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Low grip strength predicts incident diabetes among mid-life women: the Michigan Study of Women's Health Across the Nation

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Abstract

Background: skeletal muscle is the primary site of glucose uptake, yet the impact of age-related changes in muscle strength on diabetes risk is unknown.
Methods: four hundred and twenty-four participants (60% Black, 40% White) from the Michigan site of the Study of Women's Health Across the Nation contributed annual grip strength measures and were followed from 1996 to 2012 to identify incident cases of diabetes. Diabetes was defined as self-reported physician-diagnosed diabetes, use of anti-diabetic medications or measured fasting glucose ≥126 mg/dl or haemoglobin A1c > 6.5%.
Results: the 16-year diabetes incidence was 37%. The average baseline weight-normalised grip strength (NGS, kg per kg body weight) was 0.41 ± 0.12 and a mean of 0.29 ± 0.14 kg of absolute grip strength was lost per year. Each 0.1 higher NGS was associated with a 19% lower hazard of incident diabetes ($P = 0.006$) after adjustment for age, race/ethnicity, economic strain, smoking, menopause status, hormone use, physical activity and waist–hip ratio. In race/ethnic-stratified models, each 0.10 increase in NGS was associated with a 54% lower hazard of incident diabetes ($P < 0.0001$) among White women but the association among Black women was not statistically significant. In models without adjustment for waist–hip ratio or restricted to women <48 years of age at baseline, there was a statistically significant association between baseline NGS and incident diabetes among Black women. The rate of change in grip strength was not associated with diabetes incidence.
Conclusion: the mid-life is an important risk period for diabetes onset. Improving muscle strength. during mid-life may contribute to preventing diabetes among women

Keywords: *muscle strength, grip strength, diabetes, women, mid-life, older people.*

Introduction

Four-hundred-million people worldwide have diabetes but the projected prevalence in 2030 is in excess of 550 million [1], due in part to an ageing population, rising obesity rates and urbanisation. As a leading cause of multi-morbidity, the associated economic burden of diabetes has reached $550 billion in the USA alone [2]. At the population level, increases in diabetes incidence and declining mortality have led to an acceleration of lifetime risk of diabetes [3].

Muscle is a major site of glucose metabolism as up to 80% of glucose uptake occurs in the skeletal muscle [4]. Thus, loss of muscle with ageing may contribute to the development of age-related metabolic disorders [5]. Muscle weakness is independently associated with metabolic syndrome and diabetes in adults [6] and multiple large studies have demonstrated an association between muscle weakness and mortality [7, 8]. However, in the National Health and Nutrition Examination Survey (NHANES), the association of grip strength and pre-diabetes was present only among White individuals [9].

Although the global prevalence of diabetes is greater among men than women at all ages [10], emerging evidence suggests that women may be particularly at-risk for diabetes given higher rates of obesity [11] and a stronger association of obesity with diabetes risk among women [12]. In women, type 2 diabetes commonly manifests during the mid-life, often co-occuring with age and menopause-related changes in obesity and body composition [13]. Mid-life women experience lower levels of and more rapid declines in muscle strength than do age-matched men [14]. Whether these rapid declines in muscle strength among mid-life women contribute to increased metabolic risk during this time frame is largely unknown. Therefore, the goal of this study was to evaluate the longitudinal association between grip strength and incident diabetes in a large cohort of middle-aged women and to determine whether there was effect modification by race/ethnicity or baseline age.

Methods

Study population

The Study of Women's Health Across the Nation (SWAN) is a multi-ethnic observational study of the menopause transition; Michigan is one of seven clinical centres for SWAN. At enrolment in 1996, women were 42–52 years old with an intact uterus and in the previous 3 months, at least one menstrual period but no use of exogenous hormones. The full Michigan SWAN cohort included 543 women.

This analysis is based upon data from near-annual visits from 1996 to 2012/13. Retention was excellent; 75% of the still-living enrollees participated in the 2012/13 visit. Of the 543 women in the cohort, 32 were excluded due to missing grip strength data at baseline. In addition, 87 women were excluded from this analysis due to either prevalent diabetes (n = 53), history of stroke/heart attack (n = 9) or were lost to follow-up so incident diabetes status could not be ascertained (n = 25). The analytic sample includes 424 women. Women excluded from the analytic sample had slightly lower grip strength and were more likely to be obese and report economic hardship but were similar in all other respects as compared with the analytic sample. For the analysis of change in grip strength, 410 women with at least two grip strength assessments collected when the participant was non-diabetic were included.

Grip strength assessment

Grip strength was measured separately three times on both hands at each study visit with a Baseline® hydraulic hand dynamometer while the participant was seated with her elbow bent at a 90° angle. Weight-normalised grip strength (NGS), an indicator of muscle quality that accounts for body weight, was calculated as the maximum grip strength from a given visit divided by body weight. Body weight was measured to the nearest 0.1-kg at each annual visit using a balance beam scale.

Diabetes status

Diabetes status was ascertained at 13 visits over a 16-year period from 1996–2012. Diabetes was defined as: (1) self-reported doctor's diagnosis of diabetes; (2) self-reported use of anti-diabetic medications (oral medications or insulin) or (3) fasting blood glucose ≥126 mg/dl or haemoglobin A1c (HbA1c) ≥6.5%. More information on glucose and HbA1c assays is available in Supplemental Materials, *Age and Ageing* online. Incident diabetes was the first study visit in which a participant met the criteria for diabetes.

Co-variates

Baseline co-variates included age, self-reported race/ethnicity, difficulty paying for basics and smoking status (current vs. non-smoker). Co-variates assessed at each visit included menopausal status (pre-menopausal, post-menopausal, unknown menopause status due to hormone therapy or hysterectomy), self-reported exogenous hormone use, physical activity [15], measured waist and hip circumference, and measured height and weight. Body mass index (BMI) was calculated based upon measured height and weight (kg/m^2). More information on co-variates is available in Supplemental Materials, *Age and Ageing* online.

Statistical analysis

Baseline characteristics between incident diabetes cases and non-cases were compared using two-sample t-tests for continuous variables or Chi-squared tests for categorical variables. Results are presented as mean ± standard deviation or percentage as indicated. The exposures of interest were baseline NGS and absolute grip strength rate of change. Absolute grip strength rates of change were calculated from a linear mixed effects model with grip strength as the dependent variable and time as the independent variable; random intercepts and random effects for time ('random slopes') were incorporated in this model. A subject's grip strength rate of change was the sum of the population-average slope and her subject-specific random slope.

Complementary log-log models for interval-censored survival times were used to estimate hazard ratios (HR) for diabetes. This type of model describes the relationship between hazards at discrete time intervals and predictors, including time. It provides HR estimates that are equivalent to those from a continuous-time proportional hazards model when the survival times are interval-censored [16]. In this analysis, 'time-to-diabetes onset' was interval-censored because we did not know exactly when a participant developed diabetes; we only knew that she developed diabetes some time during the interval between visits. In the complementary log-log models, we modelled time using the middle point of each interval with penalised splines where smoothing parameters were selected by generalised cross-validation. This approach effectively modelled the baseline hazard of diabetes with penalised splines, while modelling the other co-variates linearly. We first ran the models in the entire analytic sample and then in each racial/ethnic group. Given emerging evidence suggesting that Black adults have an acceleration of age-related disease processes including cardiometabolic diseases [17], we also conducted sensitivity analyses by limiting our analysis to the 183 Black women (of whom 86 developed diabetes) and 120 White women (of whom 32 developed diabetes) who were younger than 48 years old at baseline. The age of 48 years was selected so as to capture women who could contribute at least 1 year of follow-up prior to age 50 years.

Analyses were completed using R software (version 3.2.2) using the function 'gam' in package 'mgcv 1.8–7'. Ethics approval was obtained from the University of Michigan Institutional Review Board.

Results

At baseline, the mean age was 46.4 ± 2.8 years, mean BMI was 31.4 ± 7.7 kg/m^2 and approximately one-half were obese (Table 1). By design, 60% of women were Black and 40% were White. The diabetes incidence in the full cohort over 16 years of follow-up was 37% (n = 157). Among those with incident diabetes, the average follow-up time was 8.7 years. Black women were more likely to have incident diabetes as compared with White women ($P < 0.0001$). Women with incident diabetes had a 14% higher baseline BMI ($P < 0.0001$), a 6% higher baseline waist-to-hip ratio ($P < 0.0001$) and were less physically active at baseline ($P < 0.0001$).

As shown in Table 2, Black women had greater baseline absolute grip strength (mean difference 2.3 kg, $P = 0.0002$) and baseline NGS (mean difference 0.023, $P = 0.037$) as compared with White women. There were no differences in absolute grip strength rate of change by race/ethnicity (mean difference 0.013 kg/year, $P = 0.34$).

Baseline grip strength and incident diabetes

At baseline, the average absolute grip strength was 32.9 ± 6.4 kg and the average NGS (kg per kg of body weight) was 0.41 ± 0.12 (Table 1). Women with incident diabetes had 9.3% lower mean baseline NGS (0.39) as compared with non-cases (0.43, $P = 0.0004$) (Table 1). Absolute baseline grip strength did not differ by incident diabetes status. In fully adjusted multi-variable models (Model 4), each 0.1 higher baseline NGS was associated with a 19% decreased hazard of incident diabetes (HR = 0.81, 95% confidence interval (CI): 0.70, 0.94) (Table 3).

Annualised rate of change in grip strength and incident diabetes

On average, women lost 0.29 ± 0.14 kg of grip strength per year. Given the average baseline grip strength of 32.9 kg, this rate of loss equates to ~1% strength loss/year. The

Table 1. Participant characteristics at baseline by incident diabetes status, Michigan site of the Study of Women's Health Across the Nation[a]

	Overall N = 424 Mean (SD)	Diabetes free during follow-up N = 267 Mean (SD)	Incident diabetes during follow-up N = 157 Mean (SD)	P-value
Age (years)	46.4 (2.8)	46.5 (2.8)	46.2 (2.8)	0.47
BMI (kg/m^2)	31.4 (7.7)	29.8 (6.9)	34.1 (8.3)	<0.0001
Waist-to-hip ratio	0.82 (0.07)	0.80 (0.07)	0.85 (0.07)	<0.0001
Active lifestyle index	2.7 (1.6)	3.0 (1.7)	2.3 (1.3)	<0.0001
Absolute grip strength (kg)	32.9 (6.4)	32.6 (6.3)	32.2 (6.6)	0.37
Weight-normalised grip strength	0.41 (0.12)	0.43 (0.11)	0.39 (0.12)	0.0004
	N (%)	N (%)	N (%)	
Race/ethnicity				
Black	252 (59.4%)	137 (51.3%)	115 (73.3%)	
White	172 (40.6%)	130 (48.7%)	42 (26.8%)	<0.0001
Obese	222 (52.4%)	117 (43.8%)	105 (66.9%)	<0.0001
Smoking status				
Current smoker	109 (25.7%)	56 (21.0%)	53 (33.8%)	
Not current smoker	315 (74.3%)	211 (79.0%)	104 (66.2%)	0.004
Difficulty paying for basics				
Very hard to pay for basics	42 (9.9%)	23 (8.6%)	19 (12.1%)	
Somewhat hard to pay for basics	138 (32.6%)	82 (30.7%)	56 (35.7%)	
Not hard at all to pay for basics	244 (57.6%)	162 (60.7%)	82 (52.2%)	0.20
Menopausal status				
Pre-menopausal	403 (95.1%)	252 (94.4%)	151 (96.2%)	0.55
Post-menopausal	3 (0.71%)	3 (1.1%)	0 (0.0%)	
Unknown	18 (4.3%)	12 (4.5%)	6 (3.8%)	

[a] Mean (SD) reported for all continuous variables. P-values were based on two-sample t-test for continuous variables and Chi-square test for categorical variables.

Table 2. Absolute and weight-normalised grip strength at baseline and absolute grip strength rate of change by race/ethnicity, Michigan site of the Study of Women's Health Across the Nation[a]

	Black *N* = 252 Mean (SD)	White *N* = 172 Mean (SD)	*P*-value
Baseline absolute grip strength (kg)	33.8 (6.7)	31.5 (5.6)	0.0002
Baseline weight-normalised grip strength	0.42 (0.12)	0.40 (0.100)	0.037
Absolute grip strength rate of change (kg/year)	−0.28 (0.16)	−0.29 (0.10)	0.34

[a] Mean (SD) reported for all continuous variables. *P*-values were based on two-sample *t*-test for continuous variables and Chi-square test for categorical variables.

Table 3. Hazard ratio (HR) of incident diabetes associated with baseline weight-normalised grip strength and annualised change in absolute grip strength among women at the Michigan site of the Study of Women's Health Across the Nation, overall and stratified by race/ethnicity

	Weight-normalised grip strength at baseline *n* = 424 women			Rate of change in absolute grip strength *n* = 410 women		
	HR[a]	95% CI	*P*-value	HR[b]	95% CI	*P*-value
Model 1[c]	0.74	(0.65, 0.85)	<0.0001	1.11	(0.96, 1.28)	0.17
Model 2[d]	0.75	(0.65, 0.86)	<0.0001	1.09	(0.94, 1.26)	0.24
Model 3[e]	0.76	(0.66, 0.87)	0.00013	1.08	(0.93, 1.25)	0.32
Model 4[f]	0.81	(0.70, 0.94)	0.0052	1.06	(0.91, 1.24)	0.42
Race/ethnicity stratified models reflecting adjustments from Model 3						
Black[g]	0.84	(0.72, 0.99)	0.034	1.13	(0.97, 1.33)	0.12
White[g]	0.44	(0.31, 0.62)	<0.0001	0.72	(0.46, 1.14)	0.16
Race/ethnicity stratified models reflecting adjustments from Model 4						
Black[h]	0.90	(0.77, 1.05)	0.17	1.13	(0.96, 1.33)	0.14
White[h]	0.46	(0.32, 0.67)	<0.0001	0.74	(0.47, 1.18)	0.21
Race/ethnicity stratified models (reflecting adjustments from Model 4), restricted to baseline age <48 years						
Black[i]	0.80	(0.66, 0.97)	0.023	1.15	(0.94, 1.40)	0.16
White[i]	0.45	(0.28, 0.73)	0.0011	0.86	(0.51, 1.46)	0.59

[a] Hazard ratio corresponds to 0.1 higher weight-normalised grip strength.

[b] Hazard ratio corresponds to per inter-quartile range faster decrease (−0.14 kg/year).

[c] Adjusted for baseline age, race/ethnicity, difficulty paying for basics and smoking status.

[d] Additionally adjusted for menopausal status and exogenous hormone use.

[e] Additionally adjusted for physical activity.

[f] Additionally adjusted for waist-to-hip ratio in models of weight-normalised baseline grip strength; additionally adjusted for time-varying BMI in models of rate of change in grip strength.

[g] Race/ethnic-stratified model, reflecting adjustments as in Model 3.

[h] Race/ethnic-stratified model, reflecting adjustments as in Model 4.

[i] Sensitivity analyses, race/ethnic-stratified model, restricted to women <48 years of age at baseline, reflecting adjustments as in Model 4.

rate of grip strength loss did not differ between women with and without incident diabetes ($P = 0.24$) and there was no statistically significant association of rate of change in grip strength and incident diabetes in the multi-variate models (Table 3).

Effect modification by race/ethnicity

In race/ethnic-stratified models (Table 3), the association between baseline NGS and incident diabetes was present among White women only. Among White women, each 0.1 greater baseline NGS was associated with a 54% lower hazard of incident diabetes (HR = 0.46, 95% CI: 0.32, 0.67) in fully adjusted models. For Black women, the association of baseline NGS and incident diabetes was not statistically significant in the fully adjusted model. However, in models without waist-to-hip ratio (Table 3, Model 3), there was evidence of a marginally statistically significant association between baseline NGS and incident diabetes (HR = 0.84, 95% CI: 0.72, 0.99) in Black women.

In age-restricted models among White women, the HR for diabetes virtually unchanged as compared with the estimates among the full sample of White women (Table 3). Among Black women, however, the association between baseline NGS and incident diabetes became stronger and statistically significant when restricting to women <48 years of age. In these younger Black women, each 0.1 greater baseline NGS was associated with a 20% decreased hazard of incident diabetes (95% CI: 0.66, 0.97).

Discussion

The principal finding of this study was that among mid-life White women, NGS at baseline was independently associated with incident diabetes across 16-years of follow-up. Cross-sectional studies have observed an association between low muscle strength and prevalent diabetes [18] but a major limitation of those studies is the inability to understand whether low muscle strength was a risk factor for diabetes or a consequence of living in a diabetic state. Evidence of a negative association between muscle strength and insulin and glucose levels even among individuals without diabetes [19] suggests that diminished strength may be present prior to the onset of diabetes. Further, greater declines in lean mass among undiagnosed diabetics as compared with prevalent cases suggests that the diabetic impact on lean mass occurs early in the disease process [20].

The association between low muscle strength and diabetes may be due to greater intramuscular adipose tissue and muscle atrophy [21] leading to insulin resistance within the skeletal muscle, triggered by detrimental effects on skeletal muscle mitochondrial function [22]. Intramuscular adipose tissue and muscle atrophy reduce the oxidative and phosphorylation activity of skeletal muscle mitochondria [23], thereby releasing reactive oxygen species [24] that damage skeletal muscle and impair glucose metabolism and disposal. Mitochondrial damage promotes the accumulation of intramuscular triglycerides [23], which can interfere with insulin signalling pathways inhibition of the insulin receptor [25].

Few longitudinal studies have examined the association between muscle strength and incident diabetes; of those that have, the results are mixed. In both the Prospective Urban–Rural Epidemiology study and the Canadian

Physical Activity Longitudinal Study, there was no association between grip strength and incident diabetes [7, 26], but in both, diabetes was based upon self-report. Given the high burden of undiagnosed diabetes, these null findings may be due to under-ascertainment of diabetes cases. When diabetes status ascertainment includes active follow-up of biochemical measures and medication histories, the evidence from longitudinal studies suggests an inverse association between muscle mass or strength and diabetes risk in certain populations. In the Health ABC, conducted among adults 70–79 years at baseline and followed for a median of 11.3 years, greater baseline muscle area and lean mass was associated with increased diabetes risk among overweight and obese women but not among men or normal weight women [27]. Conversely, in the Japanese-American Community Diabetes Study, an inverse association of handgrip strength and incident diabetes was present among lean individuals only [28]. In the Men Androgen Inflammation Lifestyle Environment and Stress Study including 1,600 men ≥35 years of age, grip strength and muscle quality but not muscle mass was associated with incident diabetes and the association was stronger in men with lower adiposity [29].

Importantly, our analysis uncovered racial/ethnic differences such that the association of low strength and diabetes risk was present among Black women only when the sample was restricted to a baseline age <48 years. Our findings are consistent with a recent analysis using data from the cross-sectional NHANES, which found an association of low grip strength and pre-diabetes among White participants only [9]. These results suggest that the role of strength on diabetes risk may be less evident in populations already at high risk of early onset, age-related diseases. Thus, younger Blacks may be at greater risk of declining muscle health due to higher fasting insulin, greater insulin resistance and lower insulin sensitivity as compared with Whites of the same age [30]. These findings may reflect a differential impact of major confounders for diabetes such as obesity and cardiometabolic risk factors by race/ethnicity. Although the Black and White women in our study had similar BMI and prevalence of obesity, evidence has shown that for a given BMI, Blacks have less visceral adipose tissue, the more metabolically active adipose tissue, as compared with Whites [31].

We did not observe an association between change in grip strength and incident diabetes. This null finding is notable and suggests that while strength declines are highly prevalent during the mid-life stage [32], it is the early measures of strength as one begins the mid-life stage that are most predictive of incident diabetes. These findings reinforce the importance of achieving maximum physical functioning during mid-life as a potential intervention to reduce diabetes later in life. Short bouts of inactivity can have major ramifications on muscle area and strength and even greater impacts on insulin sensitivity [33]. Resistance training can increase muscle mass and improve insulin sensitivity and glucose transport [34]. Regular engagement in strength training was associated with a 30% and 40% reduction in incident diabetes in the Women's Health Study (women aged 47–98 years) [35] and the Nurses' Health Study I (women 53–81 years) and II (women aged 36–55 years) [36], respectively. Thus, the potential benefits of resistance training on the prevention of metabolic disease are substantial.

This study has several notable strengths. Most importantly, the prospective design allows us to make inferences regarding the temporal relationship between muscle strength and incident diabetes. Second, examination of our question in a middle-aged population is novel as it reflects an important time in the life course marked by changes in both muscle strength and metabolic function. Third, the multi-ethnic composition of the sample allowed us to identify important racial/ethnic differences. Fourth, consideration of both self-report diabetes diagnosis and medication utilisation as well as study-ascertained fasting glucose and HbA1c values for diabetes case identification maximised our number of incident diabetes cases and eliminated concern about differential case capture by race/ethnicity. However, our study also had some limitations. While our results align with the mechanistic underpinnings of intramuscular adipose tissue and metabolic dysregulation, we did not have the necessary measures to explore this further. Given the epidemiologic and community-based nature of our study, we were limited by having grip strength measures only and not more sophisticated measures of muscle quality or whole body strength. However, like leg strength, grip strength has been shown to be an appropriate measure to identify overall muscle weakness in older adults [37]. Lastly, given our research question, we excluded prevalent diabetes cases at baseline from our analysis so we are missing some diabetes cases with mid-life onset. Therefore, the results observed in this study would likely reflect a conservative estimate of the true grip strength-diabetes association.

Conclusion

The major finding from our study was that lower mid-life NGS was predictive of incident diabetes among White women. Given the growing burden of diabetes at the population level, our findings are important for two major reasons. First, measurement of grip strength is a simple and cost-effective test and has shown to be an important biomarker of ageing given its value in predicting cardiovascular disease, cardiovascular mortality and all-cause mortality [7]. The strong association between grip strength and incident diabetes suggests that grip strength assessment may be a promising screening tool for the identification of diabetes risk, particularly earlier in the life course before the onset of other hallmark age-related risk factors for disease. Second, while current research supports a link between mid-life muscle strength and late-life functional limitations and disability [38], our findings add further support to the importance of mid-life muscle weakness as an important correlate of metabolic dysfunction in later life.

Key points

- Age-related declines in skeletal muscle may be associated with risk for cardiometabolic diseases.
- Lower weight-NGS predicted incident diabetes over 16 years of follow-up.
- Important race/ethnic differences were observed in the association of grip strength and diabetes incidence during mid-life.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Conflicts of Interest

None.

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