Lower grip strength in youth with obesity identifies those with increased cardiometabolic risk

Short Running Title: Grip strength and cardiometabolic risk

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ABSTRACT

Background We examined whether grip strength differentiates youth with obesity with increased cardiometabolic risk.

Methods: The sample comprised 43 youth with severe obesity (mean age 14.8±3.0 years) enrolled in the Childhood Overweight BioRepository of Australia. Grip strength was normalized to body mass and categorized as low and moderate/high.

Results: Youth with low grip strength had higher systolic blood pressure (mean difference 13 mmHg), low-density lipoprotein cholesterol (0.26 mmol/l), continuous metabolic syndrome score (0.36), and carotid intima-media thickness (0.05 mm) compared with those with moderate/high grip strength.

Conclusions: Low grip strength may differentiate youth with obesity with increased cardiometabolic risk.

Keywords: cardiovascular risk; physical fitness; atherosclerosis.

INTRODUCTION

Low hand grip strength is associated with cardiovascular disease and all-cause mortality in adults[1]. In children and adolescents is an independent predictor of concurrent and future risk factors for cardiometabolic disease (cardiovascular disease and type 2 diabetes)[2,3]. Recently, sex-specific thresholds for low grip strength have been proposed to detect cardiometabolic risk in youth[2]. The utility of these thresholds to discern increased cardiometabolic risk among youth with obesity has not been examined.

We used data from the Childhood Overweight BioRepository of Australia (COBRA). Our primary aim was to examine the association between low grip strength with cardiometabolic risk factors and preclinical markers of vascular and metabolic health.

METHODS

Children and adolescents were recruited into the COBRA from the Royal Children's Hospital (Melbourne, Australia) Weight Management Service as previously described[4]. The sample comprised 43 youth with obesity aged 8-19 years already enrolled in COBRA who participated in a cardiovascular risk sub-study when data on grip strength and markers of cardiovascular health were collected. Informed, written consent was obtained from the participant or their legal guardian for those aged <18 years. The study protocol was approved by the Royal Children`s Hospital Human Research Ethics Committee (#28081Q) and is in accordance with Declaration of Helsinki.

Anthropometry and clinical data were collected at a single visit, including height, weight, waist circumference, body composition by 4-point bioelectrical impedance (Tanita, USA), and pubertal status[5]. Body-mass index (BMI) was calculated by dividing weight (kg) by height in meters squared (m^2) and converted into age- and sex-specific BMI z-scores using the US Centers for Disease Control and Prevention growth reference charts[6]. Blood samples were taken after an 8-hour overnight fast. Glucose was analysed by the glucose oxidase method and HbA1c by the ion-

exchange high-performance liquid chromatography method. Serum lipids, lipoproteins and Glycoprotein acetyls (GlycA, an inflammatory biomarker) was measured by Nuclear Magnetic Resonance spectroscopy (Nightingale Health, Finland), as previously described[7].

Grip strength was measured in kilograms using a digital dynamometer (T.K.K. 5401; Takei Scientific Instruments Co., Ltd, Niigata-City, Niigata-Pref., Japan), which has the highest criterion validity and reliability in adolescent populations[8]. As grip span affects grip strength performance, we measured the hand span of participants to determine the optimal grip span for the dynamometer based on age- and sex-specific equations for children and adolescents[9]. Grip strength was then measured twice on both hands from participants according to protocols from the 2011-12 National Health and Nutrition Examination Survey[10]. The maximum value recorded from either the right or left hand was used for further analysis. As grip strength can be influenced by body mass,[11] we calculated normalized grip strength as the ratio of maximum grip strength (kg) to body mass $(kg)^2$. Participants were then divided into categories of normalized grip strength according to previously defined thresholds in children and adolescents[2]: low (normalized grip strength ≤0.33 for boys, ≤0.28 for girls); moderate (normalized grip strength >0.33 to ≤0.45 for boys, >0.28 to ≤0.36 for girls); or high (normalized grip strength >0.45 for boys, >0.36 for girls).

Right common carotid artery intima-media thickness (cIMT), elasticity, and pulsatility index was assessed approximately 1 cm proximal to the bulb using a GE Vivid I ® ultrasound system with a linear probe of at least 8MHz. The far wall mean cIMT from 5 frames assessed at the peak R-wave during the cardiac cycle was calculated with edge detection software (Carotid Analyzer for Research, Version 6, Medical Imaging Applications LLC, Iowa). Carotid elasticity (%/mmHg) was calculated using intima–intima lumen diameter (LD) as $[(LDmax - LDmin)/LDmin]$/(pulse pressure)×100%. Pulsatility index was calculated as (peak systolic velocity - end diastolic velocity)/mean blood flow velocity. Carotid-femoral pulse wave velocity and blood pressure was

assessed in the supine position after a 5 minute rest, using the SphygmoCor® XCEL system. The average of 3 readings was used in the analysis. Pulse wave velocity was determined by dividing the carotid-femoral distance by the pulse transit time. A continuous metabolic syndrome score (MetS score) was calculated according to Gurka[12] using inputs of BMI z-score, high-density lipoprotein cholesterol, triglycerides, glucose, and systolic blood pressure.

Statistical analyses

Participant characteristics were calculated as mean (standard deviation) and range (min-max) for continuous variables, and as proportions for categorical variables. The associations between normalized grip strength categories (independent variable) and cardiometabolic preclinical markers (dependent variables) were estimated using linear regression. The moderate and high normalized grip strength categories were collapsed into one category (moderate/high) due to the small number of participants (N=4) who met the cut-off for having a high normalized grip strength. Where required, the cardiometabolic variables were transformed to remove skewness, but all estimates are reported in the original units. As we had a limited sample size, data for males and females were combined and we checked for possible confounding by age, sex, and pubertal stage before considering adjustment for these variables. As age, sex, and pubertal stage were not associated with normalized grip strength (P-values 0.40, 0.29, and 0.62, respectively), we did not include them as covariates in our regression models. When GlycA was the dependent variable, we additionally adjusted for triglycerides as is recommended for values derived with Nuclear Magnetic Resonance spectroscopy[13]. For the cardiometabolic markers shown to associate with normalized grip strength, we additionally adjusted for BMI z-score as adiposity might be on the pathway (mediator) between grip strength and cardiometabolic outcomes[14], or an antecedent (confounder) of grip strength[15]. Statistical analyses were conducted using Stata (Version 15.0, StataCorp)

RESULTS

Participant characteristics are displayed in Table 1. On average, participants had a BMI z-score of 2.53, a body fat percentage of 44, a waist circumference of 109 cm, and a maximum grip strength of 32 kg. Only 4 participants (9.3 %) had a high normalized grip strength. Mean levels of cardiometabolic risk factors according to normalized grip strength categories (moderate/high vs low) are shown in Table 2. In general, participants with low normalized grip strength had poorer cardiometabolic risk makers than those with moderate/high normalized grip strength. The mean difference between normalized grip strength groups (moderate/high vs. low) was +0.05 mm for cIMT, +13 mmHg for systolic blood pressure, +0.26 mmol/l for low-density lipoprotein (LDL)-cholesterol, and +0.36 for MetS score. After adjustment for BMI z-score, the difference between groups remained largely unchanged for cIMT (+0.06 mm, +2 % from model shown in Table 2, P=0.003, N=43), whereas the difference was reduced for systolic blood pressure (+9 mmHg, -30 %, P=0.015, N=43) and LDL-cholesterol (+0.23 mmol/l, -10 %, P=0.10, N=41). As BMI z-score is a factor in the MetS score, we did not additionally adjust for this. Because systolic blood pressure and LDL-cholesterol might be intermediates between normalized grip strength and cIMT, we additionally fit a model including these covariates. The difference in cIMT between normalized grip strength groups remained (+0.06 mm, P=0.003, N=41).

DISCUSSION

We observed that low normalized grip strength can identify obese youth who have increased cardiometabolic risk. Youth with low normalized grip strength had higher systolic blood pressure, LDL-cholesterol, MetS score, and cIMT, compared with those with moderate/high grip strength.

Previously, Melo et al.[16]demonstrated that grip strength was associated with cIMT in healthy weight children aged 11-12 years. We extend this finding by showing an inverse association of normalized grip strength and cIMT in a cohort of youth aged 8-19 years with severe obesity. The difference in cIMT between low and moderate/high normalized grip strength groups in the present study was

+0.05 mm. This difference persisted after adjustment for BMI z-score, systolic blood pressure, and LDL-cholesterol, suggesting that differences in these factors are not on the pathway linking normalized grip strength to cIMT. Previously, in the Cardiovascular Risk in Young Finns Study, cIMT was shown to increase 0.0057±0.0004 mm/y in young adults[17]. Using the vascular age concept,[18] the difference observed here means that participants with low normalized grip strength were almost 9 years older in terms of vascular age than those with moderate/high normalized grip strength.

In this study, we also observed that youth with low normalized grip strength had higher systolic blood pressure (+13 mmHg), and LDL-cholesterol concentration (+0.26 mmol/l) compared with those who had moderate/high normalized grip strength. These findings are clinically important, because elevated systolic blood pressure and LDL-cholesterol in youth are independent predictors of adulthood coronary artery calcification[19]. In addition, youth with low normalized grip strength had higher MetS score, which has been associated with increased risk for future type 2 diabetes[20].

A limitation of this study, in addition to the modest sample size, is that we were not able to take into account potentially important confounders (e.g. cardiorespiratory fitness, physical activity, diet) and mediators (e.g. insulin) as they were not measured. In addition, because our analyses were cross-sectional, we cannot infer causality. Important strengths of this study include excellent exposure measurement (a single assessor using a dynamometer with the highest criterion validity and reliability in adolescent populations8, with a highly standardized protocol that accounted for grip span), and a well-phenotyped cohort.

In conclusion, our findings suggest that among youth with obesity, low grip strength might be a simple indicator of those at substantially increased cardiometabolic risk.

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ETHICS

The authors declare that all experiments on human subjects were conducted in accordance with the Declaration of Helsinki, and that all procedures were carried out with the adequate understanding and written consent of the subjects.

The authors also certify that formal approval to conduct the experiments described has been obtained from the human subjects review board of their institution and could be provided upon request.

Table 1. Participant characteristics

Variable	All Participants				Males				Females			
	N	Mean (SD)	Range (min-max)	%	N	Mean (SD)	Range (min-max)	%	N	Mean (SD)	Range (min-max)	%
Age, y	43	14.8 (3.0)	8.7-19.9		21	15.1 (2.8)	9.6-19.7		22	14.6 (3.2)	8.7-19.9	
Sex												
Female	22			51.2								
Male	21			48.8								
Pubertal stage*												
Pre-pubertal	5			11.6	2			9.5	3			13.6
Peri-pubertal	6			14.0	4			19.1	2			9.1
Post-pubertal	32			74.4	15			71.4	17			77.3
Weight, kg	43	107.9 (27.2)	57.3-179.4		21	115.1 (27.1)	64.8-179.4		22	101.0 (26.0)	57.3-155.9	
Height, m	43	1.67 (0.12)	1.38-1.95		21	1.74 (0.11)	1.51-1.95		22	1.61 (0.10)	1.38-1.77	
BMI, kg/m^2	43	38.1 (6.9)	27.0-60.9		21	37.4 (5.8)	27.0-48.2		22	38.8 (7.8)	27.6-60.9	
BMI z-score	43	2.53 (0.29)	2.03-3.12		21	2.60 (0.27)	2.07-3.12		22	2.45 (0.29)	2.03-3.02	
Body fat, %	42	44.4 (7.2)	30.4-60.8		20	42.2 (6.0)	31.6-53.7		22	46.4 (7.7)	30.4-60.8	
Truncal fat, %	42	39.6 (7.9)	22.6-58.8		20	38.5 (7.4)	27.1-58.8		22	40.7 (8.4)	22.6-53.0	
Waist circumference, cm	41	108.9 (13.2)	82-139		19	113.6 (11.4)	89-139		22	104.8 (13.4)	82-132	
Waist to height ratio	41	0.33 (0.03)	0.27-0.41		19	0.32 (0.02)	0.27-0.36		22	0.33 (0.03)	0.28-0.41	
Grip strength, kg	43	32.2 (8.3)	16.2-53.5		21	35.2 (8.8)	19.9-53.5		22	29.3 (6.9)	16.2-40.7	
Normalized grip strength	43	0.30 (0.06)	0.20-0.42		21	32.2 (6.2)	22.2-44.9		22	32.2 (5.3)	22.2-42.4	

Normalized grip strength categories							
Low	21	48.8	12	57.1	9	40.9	
Moderate	18	41.9	9	42.9	9	40.9	
High	4	9.3	0	0.0	4	18.2	

*Pre-pubertal: Tanner stage 1; peri-pubertal: Tanner stage 2 and 3; post-pubertal: Tanner stage 4 and 5.

Abbreviations: BMI, body mass index; BMI z-score, body mass index z-score according to the US Centers for Disease Control and Prevention (CDC) growth charts; N, number of participants; SD, standard deviation.

Table 2. Adjusted means of cardiometabolic risk variables according to normalized grip strength category

		Normalized grip strength category			
		Moderate/High	Low		
Cardiometabolic risk variable	N*	Mean ± SE	Mean ± SE	Mean difference (95 % CI)	P-value
Total cholesterol, mmol/L	41	2.91 ± 0.10	3.19 ± 0.12	0.27 (-0.04, 0.59)	0.08
Apolipoprotein A-I, g/L	38	1.24 ± 0.02	1.25 ± 0.02	0.01 (-0.06, 0.08)	0.80
High-density lipoprotein cholesterol, mmol/L	41	1.14 ± 0.03	1.13 ± 0.03	-0.01 (-0.11, 0.09)	0.83
Triglycerides, mmol/L	41	1.14 ± 0.07	1.24 ± 0.08	0.11 (-0.12, 0.33)	0.34
Apolipoprotein B, g/L	41	0.65 ± 0.02	0.71 ± 0.03	0.06 (-0.01, 0.14)	0.09
Low-density lipoprotein cholesterol, mmol/L	41	1.21 ± 0.08	1.46 ± 0.10	0.26 (0.00, 0.51)	0.048
HbA_{1c}, mmol/mol	41	5.30 ± 0.09	5.36 ± 0.15	0.06 (-0.19, 0.31)	0.63
Glucose, mmol/L	41	4.69 ± 0.11	4.53 ± 0.10	-0.15 (-0.44, 0.14)	0.29
Systolic blood pressure, mmHg	43	120 ± 2	133 ± 3	13 (6, 20)	0.001
Diastolic blood pressure, mmHg	43	68 ± 2	72 ± 2	3 (-2, 8)	0.20
Continuous metabolic syndrome score	41	1.16 ± 0.09	1.52 ± 0.09	0.36 (0.11, 0.62)	0.007

Glycoprotein acetyls[†], mmol/L	41	1.15 ± 0.02	1.18 ± 0.02	0.03 (-0.02, 0.08)	0.28
Carotid intima-media thickness, mm	43	0.46 ± 0.01	0.52 ± 0.01	0.05 (0.02, 0.09)	0.002
Pulse wave velocity, m/s	43	5.21 ± 0.17	5.42 ± 0.20	0.21 (-0.32, 0.74)	0.43
Carotid elasticity, %/mmHg	40	0.34 ± 0.02	0.34 ± 0.02	-0.01 (-0.07, 0.05)	0.81
Pulsatility index	43	1.99 ± 0.12	2.32 ± 0.15	0.33 (-0.05, 0.71)	0.09

*Participants in the normalized grip strength categories were 21 (low) and 22 (moderate/high) when N=43. Participants in the normalized grip strength categories were 21 (low) and 20 (moderate/high) when N=41. Participants in the normalized grip strength categories were 19 (low) and 21 (moderate/high) when N=40. Participants in the normalized grip strength categories were 19 (low) and 19 (moderate/high) when N=38. The reduced sample size for some analyses are due to participants missing data on the cardiometabolic risk variable.

[†]Model additionally adjusted for triglycerides.

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin A_{1c}; N, number of participants; SE, standard error.

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