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ORIGINAL RESEARCH ARTICLE

Muscle Weakness Thresholds for Prediction of Diabetes in Adults

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Abstract

Background Despite the known links between weakness and early mortality, what remains to be fully understood is the extent to which strength preservation is associated with protection from cardiometabolic diseases, such as diabetes.

Purpose The purposes of this study were to determine the association between muscle strength and diabetes among adults, and to identify age- and sex-specific thresholds of low strength for detection of risk.

Methods A population-representative sample of 4066 individuals, aged 20–85 years, was included from the combined 2011–2012 National Health and Nutrition Examination Survey (NHANES) data sets. Strength was assessed using a handheld dynamometer, and the single highest reading from either hand was normalized to body mass. A logistic regression model was used to assess the association between normalized grip strength and risk of diabetes, as determined by haemoglobin A_{1c} levels $\geq$6.5 % ($\geq$48 mmol/mol), while controlling for sociodemographic characteristics, anthropometric measures and television viewing time.

Results For every 0.05 decrement in normalized strength, there were 1.26 times increased adjusted odds for diabetes in men and women. Women were at lower odds of having diabetes (odds ratio 0.49; 95 % confidence interval 0.29–0.82). Age, waist circumference and lower income were also associated with diabetes. The optimal sex- and age-specific weakness thresholds to detect diabetes were 0.56, 0.50 and 0.45 for men at ages of 20–39, 40–59 and 60–80 years, respectively, and 0.42, 0.38 and 0.33 for women at ages of 20–39, 40–59 and 60–80 years, respectively.

Conclusions and Clinical Relevance We present thresholds of strength that can be incorporated into a clinical setting for identifying adults who are at risk of developing diabetes and might benefit from lifestyle interventions to reduce risk.

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Key Points

In this study, normalized grip strength was robustly associated with diabetes in adults, even after adjustment for various known predictors.

Sex-specific low-, intermediate- and high-risk categories are presented, such that the highest risk is represented at normalized grip strengths of ≤0.56, 0.50 and 0.45 for men at ages of 20–39, 40–59 and 60–80 years, respectively, and ≤0.42, 0.38 and 0.33 for women at ages of 20–39, 40–59 and 60–80 years, respectively.

Grip strength measurement is a feasible strategy, which can be easily incorporated into a clinical or community setting for identifying adults who are at risk of developing diabetes and could benefit from lifestyle interventions, such as exercise and/or weight loss to reduce risk.

1 Introduction

Worldwide, there are more than 380 million people with diabetes, and the associated economic burden has reached nearly $550 billion in the USA alone [1]. Age-related declines in physical function and morphological health further contribute to exaggerated risk at the individual level; yet increases in the incidence of diagnosed diabetes, combined with declining mortality or increased life expectancy, have led to an acceleration of lifetime risk and more years spent with diabetes at the population level [2]. Early screening and promotion efforts for healthy aging among higher-risk populations are thus vital to reduce incidence and preventable comorbidities, as well as to curtail the escalating healthcare burden associated with diabetes.

Of particular relevance to both, there is increasingly compelling evidence to highlight the importance of muscular strength as a protective factor for health across populations. Perhaps the quintessential example of this is represented by the growing body of survival studies that demonstrate an independent association between muscle weakness and early, cardiovascular and all-cause mortality [3–9]. The contribution of muscle atrophy and weakness to progression of secondary complications with aging and/or disease (e.g. frailty and mobility disability) is equally unequivocal, and recent national efforts to identify cut points or thresholds for weakness among older adults [9–11] will aid clinicians to screen individuals with greatest risk.

What remains to be fully understood is the extent to which strength preservation is associated with protection from cardiometabolic diseases, such as diabetes, and, moreover, whether age- and sex-specific cut points for strength can be established for risk stratification. Senechal et al. [12] showed that low strength is independently associated with increased odds of the metabolic syndrome in middle-aged and older men, and they were able to identify cut points for low normalized strength that best predicted increased risk. Two very recent studies from the Baltimore Longitudinal Study of Aging (BLSA) demonstrated that greater adiposity [13] and chronic hyperglycaemia [14] (two hallmark features of diabetes) are associated with persistently lower muscle quality and strength, respectively, and that these secondary consequences may be mediated by neurological factors, such as neuropathy. We and others have shown an independent, inverse association between low strength and cardiometabolic risk clustering even among adolescents [15–17], reiterating the need for early and improved clinical screening strategies across populations. Therefore, the purposes of this study were to examine the independent association between handgrip strength capacity and diabetes in a large, nationally representative sample and to explore potential age- and sex-specific thresholds of weakness, for optimal risk categorization.

2 Research Design and Methods

2.1 Study Population

The National Health and Nutrition Examination Survey (NHANES) is a programme of studies designed to assess the health and nutritional status of adults and children in the USA. The NHANES 2011–2012 survey was specifically chosen on the basis of the wealth of relevant information pertaining to markers of cardiometabolic health for diabetes and insulin resistance (IR), and direct measures of muscle strength capacity. Of the 5319 participants in the NHANES 2011–2012 who were aged 20 years and older, 4066 had (1) complete demographic and anthropometric data; (2) valid strength data from assessment with a handgrip dynamometer; (3) the necessary blood samples obtained for non-fasting haemoglobin A_{1c} (HbA_{1c}) determination; and (4) valid questionnaire data pertaining to daily and weekly physical activities and sedentary behaviours. Ethical approval was obtained through the National Center for Health Statistics (NCHS) Research Ethics Review Board (protocol #2011-17), and subsequent approval for secondary data analyses was not required. All procedures that were followed were in accordance with the ethical standards of the NCHS Research Ethics Review

Board and with the Helsinki Declaration of 1975 (as revised in 2013), and informed consent was obtained from all patients included in the study.

2.2 Demographic and Anthropometric Factors

Sociodemographic characteristics were all assessed by self-report during an in-home interview. Age was used as a continuous variable. Race/ethnicity was categorized as (1) non-Hispanic white; (2) non-Hispanic black; (3) Mexican American or other Hispanic; and (4) other, including multiracial. Education was categorized as (1) less than high school graduate; (2) high school graduate/general educational development (GED) or equivalent, and/or some college or Associate's degree (e.g. Associate of Arts or Associate of Science); and (3) college graduate or above. Annual household income was categorized as (1) ≤$24,999; (2) $25,000–$54,999; (3) $55,000–$74,999; and (4) ≥$75,000.

Weight was measured using a digital Toledo scale (Mettler-Toledo International, Inc., Columbus, OH, USA), and participants wore only underwear, a gown and foam slippers. Height was measured using a fixed stadiometer. The body mass index (BMI) was calculated as (body weight in kg)/(height in m)^2. Standard categories were applied to determine if each participant was normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9) or obese (BMI ≥30). Individuals with a BMI <18.5 kg/m^2 were excluded because of the known association between underweight status and diabetes risk in older adults [18]. Waist circumference was measured to the nearest 0.1 cm at the level of the iliac crest and was used in the analyses as a continuous variable.

2.3 Cardiometabolic Parameters

Participants were tested on routine cardiometabolic parameters. Resting systolic and diastolic blood pressures were measured 3–4 times with a mercury sphygmomanometer by trained staff. Non-fasting measures of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose and insulin concentrations were measured. Non-fasting serum measures of HbA_{1c} were included as a diagnostic test for diabetes, which reflected average plasma glucose levels for the previous ≈3 months. For a subset of individuals, fasting measures were obtained for plasma glucose and insulin, as well as a 2-h oral glucose tolerance test (OGTT). For fasting glucose and insulin, the Homeostasis Model of Assessment (HOMA) score was calculated according to the following formula: [insulin $(I)_0$ in μU per mL × glucose $(G)_0$ in mmol per L]/22.5. For the OGTT, eligible participants were administered a 75 g glucose load (Trutol) [or a calibrated dose for participants weighing <94 pounds (<42.64 kg)], and a blood sample was drawn 2 h later. Glucose was measured in plasma by a hexokinase method using a Roche/Hitachi 911 analyser and a Roche Modular P chemistry analyser (Roche Diagnostics, Indianapolis, IN, USA). The interassay coefficient of variation ranged from 0.8 to 2.6 %.

Subjects were classified with/without diabetes or IR on the basis of laboratory data from fasting and non-fasting plasma. The primary analyses were based on elevated non-fasting HbA_{1c} levels [≥6.5 % (≥48 mmol/mol)] [19], as this provided the largest sample size. A separate analysis was completed on the smaller subset of individuals with fasting plasma measures for which diabetes or IR was designated on the combined basis of (1) an elevated fasting glucose level (≥126 mg/dL); (2) an elevated 2-h glucose level during the OGTT (≥200 mg/dL); and/or (3) a HOMA score of ≥5.9, as validated against a hyperinsulinaemic–euglycaemic clamp by Tam et al. [20]. Diabetes was not categorized into type 1 or 2. Therefore, participants with diabetes who had been diagnosed at the age of 30 years or younger, and/or who were being treated with insulin alone, were excluded, as they were considered likely to have type 1 diabetes.

2.4 Exposure Variable: Grip Strength

Strength was assessed using a hydraulic handgrip dynamometer (Takei Digital Grip Strength Dynamometer, model T.K.K.5401; Takei Scientific Instruments Co., Ltd, Niigata City, Japan). Detailed descriptions of the protocol are provided in the NHANES Muscle Strength Procedures Manual [21]. Briefly, a trained examiner explained and demonstrated the protocol to the participant, then adjusted the grip size of the dynamometer to the participant's hand size and asked the participant to squeeze the dynamometer for a practice trial. Thereafter, the participant was randomly assigned to start the test with his/her dominant or non-dominant hand, and was asked to squeeze the dynamometer as hard as possible, exhaling while squeezing. The test was then repeated for the opposite hand. Each hand was tested three times, alternating hands between trials, with a 60-s rest between measurements on the same hand. The grip test was performed in the standing position unless the participant was physically limited. Participants were excluded from this component if they were unable to hold the dynamometer and perform strength testing with both hands. Participants who had undergone surgery on either hand or wrist within the previous 3 months were not tested on that particular hand. Since there is substantial covariance between strength capacity and body mass—and, moreover, the links between muscle strength and both physical function and chronic health are mediated by the

proportion of strength relative to body mass—grip strength was normalized as strength per body mass [i.e. (grip strength in kg)/(body mass in kg)].

2.5 Potential Covariate: Sedentary Behaviour

Sedentary behaviour was determined during the 2011–2012 NHANES cohort through questionnaires (variable name prefix PAQ), which was based on the World Health Organization's Global Physical Activity Questionnaire (GPAQ) [22, 23]. For this study, sedentary behaviour was analysed in two ways, including (1) participants' answers to a general question about total combined sitting time per day (i.e. in hours) during work, at home, during transportation, while reading, while playing cards, while using a computer, etc.; and (2) participants' self-reported television or video viewing time per day, during the past 30 days. For television or video viewing time, participants were asked to provide answers as relevant to the following categories: (a) <1 h; (b) 1 h; (c) 2 h; (d) 3 h; (e) 4 h; (f) ≥5 h; or (g) do not watch television or videos (which we combined with '<1 h' for the analyses). For both questions, all data from participants who refused to answer or did not know the answer were coded as missing.

2.6 Statistical Analysis

All statistical analyses were conducted using SAS version 9.3 software (SAS Institute, Cary, NC, USA) and R version 3.1.2 software (R Foundation for Statistical Computing, Vienna, Austria) with a survey package [24]. NHANES employs a multistage sampling design. Sample weights were used to adjust for oversampling, survey nonresponse and post-stratification. Further, we took into account subsample weights, since we conducted analysis on persons with non-fasting glucose measurements. These weights were used to produce unbiased estimates. To obtain correct variance estimation, information on the strata and primary sampling unit (PSU) were also utilized. Descriptive characteristics were quantified as means, standard errors and percentages. Differences in these characteristics across age categories were tested using linear regression (proc surveyreg) and logistic regression (proc surveylogistic) for continuous and categorical variables, respectively, after creation of appropriate categories and dummy coding for each. A similar strategy was used to test differences for outcomes between men and women across equivalent age categories. To assess the odds of diabetes or IR in the entire sample, we utilized the multivariate logistic regression modelling approach with the forward and backward selection procedure. Known risk factors—including sex, age, waist circumference, race, sedentary behaviour and normalized strength—were adjusted for in the model. Education, income, quadratic of age, quadratic of income, quadratic of sedentary behaviour, interaction of sex and race, and interaction of sex and normalized strength were determined if included in the final model through the forward and backward selection procedure. The logistic regression model with the highest Akaike information criterion (AIC) was retained as the final model. The performance of the final logistic regression model was evaluated through a receiver operating characteristic (ROC) curve, which was created by plotting the true positive rate (TPR) against the false positive rate (FPR) at various threshold settings. The calculations of TPR and FPR also properly accounted for sample weights, strata and PSU.

2.6.1 Threshold Analyses

We also investigated individual strength thresholds across subgroups stratified by sex and age category (20–40, 40–60 and 60–80 years). Within each group, the predictive probabilities of all subjects were calculated. A non-parametric curve with local polynomials fitted with four degrees of freedom on normalized strength versus the logit of predictive probabilities was obtained (svysmooth in the R survey package). This non-parametric smoothing curve depicts the relationship between decreased normalized strength and increased risk of diabetes [i.e. HbA_{1c} level ≥6.5 % (≥48 mmol/mol)]. We then calculated the lower and upper tertiles of predictive probabilities (33.3 and 66.7 % percentiles) of the risk of diabetes, and the corresponding normalized strength values were determined as the screening thresholds.

3 Results

Descriptive data are presented as means, standard errors and percentages across age categories in Table 1. In both men and women, the prevalence rates of abdominal obesity and most cardiometabolic risk factors were significantly higher across age categories. The diabetes prevalence rates, according to elevated HbA_{1c} levels [≥6.5 % (≥48 mmol/mol)], were higher with increasing age and were 3.2, 13.2 and 23.7 % for men at ages of 20–39, 40–59 and 60–80 years, respectively, and 3.1, 11.1 and 19.0 % for women at ages of 20–39, 40–59 and 60–80 years, respectively. Diabetes or IR prevalence rates, according to elevated fasting glucose levels (≥126 mg/dL), elevated 2-h OGTT glucose levels (≥200 mg/dL) and/or HOMA-estimated IR (HOMA-IR) (HOMA scores ≥5.9), were also greater with increasing age and were 14.9, 27.7 and 39.5 % for men at ages of 20–39, 40–59 and 60–80 years, respectively, and 14.7, 21.5 and 34.3 % for women at ages

Table 1 Demographic and cardiometabolic characteristics of the study population by sex and age category

Characteristic	Men			Women		
	Age 20–39.9 years, $n = 648$	Age 40–59.9 years, $n = 592$	Age 60–80 years, $n = 552$	Age 20–39.9 years, $n = 646$	Age 40–59.9 years, $n = 610$	Age 60–80 years, $n = 550$
Age (years)	29.17 (0.43)	49.56 (0.38)	69.00 (0.39)	29.26 (0.43)	49.61 (0.18)	70.00 (0.34)
BMI (kg/m^2)	27.83 (0.36)	29.37 (0.25)†	28.65 (0.36)	28.63 (0.30)*	29.64 (0.34)†	29.31 (0.41)
Obesity (%)[a]	30.3	35.7†	32.6	35.1*	45.2*,†	43.2*,§
Waist circumference (cm)	95.92 (0.97)	103.69 (0.67)	105.74 (0.94)	93.45 (0.79)	97.62 (0.61)	99.19 (0.92)
Abdominal obesity (%)[b]	30.1	44.0†	51.2‡,§	54.2*	71.1*,†	76.0*,‡,§
Self-reported television viewing (hours/week)	2.20 (0.10)	2.46 (0.08)†	3.16 (0.08)‡,§	2.33 (0.14)	2.35 (0.09)	3.10 (0.08)‡,§
Grip strength (kg)	50.51 (0.38)	47.30 (0.59)†	40.17 (0.63)‡,§	31.92 (0.23)*	30.38 (0.28)*,†	24.89 (0.24)*,‡,§
Normalized grip strength[c]	0.60 (0.01)	0.53 (0.01)†	0.47 (0.01)‡,§	0.44 (0.01)*	0.41 (0.01)*,†	0.35 (0.01)*,‡,§
HbA_{1c} (%)	5.37 (0.03)	5.75 (0.07)†	6.01 (0.07)‡,§	5.31 (0.03)	5.70 (0.04)†	5.92 (0.05)‡,§
Diabetes (%)[d]	3.2	13.2†	23.7‡,§	3.1	11.1†	19.0‡,§
Glucose (mg/dL)	99.05 (1.12)*	111.69 (2.66)*,†	116.56 (2.53)‡,§	95.39 (0.75)	104.07 (1.69)†	114.61 (3.20)‡,§
Insulin (μU/mL)	12.82 (0.59)	15.22 (1.47)†	13.64 (0.78)	12.84 (0.50)	13.05 (0.82)	12.90 (0.35)
HOMA score	3.31 (0.19)	4.52 (0.54)*,†	4.24 (0.45)§	3.21 (0.14)	3.59 (0.27)	3.93 (0.20)§
2-h OGTT glucose (mg/dL)	98.43 (1.51)	119.33 (4.50)*,†	130.65 (6.92)‡,§	102.48 (2.11)	112.28 (2.32)†	141.75 (4.89)*,‡,§
Diabetes or IR (%)[e]	14.9	27.7*,†	39.5‡,§	14.7	21.5†	34.3‡,§
Triglycerides (mg/dL)	121.52 (5.47)*	154.34 (6.99)*,†,‡	126.12(8.46)	105.69 (4.93)	120.02 (7.01)†	132.07 (6.11)‡,§
Total cholesterol (mg/dL)	182.37 (1.66)	200.15 (1.85)†,‡	180.86 (1.41)	182.57 (1.35)	207.14 (1.90)*,†	204.64 (2.45)*,§
HDL cholesterol (mg/dL)	47.41 (0.52)*,§	46.45 (0.62)*,‡	50.47 (1.13)*	55.64 (0.94)§	58.38 (1.23)	59.33 (1.19)
LDL cholesterol (mg/dL)	112.60 (1.81)*,§	120.92 (2.50)†,‡	105.19 (2.56)	107.72 (1.11)	125.37 (1.85)*,†,‡	118.57 (1.86)*,§
Systolic blood pressure (mmHg)	118.54 (0.53)*	124.25 (0.97)*,†	131.23 (1.01)‡,§	111.00 (0.77)	119.33 (0.70)†	134.89 (1.27)*,‡,§
Diastolic blood pressure (mmHg)	72.22 (0.59)*	77.20 (0.59)*,†,‡	71.20 (0.49)	69.90 (0.74)	73.78 (0.47)†,‡	70.90 (0.88)

The data are expressed as mean (SE), except where percentages alone are given

BMI body mass index, *HbA_{1c}* haemoglobin A_{1c}, *HDL* high-density lipoprotein, *HOMA* Homeostasis Model of Assessment, *IR* insulin resistance, *LDL* low-density lipoprotein, *OGTT* oral glucose tolerance test, *SE* standard error

*Significant difference between men and women in equivalent age category: denoted as group with higher risk

† Significant difference between the ages of 20–39.9 years and 40–59.9 years ($p < 0.01$): denoted as group with higher risk

‡ Significant difference between the ages of 40–59.9 years and 60–80 years ($p < 0.01$): denoted as group with higher risk

§ Significant difference between the ages of 20–49.9 years and 60–80 years ($p < 0.01$): denoted as group with higher risk

[a] Obesity: BMI >30 kg/m^2

[b] Abdominal obesity based on sex-specific waist circumference

[c] Normalized grip strength measured as (grip strength in kg)/(body mass in kg)

[d] Diabetes: HbA_{1c} level ≥6.5 % (≥48 mmol/mol)

[e] Diabetes or HOMA-estimated IR: glucose level ≥126 mg/dL or 2-h OGTT glucose level ≥200 mg/dL or HOMA score ≥5.9

Table 2 Multiple logistic regression models for independent predictors of diabetes [haemoglobin A_{1c} level ≥6.5 % (≥48 mmol/mol)] in adults

Model predictor	Estimate	SE	OR (95 % CI)	Pr > χ^2
Sex (reference: male)	−0.71	0.26	0.49 (0.29–0.82)	0.01
Age	0.18	0.02	1.20 (1.20–1.26)	<0.001
Waist circumference	0.04	0.01	1.04 (1.02–1.06)	<0.001
Race/ethnicity (reference: non-Hispanic white)				
Non-Hispanic black	1.01	0.23	2.75 (1.78–4.24)	<0.001
Hispanic or Mexican American	1.02	0.21	2.77 (1.83–4.18)	<0.001
Other race or multiracial	1.42	0.22	4.11 (2.67–6.32)	<0.001
Annual household income (reference: ≥$75,000)				
<$24,999	0.76	0.23	2.13 (1.35–3.35)	<0.001
$25,000–$54,999	0.18	0.20	1.19 (0.80–1.77)	0.38
$55,000–$74,999	0.59	0.24	1.82 (1.12–2.93)	0.01
Self-reported television viewing time	0.04	0.04	1.04 (0.96–1.13)	0.38
Relative grip strength	−4.61	1.39	0.79 (0.69–0.91)[a]	<0.001
Age × age	0.00	0.00	0.99 (0.99–1.00)	<0.001

CI confidence interval, *OR* odds ratio, *Pr* probability, *SE* standard error

[a] OR (95 % CI) for every 0.05 (5 %) incremental increase in relative grip strength

of 20–39, 40–59 and 60–80 years, respectively. There were no significant differences in diabetes or IR between men and women in any age category, except for a lower prevalence of the combination of elevated fasting glucose levels, elevated 2-h OGTT glucose levels and/or HOMA-IR designation among middle-aged women (aged 40–59 years) [odds ratio (OR) 0.52; 95 % confidence interval (CI) 0.36–0.75; $p < 0.001$]. Across all age categories, men were stronger than women in both absolute and normalized grip strength capacity (all $p < 0.001$); however, daily television viewing time did not differ between men and women for any age category. For both men and women, there were significantly lower grip strengths across older ages and significantly greater television viewing time in men (all $p < 0.001$). Among women, the oldest age category (aged 60–80 years) had a significantly greater daily television viewing time than both the youngest women (aged 20–39 years) and middle-aged women (aged 40–59 years) (both $p < 0.01$).

In both men and women, normalized grip strength was inversely correlated with HbA_{1c} levels ($r = -0.26$ and -0.27, respectively; $p < 0.001$), fasted glucose levels ($r = -0.22$ and -0.27, respectively; $p < 0.001$), 2-h OGTT glucose levels ($r = -0.29$ and -0.26, respectively; $p < 0.001$) and HOMA scores ($r = -0.19$ and -0.34, respectively; $p < 0.001$). In the sex-stratified univariate analyses, lower grip strength was strongly associated with increased odds of diabetes [i.e. HbA_{1c} level ≥6.5 % (≥48 mmol/mol)] in adults, such that for every 0.05 decrement in normalized strength, there were 1.51 and 1.83 increased odds ($p < 0.001$) for men and women, respectively.

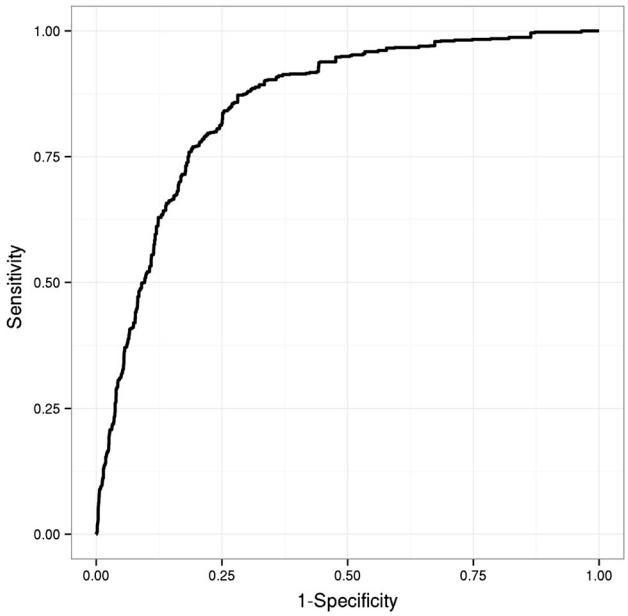

Fig. 1 Receiver operating characteristic (ROC) curve for the final, best model for the prediction of diabetes [haemoglobin A_{1c} level ≥6.5 % (≥48 mmol/mol)]. The area under the ROC curve = 0.85

In the adjusted model (Table 2), women were at lower odds of having diabetes than men, whereas non-Hispanic blacks, Mexican Americans or other Hispanics, and other races or multiracial subjects were at significantly higher odds (reference category: non-Hispanic whites; all $p < 0.001$). Moreover, age, waist circumference and lower income were each associated with diabetes; however, self-reported television viewing time was not a significant predictor. The final adjusted model with the best AIC value

Table 3 Age- and sex-specific thresholds for high and low normalized grip strength [measured as (grip strength in kg)/(body mass in kg)], with corresponding risk percentages for diabetes [haemoglobin A_{1c} level ≥6.5 % (≥48 mmol/mol)]

Relative strength threshold	Normalized grip strength (prevalence % for diabetes)					
	Men			Women		
	Age 20–39.9 years	Age 40–59.9 years	Age 60–80 years	Age 20–39.9 years	Age 40–59.9 years	Age 60–80 years
Low risk/high strength	0.65 (0.4)	0.57 (3.7)	0.50 (8.9)	0.48 (0.4)	0.44 (2.6)	0.38 (6.2)
High risk/low strength	0.56 (1.4)	0.45 (8.9)	0.45 (17.9)	0.42 (1.3)	0.38 (7.1)	0.33 (14.7)

had an area under the ROC curve of 0.85 (Fig. 1). Even after adjustment for all other model predictors, lower grip strength was still strongly associated with diabetes, such that for every 0.05 decrement in normalized strength, there were 1.26 increased odds (95 % CI 1.07–1.45). Stratification by sex in the fully adjusted models revealed no differences between men and women in the associations between strength and diabetes (data not shown).

In the smaller subset of individuals with fasted serum test results, the results were similar albeit attenuated, such that for every 0.05 decrement in normalized strength, there were 1.18 increased odds of diabetes (95 % CI 1.05–1.33), even after adjustment for all other predictors.

3.1 Threshold Analysis

Thresholds were determined as the corresponding normalized strength at the lower and upper tertiles of the predictive probabilities for the risk of diabetes, per sex and age categories, through fitting of non-parametric local polynomial curves. Age- and sex-specific thresholds for high strength and low strength are provided in Table 3, with corresponding risk percentages for diabetes [i.e. HbA_{1c} level ≥6.5 % (≥48 mmol/mol)]. These thresholds may, therefore, be used to categorize individuals into three categories of risk (i.e. low, medium and high risk) on the combined basis of sex, age, body mass and combined grip strength capacity. Figure 2 illustrates the non-parametric curves between the logit of the predicted risk of diabetes (x axis) and normalized strength (y axis), with age- and sex-specific low- and high-strength thresholds represented with vertical bars corresponding to the lower and upper tertiles of the predicted risks.

4 Discussion

The principal finding of this study was that normalized grip strength is significantly associated with type 2 diabetes in men and women of all ages, even after controlling for known sociodemographic, anthropometric and behavioural predictors. Specifically, for every 5 % decrement in the strength to body mass ratio, there were 26 % increased adjusted odds of diabetes. These findings lend additional support to the growing body of literature revealing a strong link between muscle strength and reduced risk of metabolic abnormalities and cardiovascular diseases. Our results suggest that grip strength testing may be valuable as a simple screening strategy for diabetes risk detection among adults. Herein, we provide unique sex- and age-specific thresholds of strength to predict diabetes on the basis of HbA_{1c} levels, according to the American Diabetes Association diagnostic criteria [i.e. ≥6.5 % (≥48 mmol/mol)] [25, 26]. Importantly, our modelling technique allowed for the identification of two strength cutpoints and three respective risk categories, which may be incorporated into a clinical setting for screening adults who are at low, medium and high risk of developing diabetes. In this study, we identified the highest risk of diabetes as coinciding with normalized strength of ≤0.56, 0.50 and 0.45 for men at ages of 20–39, 40–59 and 60–80 years, respectively, and 0.42, 0.38 and 0.33 for women at ages of 20–39, 40–59 and 60–80 years, respectively. As an example, a 50-year-old woman who has a body weight of 75 kg and grip strength of 26 kg has a normalized strength of 0.347 and thus would be categorized as 'high risk' for diabetes, i.e. below the low-strength threshold of 0.38 for those sex and age categories.

Such thresholds may also be useful in identifying individuals who could benefit from lifestyle interventions to improve muscular fitness and reduce risk. Indeed, among adults with and without existing risk factors, various studies have reported significantly improved insulin sensitivity and glucose tolerance with structured resistance exercise interventions [27, 28]. Since resistance exercise is known to elicit a potent insulin-sensitizing effect for hours after a single bout of training [29–31], there is some speculation about whether it is merely the repeated acute responses to habitual training that drive benefits for metabolic health, rather than any adaptive response per se. Regardless, progressive resistance exercise is a well-documented stimulus to induce both acute and chronic metabolic changes, attributable to decreases in hyperinsulinaemia, improved insulin-stimulated glucose disposal

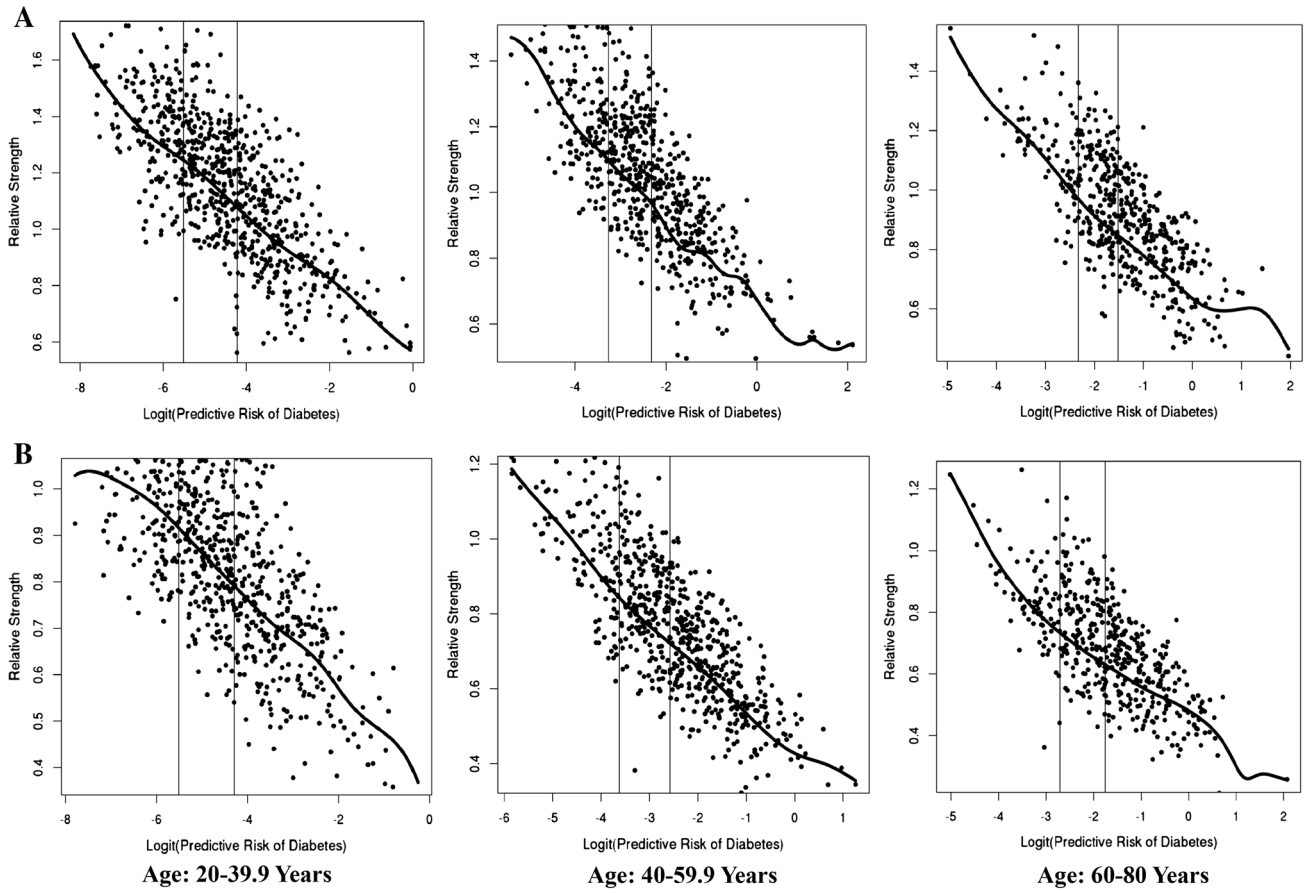

Fig. 2 Non-parametric local polynomial curves between the logit of the predicted risk of diabetes (*x* axis) and normalized grip strength (*y* axis) among men (**a**) and women (**b**). The age-specific low- and high-strength thresholds are represented by *vertical bars* corresponding to the lower and upper tertiles of the predicted risk

and enhanced insulin sensitivity [27, 32], and has recently been shown to substantially reduce the risk of prospective diabetes incidence in two large cohorts of middle-aged and older women [33].

Conversely, muscular atrophy and weakness are closely linked with chronic hyperglycaemia and diabetes, particularly with advancing age. As with all cross-sectional studies, a limitation of this investigation was the inability to disentangle the cause–effect relationship between predictors and outcomes. Whether lower relative strength capacities 'cause' an elevated risk of diabetes, or whether comorbid cardiometabolic abnormalities (e.g. diabetes or pulmonary disorders) or musculoskeletal conditions (e.g. carpal tunnel syndrome, diabetic cheiroarthropathy or flexor tenosynovitis) are themselves a cause of diminished muscle function (i.e. reverse causality) is an interesting and complex topic. Moreover, we were unable to determine if other competing risks or unmeasured confounding (e.g. time spent in different categories of physical activity or exercise participation) may have influenced the observed estimates. In their BLSA study, Kalyani et al. [14] suggested that longitudinal declines in muscle strength and quality were driven by neurological factors, such as neuropathy. While there is certainly evidence to explicate the role of diabetic complications in neuromuscular function, there is also an enormous body of literature to verify the independent link between declines in physical fitness and increased diabetes risk. For individuals at elevated risk of chronic hyperglycaemia and/or diabetes, these phenomena transpire as an accelerated circular cause and consequence of events. There is thus a dire need for more patient-specific clinical studies to identify optimal interventions that may concurrently target preservation of muscle strength capacity and achieve or maintain cardiometabolic health. Because regular exercise and drug interventions are similar in terms of their mortality benefits in secondary prevention of heart disease, rehabilitation after stroke and prevention of diabetes [34], a simplistic clinical directive that could dramatically reduce the total healthcare burden is to continue encouraging healthy lifestyles that lead to regular participation in physical activity, preservation of muscular fitness and healthy weight achievement/maintenance.

Not surprisingly, nearly all research related to the influence of obesity and related cardiometabolic abnormalities to potentiate the risk of secondary muscle dysfunction have been conducted within the context of an age-related phenomenon. However, the underlying changes in metabolic dysregulation leading to a disease such as diabetes should be regarded as a gradual continuous process throughout the lifespan rather than a discrete outcome or event. We have previously shown that even among non-obese, otherwise healthy adults, adiposity is a strong negative mediator of the relationship between muscle size and strength capacity [35]. Recent data also suggest a 'lipotoxic' effect of local adipose tissue deposition on muscular function and musculoskeletal integrity [36–38]. Thus, further evaluation of the temporal sequence of these consequences is of particular importance not only for early screening efforts to reduce diabetes progression and secondary comorbidities, but also for understanding of the roles of obesity and diabetes in the acceleration of functional declines leading to exaggerated sedentariness and mobility disability. Moreover, future research is needed to better understand the role of weakness and/or strength declines as a risk exposure for diabetes in the context of different races and ages.

Other recent efforts to calculate thresholds of weakness have used various statistical methods for defining absolute values of strength that correspond with mobility disability and early mortality among aging adults [9–11]. However, since there is a substantial covariance between strength capacity and body mass—and, moreover, the links between muscle strength and both physical function and chronic health are directly mediated by the proportion of strength relative to body mass—normalization to body mass is critical to improve the sensitivity of cutpoint values and screening efforts. Future research is certainly needed to devise strength growth curves that may be used for the purpose of normative reference testing in clinical, academic and community settings.

5 Conclusions

The purposes of this study were to examine the link between strength capacity and diabetes in a large, nationally representative sample and to explore thresholds of weakness, for optimal risk categorization. We found that normalized grip strength [measured as (grip strength in kg)/(body mass in kg)] was robustly associated with diabetes in adults, even after adjustment for various known covariates, such as age, waist circumference, important sociodemographic variables and sedentary behaviour. Moreover, we present new age- and sex-specific thresholds of normalized strength, which could be incorporated into a clinical setting for identifying adults who are at low, intermediate and high risk of developing diabetes. Future research is needed to create unique risk categorization algorithms that are specific to other clinical and global health outcomes, as well as to examine the longitudinal trajectories of strength change as an indicator of incident cardiometabolic disease and even early mortality. Such efforts will dramatically improve the personalization of screening, stratification and clinical decision making at the individual patient level.

Author contributions Mark Peterson and Soham Al Snih acquired the research data. Mark Peterson and Peng Zhang performed all of the analyses. Mark Peterson wrote the manuscript. Palak Choksi, Soham Al Snih and Kyriakos Markides reviewed/edited the manuscript and contributed to the interpretation of the results. All authors reviewed the final submitted manuscript.

Compliance with Ethical Standards

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