 0.01	−0.02 ± 0.02	0.20
Fully adjusted: model 5 plus BMI and comorbidities	1.06 ± 0.01	0.003 ± 0.01	0.87
Fully adjusted: model 6 plus BMI and comorbidities	1.06 ± 0.01	−0.005 ± 0.02	0.78
4-m walking speed (m/s)			
Base model: adjusted for sex, age, and race	1.05 ± 0.01	−0.04 ± 0.02	**0.01**
Model 2: base model plus $maxOXPHOS_{CHO}$	1.04 ± 0.01	−0.03 ± 0.02	0.12
Model 3: base model plus $maxOXPHOS_{FAO}$	1.05 ± 0.01	−0.01 ± 0.02	0.51
Model 4: base model plus VO_2peak	1.05 ± 0.01	−0.04 ± 0.02	**0.04**
Model 5: base model plus VO_2peak and $maxOXPHOS_{CHO}$	1.05 ± 0.01	−0.02 ± 0.02	0.27
Model 6: base model plus VO_2peak and $maxOXPHOS_{FAO}$	1.05 ± 0.01	0.00 ± 0.02	0.99
Fully adjusted: model 5 plus BMI and comorbidities	1.05 ± 0.01	0.003 ± 0.02	0.84
Fully adjusted: model 6 plus BMI and comorbidities	1.05 ± 0.01	0.01 ± 0.02	0.50

Boldface indicates significance accepted at $P < 0.05$. Models including $maxOXPHOS_{CHO}$ and $maxOXPHOS_{FAO}$ are adjusted for technician, and models with VO_2peak are adjusted for site.

respirometry protocols with distinct substrate combinations, we found that $maxOXPHOS_{FAO}$ respiration remains lower in the diabetes group, while $maxOXPHOS_{CHO}$ did not differ following adjustments for physical activity. This suggests that carbohydrate-supported coupled respiration may be more sensitive to levels of physical activity compared with FAO-supported respiration. This is also in line with evidence indicating reduced rates of lipid oxidation in skeletal muscle from individuals with diabetes, potentially because of mitochondrial overload and incomplete FAO (32). We also acknowledge that reduced mitochondrial oxidative capacity may be due to reduced mitochondria content. Future analysis will investigate this further.

The influence of adiposity on mitochondrial energetics has been considered in prior studies of diabetes, typically by matching control subjects for BMI (14). Some studies

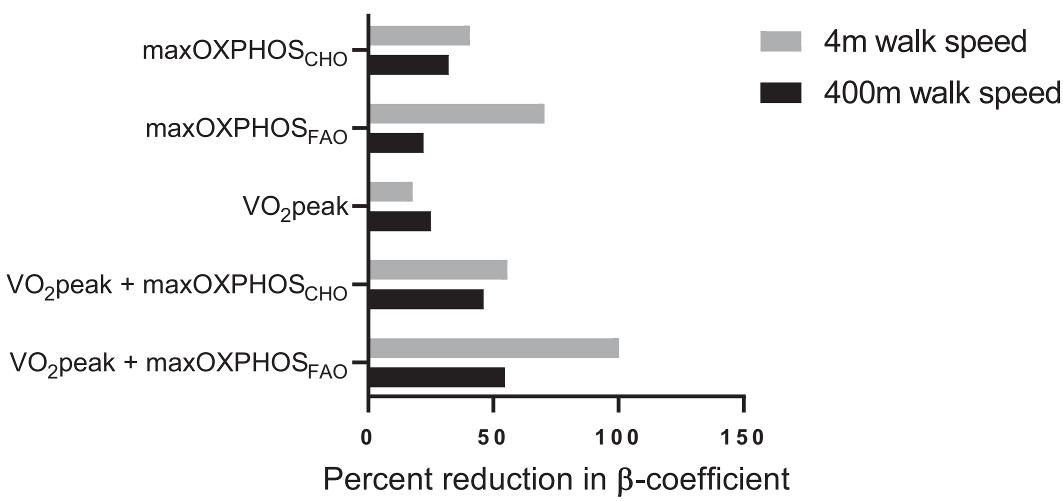

Figure 1—Percent reduction in the association between diabetes and 400-m and 4-m walking speed after adjusting for both individual and combined carbohydrate- and fatty acid–supported respiration and cardiorespiratory fitness. Bars depict the reduction in β-coefficient from linear regression models (models 2–6 compared with the base model: [1 − (β-adjusted/β-base adjusted)]. Base model includes age, sex, and race; model 2 includes base model plus $maxOXPHOS_{CHO}$; model 3 includes base model plus $maxOXPHOS_{FAO}$; model 4 includes base model plus VO_2peak, model 5 includes base model plus VO_2peak and $maxOXPHOS_{CHO}$; and model 6 includes base model plus VO_2peak and $maxOXPHOS_{FAO}$.

(15,16), but not all (12,13,17), indicated no differences between patients with diabetes and BMI-matched control subjects, suggesting that obesity per se may underlie the lower muscle oxidative capacity. Here, we examined the influence that BMI and individual adipose depots (ASAT, VAT, and QFI) and VAT/ASAT ratio had on muscle mitochondrial energetics in diabetes. However, regardless of whether adiposity was adjusted for BMI alone or combined with individually objectively measured adipose depots, mitochondrial respiration generally remained significantly lower in participants with diabetes. Taken together, these findings indicate that adiposity and physical activity largely (there were some exceptions) do not entirely explain lower mitochondrial respiration in older adults with diabetes.

Metformin is one of the most commonly prescribed medications for diabetes, and although its mechanism of action remains highly debated, there is evidence of an inhibitory effect on complex I of the electron transport chain (33,34). Both preclinical and clinical studies reported maladaptation of mitochondrial function following metformin treatment, and blunting of exercise induced increases in muscle hypertrophy and cardiorespiratory fitness, specifically in older adults (33,35,36). Conversely, others have reported that metformin can improve mitochondrial function via effects on mitophagy, autophagy (37), or AMPK activation (38). Our current understanding of how metformin impacts skeletal muscle mitochondrial function of older adults is reviewed in detail elsewhere (39,40). Here, we reveal lower ATPmax in older adults with diabetes taking hypoglycemic medication or metformin alone compared with older adults with diabetes not taking medications. Interestingly, we did not observe an association of metformin with diabetes status in the respiration assays, suggesting different sensitivities to metformin based on whether mitochondrial energetics are assessed in vivo (ATPmax) compared with PmFB preparations ex vivo. However, an important caveat is that participants were asked to withhold medication prior to the muscle biopsy and respirometry assays but not on the day of ^{31}P-MRS assessments. In addition, others have reported no effect on mitochondrial respiration after a 2-week metformin treatment compared with control subjects (41) or patients with long-term diabetes (42). Given that metformin is water soluble, it is also plausible that the inhibitory effect of metformin is lost when the muscle fiber bundles are washed in preparation for the respirometry assay. Further work is needed to decipher the impact metformin has on skeletal muscle mitochondrial energetics in older adults with diabetes.

Zhao et al. (43) reported that adults with diabetes were 31–34% less likely to participate in physical activity, which in turn may contribute to lower VO_2peak. In line with these reports, SOMMA participants with diabetes were significantly less active and significantly more sedentary. Additional adjustments for physical activity did not resolve differences in VO_2peak between groups, suggesting that lower VO_2peak in older adults with diabetes is independent of physical activity in this cohort. In addition, independent of adiposity measured by BMI or combined BMI with ASAT, VAT, VAT/ASAT, and QFI, VO_2peak remained significantly lower in participants with diabetes compared with those without. Taken together, our work suggests that physical activity and adiposity may not be implicated in lower cardiorespiratory fitness in older adults with diabetes and that other factors, including perhaps genetics and heritability, are more important determinants of low cardiorespiratory fitness in diabetes.

Previous work from our laboratory and others revealed a significant relationship between walking speed and both VO_2peak and mitochondrial energetics in older adults (9,28,44). Here, we explored the contribution of both mitochondrial respiration and cardiorespiratory fitness to mobility in older adults with diabetes. We report that mitochondria respiration, both independently (~40–70%) and combined with VO_2peak (~55–100%), mediated the variance in 4-m walking speed in participants with diabetes. Differences between groups are further explained by additional adjustments for potential confounders/mediators, including BMI and comorbidities. Reports have indicated that muscle mass is lost at an accelerated rate in older adults with diabetes (7), contributing to reductions in muscle strength and quality (6) and ultimately reducing physical function and mobility (5,45). We extend these findings by highlighting how mitochondrial respiration may independently and combined with cardiorespiratory fitness also contribute to lower walking speed in older adults with diabetes. This finding is of particular interest because slower walking speed is an important indicator of health and has been shown to associate with survival in older adults (28). Further assessments of specific aspects of the cardiorespiratory system (e.g., pulmonary function, oxygen transportation, muscle capillarization) and mitochondrial function (e.g., H_2O_2 emission, calcium retention capacity, membrane potential) may reveal novel targets to prevent mobility loss in older adults with diabetes.

Our study has several strengths but also a few notable weaknesses that we are well positioned to address in the future. First, the duration of diabetes status and the length of time that participants have been taking oral hypoglycemic agents were not recorded. However, this cohort is being followed longitudinally, so there is opportunity to capture that data in the future and for powerful analysis of changes over time in the same individuals. In addition, participants were predominantly (85.6%) non-Hispanic White, limiting our ability to generalize to other racial/ethnic groups where mobility disability is more prevalent (46). The participants recruited were able to complete a 4-m walking test at a gait speed of ≥0.6 m/s, which may be faster than those with more advanced diabetes who are unable to complete mobility-related tasks (2). However, longitudinal assessments will provide an opportunity to study decline in mobility and incident mobility disability in those with diabetes in the future. The strengths of our study design include the collection of muscle biopsies and use of two measurements of mitochondrial oxidative capacity in a large cohort of older individuals combined with rigorous assessment of objectively measured physical activity, fitness, and body composition. This unique study design allows us to link a fundamental biological process in muscle biopsies to a key clinical outcome. Furthermore, the collection of these biological resources, and the foundational work completed in the present study, will support future analysis focused on further understanding the biological qualities of muscle, including measures of mitochondrial content, that contribute to slower walking speed in older adults with diabetes.

In summary, our findings highlight that mitochondrial respiration independently and combined with cardiorespiratory fitness contribute to slower 400-m and 4-m walking speeds in older adults with diabetes. Additionally, future work should aim to decipher the impact of diabetes medication on mitochondrial function, as this remains a gap in the literature.

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Duality of Interest. S.R.C. and P.M.Ca. are consultants to Bioage Laboratories. P.M.Ca. is a consultant to and owns stock in MyoCorps. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.V.R. and L.-Y.L. completed the statistical analysis, with final review from the statistical team at the coordinating center. S.R.C., P.M.Ca., A.B.N., R.T.H., S.B.K., and B.H.G. enabled the study with either funding acquisition, project administration, and/or conceptualization of the study. S.V.R. and P.M.Co. conceived the idea and cowrote the manuscript. G.D., L.-Y.L., P.K., I.J.S., F.M.B., D.J.M., E.S., and P.M.Co. completed experiments or quality control, validation, and interpretation of data. G.D., L.-Y.L., P.M.Ca., P.K., T.M., M.J.J., A.J.M., E.E.K., D.J.M., F.G.S.T., A.B.N., R.T.H., S.B.K., B.H.G., and S.R.C. edited the manuscript. P.M.Co. 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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References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report. Accessed 29 November 2023. Available from https://www.cdc.gov/diabetes/data/statistics-report/index.html
2. Gregg EW, Beckles GL, Williamson DF, et al. Diabetes and physical disability among older U.S. adults. Diabetes Care 2000;23:1272–1277
3. 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
4. Gregg EW, Mangione CM, Cauley JA, et al.; Study of Osteoporotic Fractures Research Group. Diabetes and incidence of functional disability in older women. Diabetes Care 2002;25:61–67
5. Volpato S, Bianchi L, Lauretani F, et al. Role of muscle mass and muscle quality in the association between diabetes and gait speed. Diabetes Care 2012;35:1672–1679
6. Park SW, Goodpaster BH, Strotmeyer ES, et al. Decreased muscle strength and quality in older adults with type 2 diabetes: the health, aging, and body composition study. Diabetes 2006;55:1813–1818
7. Park SW, Goodpaster BH, Lee JS, et al.; Health, Aging, and Body Composition Study. Excessive loss of skeletal muscle mass in older adults with type 2 diabetes. Diabetes Care 2009;32:1993–1997
8. Coen PM, Jubrias SA, Distefano G, et al. Skeletal muscle mitochondrial energetics are associated with maximal aerobic capacity and walking speed in older adults. J Gerontol A Biol Sci Med Sci 2013;68:447–455
9. Gonzalez-Freire M, Scalzo P, D'Agostino J, et al. Skeletal muscle ex vivo mitochondrial respiration parallels decline in vivo oxidative capacity, cardiorespiratory fitness, and muscle strength: the Baltimore Longitudinal Study of Aging. Aging Cell 2018;17:e12725
10. Choi S, Reiter DA, Shardell M, et al. ^{31}P magnetic resonance spectroscopy assessment of muscle bioenergetics as a predictor of gait speed in the Baltimore Longitudinal Study of Aging. J Gerontol A Biol Sci Med Sci 2016;71:1638–1645
11. Newman AB, Haggerty CL, Kritchevsky SB, Nevitt MC; Health ABC Collaborative Research Group. Walking performance and cardiovascular response: associations with age and morbidity–the Health, Aging and Body Composition Study. J Gerontol A Biol Sci Med Sci 2003;58:715–720
12. Phielix E, Schrauwen-Hinderling VB, Mensink M, et al. Lower intrinsic ADP-stimulated mitochondrial respiration underlies in vivo mitochondrial dysfunction in muscle of male type 2 diabetic patients. Diabetes 2008;57:2943–2949
13. Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes 2002;51:2944–2950
14. Mogensen M, Sahlin K, Fernström M, et al. Mitochondrial respiration is decreased in skeletal muscle of patients with type 2 diabetes. Diabetes 2007;56:1592–1599
15. Boushel R, Gnaiger E, Schjerling P, Skovbro M, Kraunsøe R, Dela F. Patients with type 2 diabetes have normal mitochondrial function in skeletal muscle. Diabetologia 2007;50:790–796
16. Larsen S, Ara I, Rabøl R, et al. Are substrate use during exercise and mitochondrial respiratory capacity decreased in arm and leg muscle in type 2 diabetes? Diabetologia 2009;52:1400–1408
17. Schrauwen-Hinderling VB, Kooi ME, Hesselink MK, et al. Impaired in vivo mitochondrial function but similar intramyocellular lipid content in patients with type 2 diabetes mellitus and BMI-matched control subjects. Diabetologia 2007;50:113–120
18. Distefano G, Standley RA, Zhang X, et al. Physical activity unveils the relationship between mitochondrial energetics, muscle quality, and physical function in older adults. J Cachexia Sarcopenia Muscle 2018;9:279–294
19. Leite SA, Monk AM, Upham PA, Bergenstal RM. Low cardiorespiratory fitness in people at risk for type 2 diabetes: early marker for insulin resistance. Diabetol Metab Syndr 2009;1:8
20. Lee DC, Sui X, Church TS, Lee IM, Blair SN. Associations of cardiorespiratory fitness and obesity with risks of impaired fasting glucose and type 2 diabetes in men. Diabetes Care 2009;32:257–262
21. Cummings SR, Newman AB, Coen PM, et al. The Study of Muscle, Mobility and Aging (SOMMA): a unique cohort study about the cellular biology of aging and age-related loss of mobility. J Gerontol A Biol Sci Med Sci 2023;78:2083–2093
22. Montoye AHK, Clevenger KA, Pfeiffer KA, et al. Development of cut-points for determining activity intensity from a wrist-worn ActiGraph accelerometer in free-living adults. J Sports Sci 2020;38:2569–2578

23. Balady GJ, Arena R, Sietsema K, et al.; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010;122:191–225
24. Mau T, Lui L-Y, Distefano G, et al. Mitochondrial energetics in skeletal muscle are associated with leg power and cardiorespiratory fitness in the Study of Muscle, Mobility and Aging. J Gerontol A Biol Sci Med Sci 2023;78:1367–1375
25. Amara CE, Marcinek DJ, Shankland EG, Schenkman KA, Arakaki LS, Conley KE. Mitochondrial function in vivo: spectroscopy provides window on cellular energetics. Methods 2008;46:312–318
26. Meyerspeer M, Boesch C, Cameron D, et al.; Experts' Working Group on ^{31}P MR Spectroscopy of Skeletal Muscle. ^{31}P magnetic resonance spectroscopy in skeletal muscle: experts' consensus recommendations. NMR Biomed 2020; 34:e4246
27. Borga M, Ahlgren A, Romu T, Widholm P, Dahlqvist Leinhard O, West J. Reproducibility and repeatability of MRI-based body composition analysis. Magn Reson Med 2020;84:3146–3156
28. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA 2011;305:50–58
29. Toledo FG, Menshikova EV, Ritov VB, et al. Effects of physical activity and weight loss on skeletal muscle mitochondria and relationship with glucose control in type 2 diabetes. Diabetes 2007;56:2142–2147
30. Coen PM, Menshikova EV, Distefano G, et al. Exercise and weight loss improve muscle mitochondrial respiration, lipid partitioning, and insulin sensitivity after gastric bypass surgery. Diabetes 2015;64:3737–3750
31. Pruchnic R, Katsiaras A, He J, Kelley DE, Winters C, Goodpaster BH. Exercise training increases intramyocellular lipid and oxidative capacity in older adults. Am J Physiol Endocrinol Metab 2004;287:E857–E862
32. Kelley DE, Simoneau JA. Impaired free fatty acid utilization by skeletal muscle in non-insulin-dependent diabetes mellitus. J Clin Invest 1994;94:2349–2356
33. Wessels B, Ciapaite J, van den Broek NM, Nicolay K, Prompers JJ. Metformin impairs mitochondrial function in skeletal muscle of both lean and diabetic rats in a dose-dependent manner. PLoS One 2014;9:e100525
34. Brunmair B, Staniek K, Gras F, et al. Thiazolidinediones, like metformin, inhibit respiratory complex I: a common mechanism contributing to their antidiabetic actions? Diabetes 2004;53:1052–1059
35. Konopka AR, Laurin JL, Schoenberg HM, et al. Metformin inhibits mitochondrial adaptations to aerobic exercise training in older adults. Aging Cell 2019;18:e12880
36. Walton RG, Dungan CM, Long DE, et al. Metformin blunts muscle hypertrophy in response to progressive resistance exercise training in older adults: a randomized, double-blind, placebo-controlled, multicenter trial: the MASTERS trial. Aging Cell 2019;18:e13039
37. Bharath LP, Agrawal M, McCambridge G, et al. Metformin enhances autophagy and normalizes mitochondrial function to alleviate aging-associated inflammation. Cell Metab 2020;32:44–55.e6
38. de Marañón AM, Díaz-Pozo P, Canet F, et al. Metformin modulates mitochondrial function and mitophagy in peripheral blood mononuclear cells from type 2 diabetic patients. Redox Biol 2022;53:102342
39. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. Cell Metab 2020;32:15–30
40. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia 2017;60:1577–1585
41. McKenzie AI, Mahmassani ZS, Petrocelli JJ, et al. Short-term exposure to a clinical dose of metformin increases skeletal muscle mitochondrial H_2O_2 emission and production in healthy, older adults: a randomized controlled trial. Exp Gerontol 2022;163:111804
42. Larsen S, Rabøl R, Hansen CN, Madsbad S, Helge JW, Dela F. Metformin-treated patients with type 2 diabetes have normal mitochondrial complex I respiration. Diabetologia 2012;55:443–449
43. Zhao G, Ford ES, Li C, Balluz LS. Physical activity in U.S. older adults with diabetes mellitus: prevalence and correlates of meeting physical activity recommendations. J Am Geriatr Soc 2011;59:132–137
44. Coen PM, Hames KC, Leachman EM, et al. Reduced skeletal muscle oxidative capacity and elevated ceramide but not diacylglycerol content in severe obesity. Obesity (Silver Spring) 2013;21:2362–2371
45. 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
46. Okoro CA, Hollis ND, Cyrus AC, Griffin-Blake S. Prevalence of disabilities and health care access by disability status and type among adults - United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:882–887