Independent and Combined Association of Muscle Strength and Cardiorespiratory Fitness in Youth With Insulin Resistance and β-Cell Function in Young Adulthood

The European Youth Heart Study

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OBJECTIVE—To examine the independent and combined association of isometric muscle strength of the abdomen and back and cardiorespiratory fitness (CRF) in youth with indices of glucose metabolism in young adulthood among boys and girls from the European Youth Heart Study.

RESEARCH DESIGN AND METHODS—We used data from a population-based prospective cohort study among youth followed up for up to 12 years ($n = 317$). In youth, maximal voluntary contractions during isometric back extension and abdominal flexion were determined using a strain-gauge dynamometer and CRF was obtained from a maximal cycle ergometer test. Insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]) and β-cell function (homeostasis model assessment of β-cell function [HOMA-B]) were estimated from fasting serum insulin and glucose that were obtained in youth and at follow-up in young adulthood.

RESULTS—For each 1-SD difference in isometric muscle strength (0.16 N/kg) in youth, fasting insulin, HOMA-IR, and HOMA-B in young adulthood changed by −11.3% (95% CI −17.0 to −5.2), −12.2% (−18.2 to −5.7), and −8.9% (−14.4 to −3.0), respectively, in young adulthood after adjustment for CRF and personal lifestyle and demographic factors. Results for CRF were very similar in magnitude, and the magnitude of associations for both exposures was unchanged with additional adjustment for general or abdominal adiposity in youth. Combined associations of muscle strength and CRF with fasting insulin, HOMA-IR, and HOMA-B were additive, and adolescents in the highest sex-specific tertile for both isometric muscle strength and CRF had the lowest levels of these glucose metabolism outcomes.

CONCLUSIONS—Increasing muscle strength and CRF should be targets in youth primordial prevention strategies of insulin resistance and β-cell dysfunction.

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P reviously, type 2 diabetes was very rare in young people. Today, it is more common not only in young adults but also in youth, and a similar trend has been observed for impaired fasting glucose and impaired glucose tolerance (1–3), which are considered precursors of type 2 diabetes. Youth and young adults with type 2 diabetes or prediabetes are at risk for premature mortality and early complications (4,5), making prevention critical. Numerous prospective epidemiological studies among adults suggest that regular participation in aerobic moderate-to-vigorous physical activity (MVPA) and high cardiorespiratory fitness (CRF) reduce the risk of type 2 diabetes and are associated with healthier glucose metabolism (6,7). However, less is known from prospective studies about the importance of fitness in childhood and adolescence (8). In addition, it is unknown whether muscle strength in youth is associated with impaired glucose metabolism in adulthood independent of CRF. In this study, we aimed to examine the independent and combined association of isometric muscle strength of the abdomen and back and CRF in youth with fasting glucose, insulin, insulin resistance, and β-cell function in young adulthood among men and women from the European Youth Heart Study (EYHS) followed up for a period of up to 12 years. We also assessed the extent to which these associations were mediated or confounded by general and abdominal adiposity.

RESEARCH DESIGN AND METHODS

Design

We used data from the Danish cohort of the EYHS, an international, population-based, multicenter study that addresses cardiovascular disease risk factors in children and adolescents. A detailed description of the EYHS has been published elsewhere (9). In this study, a random sample of 658 15-year-olds was invited to participate in 1997–1998, of whom 429 (65%) agreed to take part in the study. Isometric muscle strength was assessed in a subgroup of 243 participants in 1997–1998. In 2003–2004, another random sample of 771 15-year-olds was invited, of whom 444 (58%) agreed to take part, and 441 of these participants had isometric muscle strength evaluated. In 2009–2010, a 6- or 12-year follow-up was conducted in which all originally

invited participants from the 1997–1998 and 2003–2004 studies were reinvited. In this study, 317 participants had complete data for all outcomes, exposures, and covariates. Ninety-four percent of the participants were postpubertal based on Tanner stage evaluation. The local scientific Ethics Committee approved the study, and all participants gave informed consent to participate.

Muscle strength
We obtained isometric muscle strength during maximal voluntary contraction of abdominal and back muscles using a strain-gauge dynamometer (10). The participants were standing upright and positioned with a strap around the shoulders connected to the dynamometer. Abdominal maximal voluntary contraction was performed with the back against the dynamometer performing maximal forward flexion. For maximal voluntary contraction of the low back muscles, the participants were positioned with the front against the dynamometer, performing maximal backward extension. Isometric muscle strength was expressed as the mean of abdominal and back strength relative to body weight. High reliability of these particular isometric strength measures (intraclass correlation coefficient >0.9) has been reported in a previous study among Danish adults (11).

Cardiorespiratory fitness
CRF was assessed during a progressive maximal ergometer bicycle test (Ergomedic 839; Monark, Varberg, Sweden) as previously described (9). During the test, heart rate was recorded every 5 s using a heart rate monitor (Polar Vantage). Criteria for maximal effort were heart rate of ≥185 bpm and a subjective judgment by the observer that the participant could no longer continue, even after encouragement. Maximal power output (watt$_{max}$) was used to estimate maximal oxygen uptake using the following equation: VO_{2max} (mL) = 0.465 + (0.0112*watt$_{max}$) + (0.172*sex), where sex represents boys = 1 and girls = 0 (12). This particular fitness test is highly reproducible (coefficient of variation 2.5–4.8%). Furthermore, a validation study among 15-year-olds has shown that this measure is highly correlated with VO_{2max} assessed directly (r > 0.90; P < 0.001) (13).

Other covariates
Height and weight were measured while the participants were wearing light clothing, without shoes, using standard anthropometric procedures. Waist circumference was measured to the nearest 1 mm at the midpoint between the lower ribs and the iliac crest with a flexible tape. Smoking status (yes or no), television viewing (hours per day), monthly frequency of soft drink consumption, and monthly fruit and vegetable intake were obtained by self-report of adolescence using a computer-based questionnaire as described previously (9,14). Family history of diabetes (paternal or maternal, yes or no) and parental educational level were obtained by parental self-report. Parental educational status was defined according to the International Standard Classification of Education (United Nations Educational, Scientific, and Cultural Organization 1997). However, because the details obtained regarding the description of education were insufficient, the International Standard Classification of Education seven-point scale was combined into three new groups (I = level 1–2, II = level 3–4, and III = level 5–7). MVPA was assessed using accelerometry with data reduction as described previously (15). Specifically, an accelerometer output >2,000 counts/min (equivalent to walking ~4 km/h) was defined as MVPA and expressed as percentage of total registered time. Weight-bearing activity such as resistance exercise is grossly underestimated when using accelerometry-measured activity.

Fasting insulin and glucose
A fasting blood sample (overnight) was taken in the morning from the antecubital vein. Samples were aliquoted and separated within 30 min and then stored at −80°C until they were transported to World Health Organization–certified laboratories in Bristol (U.K.) for analysis of baseline samples and Cambridge (U.K.) for analysis of follow-up samples. Samples were analyzed for serum glucose and insulin. Glucose was analyzed using the hexokinase method (Olympus AU600 autoanalyzer; Olympus Diagnostica, Hamburg, Germany) at baseline and on a Dade Behring Dimension RxL autonalyzer (Siemens Healthcare, Camberley, U.K.) at follow-up. Insulin was analyzed using enzyme immunoassay (microtiter plate format, Dako Diagnostics [at baseline]; 1235 AutoDELFIA automatic immunoassay [at follow-up]). Between-laboratory correlations for glucose and insulin for 30 randomly selected samples analyzed at both laboratories were 0.94–0.98 at baseline (16).

The homeostasis model assessment of insulin resistance (HOMA-IR; fasting glucose [mmol/L] × insulin [μU/mL] / 22.5) and homeostasis model assessment of β-cell function (HOMA-B; insulin [μU/mL] × 20 / glucose [mmol/L] − 3.5) were used to quantify the level of insulin resistance and secretion (17). Both these measures have been validated as indices of insulin resistance and pancreatic β-cell function in healthy adolescents (18).

Statistics
We analyzed the associations of isometric muscle strength and CRF in adolescence with fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood using multiple linear regression analyses with baseline levels of respective variables included as a covariate. In basic models, age in adolescence, age in young adulthood, sex, and recruitment period were adjusted for. Values of insulin, HOMA-IR, and HOMA-B were natural log transformed. Thus, regression coefficients from these models were exponentiated to give ratios of geometric means (expressed in percent) per SD difference in isometric muscle strength and CRF. In multivariable analyses, we additionally adjusted for parental educational level, current smoking, family history of diabetes, frequency of intake of soft drinks, and intake of fruit and vegetables. Muscle strength and CRF in youth also were included in the same model to examine their independent influence on glucose, insulin, HOMA-IR, and HOMA-B in young adulthood. We then analyzed the association of muscle strength with the odds of insulin resistance, defined as HOMA-IR value >75th percentile in young adulthood (19), using multiple logistic regression adjusting for the same covariates as in the linear models including HOMA-IR at baseline. Finally, we assessed the joint association of muscle strength and CRF by constructing a joint variable of tertiles of muscle strength and CRF, respectively, and associated that with the outcomes in multivariable models. Because no sex-dependent or recruitment period–dependent associations for any outcomes were observed, we present all analyses for men, women, and recruitment period (follow-up time) combined, but with appropriate statistical adjustment. Standard linear regression diagnostics were performed, including examining linearity and normality of residuals.

In sensitivity analyses, we compared associations of the nonimputed sample

with a sample with imputed data. We imputed missing information for covariates and outcomes ($n = 12$ to $n = 556$, depending on variable) among the total sampled population at baseline ($n = 873$) using chained equations ("mi impute chained" in STATA) (20). All covariates and respective outcomes were included in the imputation approach. We obtained β-coefficients and SEs based on 20 imputed datasets. We also performed an analysis additionally adjusting for accelerometry-measured MVPA to examine if any residual confounding by MVPA remained that CRF may not have captured. Because 35% of the participants with otherwise full data had missing information regarding accelerometer-measured MVPA, we imputed missing values for MVPA using a multiple linear regression imputation approach including all covariates and the outcome. All statistical analyses were performed in STATA 12.1 with $\alpha = 0.05$ (two-sided).

RESULTS—Baseline characteristics adjusted for sex by tertiles of isometric muscle strength in adolescence are shown in Table 1. Isometric muscle strength in adolescence was inversely associated with adolescence BMI, waist circumference,

fasting glucose, fasting insulin, HOMA-IR, and television viewing and was positively associated with cardiovascular fitness and intake of fruits and vegetables at baseline.

Isometric muscle strength and CRF in youth were both significantly inversely associated with fasting insulin, HOMA-IR, and HOMA-B in young adulthood in multivariable-adjusted analyses (Table 2). Although associations of adolescent muscle strength and CRF with fasting glucose in young adulthood were in the expected inverse direction, these did not reach statistical significance. When muscle strength and CRF were included in the same multivariable models, associations with insulin, HOMA-IR, and HOMA-B were only marginally attenuated for both variables. For each 1-SD difference in muscle strength (0.16 N/kg) in youth, fasting insulin, HOMA-IR, and HOMA-B in young adulthood changed by −11.3, −12.2, and −8.9%, respectively. The magnitudes of associations for CRF were fairly similar; for each SD difference in CRF in youth, fasting insulin, HOMA-IR, and HOMA-B in young adulthood changed −12.8, −13.3, and −10.0%, respectively. When we additionally adjusted our analyses for waist

circumference measured at baseline, estimates of associations were only slightly attenuated for both exposures (Table 2, model 4). Using BMI instead of waist circumference as a confounder or mediator gave the same results (data not shown). Furthermore, additional adjustment for accelerometer-measured MVPA did not materially change the associations (data not shown). When we repeated the analyses based on imputed samples ($n = 873$), associations were essentially similar to the nonimputed analyses (Supplementary Table 1). Analyzing isometric abdominal and back strength separately also yielded fairly similar associations compared with using the mean of abdominal and back isometric strength (Supplementary Table 2).

For the association of muscle strength and CRF in youth (in the same multivariable-adjusted model) with the odds of insulin resistance in young adulthood, each 1-SD difference in muscle strength (0.16 N/kg) and CRF (6.8 mL O_2/min/kg) in youth was significantly associated with 0.56 (95% CI 0.39–0.81) and 0.63 (0.43–0.94) lower odds of adverse levels of HOMA-IR in young adulthood, respectively. Participants in the third sex-specific tertile of isometric muscle strength had 0.31 (0.15–0.66) lower odds of insulin resistance in young adulthood. Furthermore, participants in the third sex-specific tertile of CRF had 0.48 (0.23–1.01) lower odds of insulin resistance in young adulthood. There were no indications of the associations of muscle strength or CRF with HOMA-IR being nonlinear in these models.

Finally, Table 3 shows the joint associations of isometric muscle strength and CRF in adolescence with fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood. The inverse associations of isometric muscle strength with insulin, HOMA-IR, and HOMA-B in young adulthood were generally observed in each tertile of CRF. There was no statistical evidence of multiplicative interactions between muscle strength and CRF on these outcomes, and results suggested an additive effect of muscle strength and CRF on glucose metabolism outcomes.

CONCLUSIONS—In this prospective study of a population sample of Danish men and women, isometric muscle strength and CRF in youth were inversely associated with fasting insulin and inversely associated with markers of insulin

Table 1—*Baseline characteristics adjusted for sex by tertiles of maximal voluntary isometric trunk muscle strength in adolescence*

	Muscle strength in adolescence (tertiles)			
	0.71 (0.08) N/kg ($n = 105$)	0.86 (0.08) N/kg ($n = 106$)	1.04 (0.09) N/kg ($n = 106$)	P
Age, years	15.6 (0.4)	15.6 (0.4)	15.6 (0.4)	0.57
BMI, kg/m^2	21.9 (2.6)	20.6 (2.5)	20.4 (2.6)	<0.001
Waist circumference, cm	75.3 (6.4)	72.0 (6.2)	70.5 (6.5)	<0.001
Glucose, mmol/L	5.17 (0.39)	5.11 (0.38)	4.98 (0.39)	0.002
Log insulin, pmol/L	2.29 (0.46)	2.21 (0.45)	2.04 (0.47)	0.001
Log HOMA-IR	0.82 (0.49)	0.72 (0.48)	0.53 (0.50)	<0.001
Log HOMA-B	4.80 (0.46)	4.76 (0.45)	4.70 (0.47)	0.17
Cardiorespiratory fitness, mL O_2/min/kg	43.5 (5.5)	46.8 (5.4)	48.6 (5.6)	<0.001
Television viewing, h/day	1.8 (1.1)	1.6 (1.1)	1.3 (1.1)	0.01
Soft drinks, servings/month	8.7 (8.4)	9.4 (8.2)	9.4 (8.6)	0.79
Fruits and vegetables, servings/month	35.1 (17.2)	37.2 (16.8)	44.5 (17.6)	<0.001
Smoking status, %	12.0	13.7	14.3	0.88
Parental education level, % I/II/III*	6.8/36.1/57.0	9.5/22.1/68.4	7.2/20.9/71.9	0.13
Family history of diabetes, %	1.8	1.9	7.2	0.13

Data are means (SD) or n (%) adjusted for sex unless otherwise indicated. *Based on educational level (International Standard Classification of Education) (United Nations Educational, Scientific, and Cultural Organization 1997). I, basic education; II, secondary or postsecondary education; and III, tertiary education.

Table 2—Isometric trunk muscle strength and cardiorespiratory fitness in youth and fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood

	Model 1		Model 2		Model 3		Model 4	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Muscle strength								
Glucose*	−0.03 (−0.08 to 0.02)	0.21	−0.03 (−0.08 to 0.02)	0.27	−0.02 (−0.08 to 0.03)	0.41	−0.02 (−0.08 to 0.03)	0.40
Insulin†	−15.3 (−20.4 to −9.0)	<0.001	−14.6 (−20.0 to −9.0)	<0.001	−11.3 (−17.0 to −5.2)	<0.001	−11.2 (−16.9 to −5.0)	0.001
HOMA-IR†	−16.3 (−21.7 to −10.5)	<0.001	−15.6 (−21.2 to −9.5)	<0.001	−12.2 (−18.2 to −5.7)	<0.001	−12.1 (−18.2 to −5.6)	<0.001
HOMA-B†	−12.1 (−17.0 to −6.9)	<0.001	−11.8 (−16.8 to −6.4)	<0.001	−8.9 (−14.4 to −3.0)	0.004	−8.8 (−14.3 to −2.9)	0.004
Cardiorespiratory fitness								
Glucose*	−0.04 (−0.09 to 0.01)	0.16	−0.03 (−0.08 to 0.03)	0.30	−0.02 (−0.08 to 0.04)	0.48	−0.02 (−0.09 to 0.05)	0.49
Insulin†	−17.0 (−22.7 to −10.9)	<0.001	−16.6 (−22.5 to −10.2)	<0.001	−12.8 (−19.2 to −5.8)	0.001	−11.4 (−19.0 to −3.2)	0.008
HOMA-IR†	−17.8 (−23.9 to −11.3)	<0.001	−17.3 (−23.6 to −10.5)	<0.001	−13.3 (−20.1 to −5.9)	0.001	−12.1 (−20.1 to −3.2)	0.009
HOMA-B†	−13.2 (−18.7 to −7.4)	<0.001	−13.2 (−18.8 to −7.2)	<0.001	−10.0 (−16.1 to −3.4)	0.004	−9.2 (−16.5 to −1.4)	0.02

Model 1 was adjusted for baseline levels of risk factor, age, sex, and recruitment period. Model 2 was as model 1 but with additional adjustment for television viewing, parental education level, smoking status, intake of soft drinks, fruit and vegetable intake, and family history of diabetes. Model 3 was as model 2 and included both muscle strength and CRF (mutually adjusted). Model 4 was as model 3 but with additional adjustment for waist circumference. *β-coefficient (95% CI) represents mmol/L change in glucose in young adulthood per each 1-SD difference in muscle strength or CRF in adolescence. †β-coefficient (95% CI) represents change in ratios of geometric means (expressed in percentage) in insulin, HOMA-IR, or HOMA-B in young adulthood per each 1-SD difference in muscle strength or CRF in adolescence.

resistance and β-cell function in young adulthood. These associations were independent of adiposity and demographic, personal, and lifestyle factors, and they suggest that muscle strength in youth is equally important as CRF for maintaining healthy insulin sensitivity and β-cell function later in life.

The current guidelines for physical activity among children and adults recommend participation in activities that maintain or increase muscular strength and endurance for ≥2 days (adults) or ≥3 days (children and adolescents) each week in addition to participation in aerobic MVPA (≥30 min/day for adults and ≥60 min/day for youth) (21,22). Our results generally support these guidelines; however, they also suggest that an even greater emphasis could be placed on maintaining or increasing muscle strength among youth. Because associations between CRF and strength with insulin resistance and β-cell function were independent of each other, this supports the view that aerobic activities and muscle strengthening activities should be targeted separately. Furthermore, the analyses of continuous trait and binary outcomes suggested that muscle strength and CRF were linearly associated with fasting insulin, insulin resistance, and β-cell function, indicating that there is no clear threshold effect of an increase in insulin secretion or action at a particular low level of fitness or muscle strength. Efforts to shift the population distribution of muscle strength and CRF upwards are therefore likely to be valuable for primordial prevention of type 2 diabetes.

We are aware of three randomized controlled trials conducted among youth comparing the effect of resistance training on insulin resistance or glycemic control with a pure control group. A small-scale trial among 22 overweight Latino adolescent males found that 16 weeks of resistance training performed twice per week markedly increased insulin sensitivity (23). Another randomized trial among 78 overweight or obese children and adolescents from New Zealand reported that the effect of 8 weeks of resistance training performed twice per week had no significant effect on insulin resistance; however, results were in the expected direction and the training improved abdominal and general adiposity (24). A recent efficacy trial among 45 obese adolescent boys reported that both aerobic exercise and resistance training were effective for reducing adiposity, but only

Table 3—*Joint association of sex-specific tertiles of isometric trunk muscle strength and cardiorespiratory fitness in adolescence with fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood*

| | Cardiorespiratory fitness (mL O_2/min/kg) | | | |
| | Least squares means or ratio of geometric means (95% CI) | | | |
Isometric muscle strength, N/kg	1st tertile	2nd tertile	3rd tertile	*P*
Glucose				
1st tertile	5.05 (4.49–5.15)	5.17 (5.02–5.32)	5.01 (4.85–5.17)	0.26
2nd tertile	5.09 (4.94–5.23)	5.02 (4.90–5.14)	5.03 (4.91–5.16)	
3rd tertile	5.00 (4.83–5.17)	5.08 (4.96–5.20)	4.97 (4.85–5.08)	
Insulin				
1st tertile	0 (reference)	−2.7 (−23.2 to 23.2)	−22.3 (−39.9 to 0.43)	0.28
2nd tertile	6.0 (−15.9 to 33.6)	−18.1 (−33.7 to 1.2)	−29.0 (−42.7 to −11.8)	
3rd tertile	−31.4 (−47.0 to −11.1)	−30.9 (−44.2 to −14.5)	−32.1 (−44.8 to −16.5)	
HOMA-IR				
1st tertile	0 (reference)	−0.8 (−23.0 to 27.8)	−23.8 (−42.2 to 0.3)	0.30
2nd tertile	6.3 (−17.0 to 36.2)	−18.6 (−35.0 to 2.0)	−29.9 (−44.5 to −11.5)	
3rd tertile	−32.9 (−49.2 to −11.1)	−31.3 (−45.4 to −13.6)	−34.2 (−47.4 to −17.8)	
HOMA-B				
1st tertile	0 (reference)	−9.5 (−27.3 to 12.7)	−13.1 (−31.3 to 9.9)	0.62
2nd tertile	4.9 (−15.4 to 30.0)	−16.7 (−31.5 to 1.2)	−27.5 (−40.7 to −11.3)	
3rd tertile	−24.7 (−40.8 to −4.3)	−29.8 (−42.3 to −14.6)	−25.3 (−38.2 to −9.6)	

Estimates are least squares means (fasting glucose) or ratios of geometric means expressed in percent (insulin, HOMA-IR, and HOMA-B) adjusted for baseline levels of the outcome, age at baseline, age at follow-up, sex, recruitment period, television viewing, parental education level, smoking status, intake of soft drinks, fruit and vegetable intake, and family history of diabetes.

the resistance exercise group improved insulin sensitivity (25). Although we have no data to support that participants with high isometric muscle strength of the abdomen and back engage more often in muscle-strengthening activities compared with participants with low muscle strength, findings from these and other exercise training studies clearly indicate that resistance training increases muscular strength (26). Our results are also largely in agreement with three previous cross-sectional studies among children and adolescents. A population-based study among Norwegian children and adolescents found that muscle fitness indicated by handgrip strength, standing broad jump, abdominal muscle endurance, and back muscle endurance were inversely associated with insulin resistance independent of CRF (27). A study among European children and adolescents have reported inverse associations of handgrip strength and standing long jump with insulin resistance; however, it was not reported whether these associations were independent of cardiovascular fitness (28). Finally, in a cross-sectional study among children and adolescents from New Zealand, maximal upper body muscle strength (bench press) was inversely associated with insulin resistance independent of CRF (29). Our results

extend these previous observations by the prospective nature of our study and the adjustments for putative lifestyle behaviors and sociodemographic confounders. The finding that CRF in childhood or youth is important for the prevention of insulin resistance in adulthood is supported by a previous study among Australian children and adolescents followed up for a period of 20 years (8).

The similar magnitude of association of muscle strength and cardiovascular fitness with insulin resistance that we observed in the current study is in agreement with findings from experimental and observational studies among adults. The two largest trials among individuals with type 2 diabetes have not provided clear evidence that aerobic exercise is superior to resistance exercise for glycemic control (30,31). However, these studies indicated that the combination of aerobic and resistance exercise results in greatest improvement in glycemic control compared with either type of activity alone. The comparable effects of these two exercise regimes are also supported by a recent experimental study reporting that a single session of either aerobic or resistance exercise provided similar effects on 24-h postexercise glycemic control in insulin-resistant individuals with

and without type 2 diabetes (32). Finally, in a prospective study of men from the Health Professionals Follow-up study, engagement in weight training and aerobic MVPA were both independently associated with reduced risk of incident type 2 diabetes with fairly comparable risk reduction sizes (33).

An important strength of the current study was that we were able to examine the independent associations for strength and CRF, and we were able to control for important confounding factors. Furthermore, all participants were young and healthy at baseline and, therefore, very likely to be free from subclinical conditions that may have affected muscle strength at baseline and progression of insulin resistance and β-cell dysfunction during follow-up. There are also a number of limitations to the study. First, the attrition analyses indicated a possibility of selective nonresponse; however, associations were very similar in imputed and nonimputed samples, which suggests that associations are unaffected by selection bias, and our results may have wider external validity. Second, the moderate study size precluded us from adequately powered subgroup analysis. Third, although we used a standardized test for the assessment of isometric muscle strength of the abdomen and back,

additional components of strength such as dynamic strength also may be important and their assessment would have provided more extensive information on overall muscle strength. Fourth, the observational nature of our study precludes us from excluding the possibility that unknown confounders or residual confounding explain our results. One such likely factor is diet, because the assessment of dietary intake was relatively crude in this study. Finally, a caveat of the study was that we assessed insulin resistance and β-cell function via HOMA-IR and HOMA-B, which mainly describe hepatic insulin resistance and steady-state insulin secretion, and generalizability to peripheral insulin resistance and insulin secretion in the stimulated state is uncertain (34).

In conclusion, our results show that lower isometric muscle strength and CRF in youth were independently associated with adverse levels of fasting insulin, insulin sensitivity, and β-cell function in young adulthood. The magnitude of associations for isometric muscle strength and for CRF were very similar, suggesting that participation in muscle-strengthening activities may be equally important as participating in aerobic activities in youth for maintaining healthy insulin sensitivity and β-cell function later in life. Furthermore, because associations for isometric muscle strength and CRF with these outcomes appeared additive, it may be beneficial to increase muscle strength at any level of CRF. Further studies are warranted to examine which specific physical activities explain the associations of isometric muscle strength with insulin sensitivity and β-cell function, and to what extent these associations are explained by skeletal muscle mass relative to body size. In addition, further studies should investigate whether the effects of strength and fitness in adolescence persist in adulthood despite changes in these physical fitness characteristics in adulthood.

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