

Childhood cardiorespiratory fitness, muscular fitness and adult measures of glucose homeostasis

Short Running Title: Child fitness and adult glucose homeostasis

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Abstract

Objectives: To assess whether childhood cardiorespiratory fitness (CRF) and muscular fitness phenotypes (strength, power, endurance) predict adult glucose homeostasis measures.

Design: Prospective longitudinal study.

Methods: Study examining participants who had physical fitness measured in childhood (aged 7-15 years) and who attended follow-up clinics approximately 20 years later and provided a fasting blood sample which was tested for glucose and insulin. Physical fitness measurements included muscular strength (right and left grip, shoulder flexion, shoulder and leg extension), power (standing long jump distance) and endurance (number of push-ups in 30 seconds), and CRF (1.6km run duration). In adulthood, fasting glucose and insulin levels were used to derive glucose homeostasis measures of insulin resistance (HOMA2-IR) and beta cell function (HOMA2- β).

Results: A standard deviation increase in childhood CRF or muscular strength (males) was associated with fasting glucose (CRF: $\beta=-0.06\text{mmol/L}$), fasting insulin (CRF: $\beta=-0.73\text{mU/L}$; strength: $\beta=-0.40\text{mU/L}$), HOMA2-IR (CRF: $\beta=-0.06$; strength: $\beta=-0.05$) and HOMA2- β (CRF: $\beta=-3.06\%$; strength: $\beta=-2.62\%$) in adulthood, independent of the alternative fitness phenotype (all $p<0.01$). Adjustment for childhood waist circumference reduced the effect by 17-35% for CRF and 0-15% for muscular strength (males) and statistical significance remained for all associations except between CRF, fasting glucose and HOMA2- β ($p>0.06$).

Conclusion: CRF and muscular fitness in childhood were inversely associated with measures of fasting insulin, insulin resistance and beta cell function in adulthood. Childhood CRF and muscular fitness could both be potential independent targets for strategies to help reduce the development of adverse glucose homeostasis.

Keywords: Muscle Strength, Physical Fitness, Insulin Resistance, Beta Cell Function, Epidemiology, Cohort

Introduction

Impaired glucose homeostasis and type 2 diabetes (T2DM) are becoming increasingly prevalent^{1, 2} and remain a major public health concern. Efforts continue to identify effective strategies to prevent these conditions. Physical fitness, a product of both cardiorespiratory fitness (CRF) and muscular fitness, is a potential target for these prevention strategies. Associations between childhood physical fitness and adult cardiometabolic health outcomes³⁻⁵, including T2DM⁶, have been reported previously. These data suggest prevention strategies targeting childhood physical fitness could be fundamental in improving glucose homeostasis in later life, although further research is required.

Previous research using data from the Childhood Determinants of Adult Health (CDAH) Study has shown high childhood CRF and muscular fitness, incorporating strength, power, and endurance, to associate with decreased risk of metabolic syndrome in adulthood^{3, 4}. Although metabolic syndrome is a condition of clustering risk factors including high fasting glucose, more work is required to explore the association between childhood physical fitness and adult glucose homeostasis outcomes including fasting insulin, insulin resistance and beta cell function. These associations have been examined in part previously. Additional work using CDAH data showed a decline in CRF between childhood and adulthood (n=647, baseline age=9, 12, 15 years, follow-up=20 years) to associate with increased odds of adult insulin resistance⁷. However, this study focused only on CRF and did not include muscular fitness. Furthermore, the European Youth Heart Study reported increased muscular strength and CRF in childhood (n=317, age 15 years) to be associated with decreased insulin resistance and beta cell function 6-12 years later⁸. However, whether this longitudinal association exists between an increased range of muscular fitness phenotypes in younger children, after an extended length of follow-up, is of interest.

Therefore, using data from the CDAH Study, we aimed to determine whether CRF, muscular strength, muscular power, and muscular endurance in children aged 7-15 years independently predict adult glucose homeostasis measures 20-years later.

Methods

The CDAH study collected baseline data on a nationally representative sample of 8,498 Australian schoolchildren in 1985. Children aged 7-15 years provided anthropometric, CRF, muscular power and muscular endurance data. Muscular strength was measured in a subset of children aged 9, 12 and 15 years. Of those who provided a measure of childhood physical fitness, 2417 participants (28.4%) had a fasting blood sample collected and tested for fasting glucose and/or insulin in adulthood, either by attending one of 34 follow-up clinics held across Australia from 2004-2006 or if unable to attend clinics, at remote pathology centres. Of these, 53 women were currently pregnant and excluded from analyses. See Figure S1 for a flow chart of participation. At baseline, consent was obtained from parent and assent from child, whilst the participant provided written informed consent at follow-up. The State Directors General of Education approved the baseline study and the Southern Tasmania Health and Medical Human Research Ethics Committee approved the follow-up study.

Using isometric dynamometers (Smedley's Dynamometer, TTM, Tokyo, Japan), childhood muscular strength was measured as maximum voluntary contractile force of right and left grip, shoulder flexion and extension, and leg. Right and left grip strength was measured by gripping the dynamometer with maximum force with one hand. Shoulder flexion and extension strength was measured by participants holding the dynamometer in front of their chest with both hands parallel to the ground and then either pulling (extension) or pushing (flexion) with maximum effort. Leg strength was measured as participants stood on a leg-back dynamometer with flat feet, a straight back and with their body flat against a wall behind them. Participants held a bar with an overhand grip, whilst they flexed their knees until reaching an angle of 115° at which point a chain was attached from the dynamometer to the bar. Participants then pulled the bar as far upwards as possible by sliding their body up the wall. The maximum of two attempts at each strength measure was used in analyses. A combined muscular strength score was obtained via principal component analysis and estimating the first principal component of each of the five muscular strength measures⁹. Muscular power was measured as the best resulting distance in centimetres from two attempts at a standing long jump, with each jump requiring a two-footed take-off. Muscular endurance was estimated by the number of correctly completed

inclined push-ups in 30 seconds. Participants started by placing their hands shoulder width apart on the front edge of a chair, arms fully extended at a 90° angle to the body and with their legs straight. A *correct* push up was defined when participants' bodies were lowered until their chests touched the chair and then raised until their arms were fully extended. Additional methodology detail is reported elsewhere^{3, 10}. To create measures of muscular fitness not attributable to body weight, body weight was regressed on each phenotype and the residuals were used⁹. All muscular fitness phenotypes were standardised for age and sex (see Table S1 for summary statistics). Previous systematic reviews have highlighted the reliability of these muscular fitness measures^{11, 12}. In childhood, non-significant test-retest differences have been shown for grip strength (males: 0.3 ± 2.5 kg; females: 0.0 ± 1.8 kg) and standing long jump distance (males: -0.3 ± 12.9 cm; females: 0.3 ± 9.0 cm)¹³, and high intraclass reliability estimates have been presented for one version of the push up test ($R=0.98$ ($0.97, 0.99$))¹⁴.

Childhood CRF was estimated by the duration of a 1.6km run performed over a level, marked course. Verbal support was provided to encourage maximum effort. The reliability of the 1.6km run test has been reported previously (males: intraclass correlation coefficient (ICC)= 0.80 ($0.70, 0.86$); females: ICC= 0.87 ($0.78, 0.92$))¹⁵. The duration of the 1.6km run strongly correlates with maximal oxygen consumption (VO_2 max) (-0.85 to -0.73)¹⁶. To assist with interpretation, 1.6km run duration was used to estimate VO_2 max using the equation by Cureton et al¹⁷. Estimated VO_2 max was standardised for age and sex (summary statistics shown in Table S1).

In childhood, a constant-tension tape was used to measure waist circumference at the level of the umbilicus, to the nearest 0.1cm. Using regularly calibrated scales, body mass was measured to the nearest 0.5kg, whilst a Kawe height tape was used to measure height to the nearest 0.1cm. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters squared).

In adulthood, fasting status was enquired from participants. Fasting glucose and insulin levels were measured using blood samples collected from those who observed a 12 hour fast. An Olympus

AU5400 automated analyser (Olympus Optical, Tokyo, Japan) was used to enzymatically measure fasting glucose, whilst a microparticle enzyme immunoassay kit (AxSYM; Abbot Laboratories, Abbot Park, IL) or an electrochemiluminescence immunoassay (Elecsys Modular Analytics E170; Roche Diagnostics, Mannheim, Switzerland) with interassay standardisation was used to measure fasting insulin⁷.

Adult glucose homeostasis measures included insulin resistance (HOMA2-IR) and beta cell function (HOMA2- β)^{18, 19}. These measures were calculated by a homeostasis model assessment (HOMA2) calculator (version 2.2.3 available from <http://www.dtu.ox.ac.uk/homacalculator>) using fasting glucose and fasting insulin²⁰. Participants with fasting glucose levels outside the range 3.5-25 mmol/L (n=0) and fasting insulin levels outside the range 2.88-57.60 mU/L (20-400 pmol/L) (n=167) were excluded from HOMA2 calculations as these values were outside the range of clinically realistic fasting values accepted by the calculator²⁰.

All statistical analyses were performed using Stata (Version 15.0, StataCorp, College Station, Texas). Participant baseline and follow-up characteristics are stratified by sex and summarised as mean and standard deviation (SD) for normally distributed data or median and interquartile range for skewed data.

Linear regression was used to estimate associations between childhood physical fitness phenotypes and adult glucose homeostasis measures. Where necessary, outcome variables were transformed (e.g. by taking logarithms) prior to analysis to remove skewness. Inverse probability weighting was used to account for missing data at follow-up, with multiple imputation of incomplete baseline data, following the approach of Seaman et al²¹. Three multivariable models with successive adjustment were considered for each association. Model one adjusted for childhood age, sex and length of follow-up; model two adjusted for model one covariates and additionally for another childhood physical fitness phenotype (associations with muscular strength, power and endurance were adjusted for CRF, and associations with CRF were adjusted for muscular strength, as strength was the muscular fitness

phenotype most strongly associated with these adult outcomes); model three adjusted for model two covariates and additionally for childhood waist circumference. A statistically significant sex interaction was present for muscular strength, therefore muscular strength analyses are sex stratified. There were no significant differences in association by age.

Results

Length of follow-up between childhood and adulthood ranged from 18.7 to 21.7 years, with a mean (SD) length of follow-up of 19.9 (0.6) years. Participant characteristics are presented in Table 1.

Compared to females, males had greater childhood muscular fitness and CRF, and had greater adult fasting glucose and fasting insulin levels. Females had greater beta cell function (HOMA2- β) values than males.

The longitudinal associations between childhood physical fitness phenotypes and adult glucose homeostasis measures are shown in Table 2 and Table 3. Independent of age, sex and length of follow-up, the childhood physical fitness phenotypes most strongly associated with fasting insulin, insulin resistance (HOMA2-IR) and beta cell function (HOMA2- β) were CRF and muscular strength (males). Adjusting the CRF associations for muscular strength reduced the statistically significant regression coefficients by 0-34%, whereas adjusting the statistically significant muscular strength associations for CRF produced changes of 29-33% (males) and 24-44% (females) (Model 2). Similarly, adjusting the muscular power and muscular endurance associations for CRF reduced the absolute size of the statistically significant regression coefficients by 18-65% (Model 2). Additional adjustment for childhood waist circumference reduced the absolute value of the associations for muscular strength by 0-15% (males) and 39-50% (females), muscular power by 26-73%, muscular endurance by 0-100% and CRF by 17-35% (Model 3).

To identify which component of muscular strength in males was having the greatest effect on adult glucose homeostasis, associations were repeated using the five measures of muscular strength as individual exposures. Right grip strength was the childhood muscular strength measure most strongly associated with these adult outcomes (Table S2).

In sensitivity analyses, we included childhood socioeconomic status, smoking status and diet quality, and adult waist circumference and physical fitness (methods presented online) as additional covariates

to Model 3. Adjustment for these childhood factors reduced statistically significant effect estimates by 0-13%. Additional adjustment for adult physical fitness levels attenuated effect estimates by 30-77%, whereas including adult waist circumference in the model reduced statistically significant effect estimates by 0-84%. In all cases, longitudinal associations remained.

Discussion

In this study, childhood CRF and muscular fitness were associated with fasting insulin, insulin resistance and beta cell function in adulthood after a period of 20 years. CRF and muscular strength in males were the physical fitness phenotypes most strongly associated with glucose homeostasis measures, independent of the alternative fitness type and childhood waist circumference. Childhood muscular endurance was similarly associated with these adult outcomes. Collectively, these results suggest childhood physical fitness is associated with adult glucose homeostasis.

In our study, a marked and statistically significant sex difference was present for the association between childhood muscular strength and adult glucose homeostasis measures, whereby associations were stronger for males. This may be because there was greater variation between males than females in each of the individual strength measures, resulting in the combined muscular strength score better discriminating between fit males and unfit males than between fit females and unfit females. We do not expect this sex difference to be explained by males having a higher degree of tracking (persistence) in muscular strength levels from childhood to adulthood than females, as previously we observed no consistent difference in muscular strength tracking between sexes¹⁰. Although we observed no significant differences in the effects by age between each sex, variations in muscular strength levels indicating differences in muscle mass between males and females could potentially explain the sex difference.

Our results suggested associations between childhood physical fitness phenotypes and adult fasting insulin, insulin resistance, and beta cell function, were strong and significant, whereas associations with fasting glucose were lacking. The natural history of T2DM could explain these results. Progression toward T2DM begins with increased insulin secretion and insulin resistance, whilst fasting glucose concentration increases at a slower rate than insulin over time²². As glucose homeostasis measurement was conducted in young adulthood (age 26-36 years), participants could be in the early stage of disease progression. This might explain why associations were stronger with insulin based outcomes, compared with isolated fasting glucose. If these same participants are

followed up again as older adults, we hypothesise that childhood physical fitness will predict adult fasting glucose, and the prediabetic state of impaired fasting glucose.

In our study, additional adjustment for childhood waist circumference reduced the effect estimate within each association. Waist circumference mediating the association between childhood physical fitness phenotypes and adult cardiometabolic outcomes could potentially explain these results; however, waist circumference could also be a confounder. Our results suggest childhood physical fitness could be having both a direct and indirect effect on adult glucose homeostasis. The indirect pathway could be explained by increased childhood physical fitness leading to decreased adiposity, with decreased adiposity having a beneficial effect on glucose homeostasis. Alternatively, these results could be partially explained by physical fitness tracking between child and adulthood, whereby fit children are likely to become fit adults¹⁰. Adjustment for adult fitness attenuated our effect estimates, although longitudinal associations remained. The direct effect however could be explained by CRF improving insulin sensitivity through enhanced glucose uptake and disposal²³ or by correcting a mismatch between fatty acid uptake and fatty acid oxidation in the skeletal muscle²⁴. Further, higher levels of muscular strength are likely due to increased participation in muscle strengthening exercises that have been shown to improve insulin sensitivity by stimulating key proteins in the insulin signalling pathway²⁵, with this effect being previously reported among individuals with and without T2DM²⁵.

The results of our study are consistent with trends published elsewhere. In adulthood, increased levels of muscular fitness and CRF were associated with a decreased risk of T2DM^{26, 27}. This association is consistent in longitudinal data spanning late adolescence to adulthood, whereby physical fitness at age 18 years was associated with adult T2DM⁶. In relation to insulin resistance, cross-sectional data in childhood has shown muscular strength and CRF to be strong independent predictors of HOMA2-IR²⁸, whilst previous longitudinal research using CDAH data has shown lower levels of CRF (physical work capacity at 170 beats per minute) to associate with increased odds of adult HOMA1-IR⁷.

Of greatest similarity to our findings, are longitudinal data presented by the European Youth Heart Study (n=317, age 15 years, length of follow-up=12 years). In this study, childhood muscular strength and CRF were associated with fasting insulin, insulin resistance and beta cell function in adulthood⁸. Limitations acknowledged by the investigators included the use of HOMA1-based measures as outcomes and the absence of a dynamic strength measure exposure⁸. Our study addressed these gaps. We used HOMA2-based glucose homeostasis measures as outcomes which although do not provide information regarding the stimulated state, these measures have a strong physiological basis^{18, 19} and consider differences in hepatic and peripheral insulin resistance, the rise in the insulin secretion curve for plasma glucose concentrations above 10mmol/L and the influence of circulating proinsulin^{19, 20}. Further, our study includes strength, power and endurance as muscular fitness exposures, providing an example of static, explosive and dynamic aspects of muscular fitness²⁹. By examining the association between childhood physical fitness, including an alternative phenotype of CRF, three phenotypes of muscular fitness and HOMA2-based measures of glucose homeostasis in adulthood, our results expand on previous findings. We found childhood CRF, muscular endurance and muscular strength (males) to be significantly associated with measures of insulin resistance and beta cell function in adulthood, independent of the alternative physical fitness phenotype and a measure of adiposity. Of these, the strongest associations were with right grip strength (males). For example, a 3.57kg (equivalent to one standard deviation) increase in right grip strength for a 9-year old male would be associated with a 0.52mU/L decrease in adult fasting insulin and a 0.08 decrease in HOMA2-IR. Right grip strength could be increased by this amount through participation in a 10-week exercise program which incorporates aerobic and resistance training three times a week, as shown previously in a cohort of obese children (n=44, aged: 12-14 years)³⁰.

The results of our study highlight muscular fitness as having protective effects independent of CRF, suggesting both aspects of physical fitness are beneficial to future cardiometabolic health. Muscular fitness activities have recently been included within the World Health Organisation physical activity guidelines³¹. These guidelines now suggest muscular strengthening activities, in addition to aerobic

exercise, should be performed at least 3 days a week in childhood³¹. Although our conclusions are based on physical fitness phenotypes used as proxy measures of physical fitness behaviours, our results support these new physical activity guidelines and emphasise the importance of promoting both forms of fitness in childhood.

Potential limitations of our longitudinal study include differential loss to follow-up; however, our statistical analyses included inverse probability weighting to account for missingness. The statistical procedure used is not as appropriate if missing data were missing not at random, however we have no reason to believe that this is the case. Further, we do not have childhood glucose homeostasis measures, therefore we could not determine the potential intermediary role of these baseline measures. An additional limitation includes pubertal status not being measured at baseline, therefore we could not examine the effect puberty had on our longitudinal associations. Lastly, T2DM (fasting glucose ≥ 7.0 mmol/L) was not included as a study outcome owing to low case numbers in this young adult cohort (n=6). However, impaired glucose homeostasis can lead to T2DM²², therefore our results could potentially contribute to strategies aimed to assist in T2DM prevention. Our study had numerous strengths, including a long follow-up of a large national sample with baseline ages younger than past studies and examining a large range of physical fitness phenotypes. Past systematic reviews have determined the reliability of fitness tests and reported grip-strength, standing long jump, and the 1.6km run as valid tests to measure muscular strength, muscular power and CRF^{11, 12}. Although limited evidence exists on the validity of the push-up test to measure childhood muscular endurance, a previous study showed high test-retest reliability¹⁴. Furthermore, our HOMA2-based outcomes have a strong physiological basis^{18, 19} and correlate with gold standard hyperinsulinemic-euglycemic clamp ($r=0.78$) and hyperglycemic clamp ($r=0.87-0.90$) methods¹⁸.

Conclusion

In conclusion, childhood CRF and muscular endurance for both sexes, and muscular strength for males, were associated with adult glucose homeostasis measures. These findings reinforce the importance of encouraging both CRF and muscular fitness in childhood and suggest strategies aimed

at improving childhood physical fitness levels could help reduce adverse glucose homeostasis in later life.

Practical Implications

- Childhood CRF and muscular fitness levels predicted fasting insulin, insulin resistance and beta cell function in adulthood. Increasing CRF and muscular fitness in childhood could help contribute to achieving a healthier adult glucose homeostasis profile.
- Childhood CRF and muscular fitness levels were associated with adult measures of glucose homeostasis, independent of the alternative fitness phenotype. These data support the stance that both CRF and muscular fitness should be encouraged in childhood.
- Prevention strategies aimed at reducing future adverse glucose homeostasis could target childhood CRF and muscular fitness levels. Strategies aimed at increasing both childhood CRF and muscular fitness levels could help improve future cardiometabolic health.

References

1. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. *Diabetes Care*. 2011;34(6):1249-57.
2. Tabak AG, Herder C, Rathmann W, et al. Prediabetes: a high-risk state for diabetes development. *Lancet*. 2012;379(9833):2279-90.
3. Fraser BJ, Huynh QL, Schmidt MD, et al. Childhood Muscular Fitness Phenotypes and Adult Metabolic Syndrome. *Med Sci Sports Exerc*. 2016;48(9):1715-22.
4. Schmidt MD, Magnussen CG, Rees E, et al. Childhood fitness reduces the long-term cardiometabolic risks associated with childhood obesity. *Int J Obes (Lond)*. 2016;40(7):1134-40.
5. Grontved A, Ried-Larsen M, Moller NC, et al. Muscle strength in youth and cardiovascular risk in young adulthood (the European Youth Heart Study). *Br J Sports Med*. 2015;49(2):90-4.
6. Crump C, Sundquist J, Winkleby MA, et al. Physical Fitness Among Swedish Military Conscripts and Long-Term Risk for Type 2 Diabetes Mellitus: A Cohort Study. *Ann Intern Med*. 2016;164(9):577-84.
7. Dwyer T, Magnussen CG, Schmidt MD, et al. Decline in physical fitness from childhood to adulthood associated with increased obesity and insulin resistance in adults. *Diabetes Care*. 2009;32(4):683-7.
8. Grontved A, Ried-Larsen M, Ekelund U, et al. Independent and combined association of muscle strength and cardiorespiratory fitness in youth with insulin resistance and beta-cell function in young adulthood: the European Youth Heart Study. *Diabetes Care*. 2013;36(9):2575-81.
9. Quan HL, Blizzard CL, Sharman JE, et al. Resting heart rate and the association of physical fitness with carotid artery stiffness. *Am J Hypertens*. 2014;27(1):65-71.

10. Fraser BJ, Schmidt MD, Huynh QL, et al. Tracking of muscular strength and power from youth to young adulthood: Longitudinal findings from the Childhood Determinants of Adult Health Study. *J Sci Med Sport*. 2017;20(10):927-31.
11. Castro-Pinero J, Artero EG, Espana-Romero V, et al. Criterion-related validity of field-based fitness tests in youth: a systematic review. *Br J Sports Med*. 2010;44(13):934-43.
12. Artero EG, Espana-Romero V, Castro-Pinero J, et al. Reliability of field-based fitness tests in youth. *Int J Sports Med*. 2011;32(3):159-69.
13. Ortega FB, Artero EG, Ruiz JR, et al. Reliability of health-related physical fitness tests in European adolescents. The HELENA Study. *Int J Obes*. 2008;32:S49-S57.
14. Saint Romain B, Mahar MT. Norm-referenced and criterion-referenced reliability of the push-up and modified pull-up. *Meas Phys Educ Exerc Sci*. 2001;5(2):67-80.
15. Beets MW, Pitetti KH. Criterion-referenced reliability and equivalency between the PACER and 1-mile run/walk for high school students. *Journal of Physical Activity and Health*. 2006;3(s2):S21-S33.
16. George JD, Vehrs PR, Allsen PE, et al. VO₂max estimation from a submaximal 1-mile track jog for fit college-age individuals. *Med Sci Sports Exerc*. 1993;25(3):401-6.
17. Cureton KJ, Sloniger MA, O'Bannon JP, et al. A generalized equation for prediction of VO₂peak from 1-mile run/walk performance. *Med Sci Sports Exerc*. 1995;27(3):445-51.
18. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487-95.
19. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care*. 1998;21(12):2191-2.

20. The Oxford Centre for Diabetes. Endocrinology & Metabolism. Diabetes Trial Unit. HOMA Calculator. [10 February, 2017]. Available from:
<http://www.dtu.ox.ac.uk/homacalculator/>.
21. Seaman SR, White IR, Copas AJ, et al. Combining multiple imputation and inverse-probability weighting. *Biometrics*. 2012;68(1):129-37.
22. Ramlo-Halsted BA, Edelman SV. The natural history of type 2 diabetes: practical points to consider in developing prevention and treatment strategies. *Clin Diabetes*. 2000;18(2):80-4.
23. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiol Rev*. 2013;93(3):993-1017.
24. Turcotte LP, Fisher JS. Skeletal muscle insulin resistance: roles of fatty acid metabolism and exercise. *Phys Ther*. 2008;88(11):1279-96.
25. Holten MK, Zacho M, Gaster M, et al. Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. *Diabetes*. 2004;53(2):294-305.
26. Katzmarzyk PT, Craig CL, Gauvin L. Adiposity, physical fitness and incident diabetes: the physical activity longitudinal study. *Diabetologia*. 2007;50(3):538-44.
27. Sawada SS, Lee IM, Naito H, et al. Muscular and performance fitness and the incidence of type 2 diabetes: prospective study of Japanese men. *J Phys Act Health*. 2010;7(5):627-32.
28. Benson AC, Torode ME, Singh MA. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. *Int J Pediatr Obes*. 2006;1(4):222-31.
29. Nicks DC, Fleishman EA. What do Physical Fitness Tests Measure?—A Review of Factor Analytic Studies 1. *Educ Psychol Meas*. 1962;22(1):77-95.

30. Lee YH, Song YW, Kim HS, et al. The effects of an exercise program on anthropometric, metabolic, and cardiovascular parameters in obese children. *Korean Circ J*. 2010;40(4):179-84.
31. World Health Organization. Global Recommendations on Physical Activity for Health. Geneva, Switzerland: WHO Press; 2010.

Tables

Table 1. Characteristics of participants at baseline and follow-up.

Characteristic	n	Sex	
		Male	Female
		Statistic*	Statistic*
Childhood (baseline)			
Age, years	2363	11.2 (2.5)	11.0 (2.6)
Right grip strength, kg	810	26.1 (10.7)	21.0 (6.7)
Left grip strength, kg	809	25.6 (10.6)	20.2 (6.3)
Shoulder flexion, kg	798	21.6 (14.2)	18.3 (8.9)
Shoulder extension, kg	799	18.0 (9.5)	13.8 (6.1)
Leg strength, kg	804	119.2 (59.4)	84.0 (34.5)
Combined muscular strength score	793	0.17 (1.59)	0.09 (1.65)
Standing long jump, cm	2361	154.0 (31.4)	137.7 (25.3)
Push-ups	2356	13.7 (6.1)	7.8 (5.8)
1.6km run, mins	2202	8.2 (1.5)	9.9 (1.8)
Estimated VO ₂ max, ml/kg/min	2201	50.7 (4.1)	44.9 (3.8)
Height, cm	2362	148.7 (16.2)	145.6 (14.3)
Weight, kg	2363	41.2 (13.6)	39.5 (12.2)
BMI, kg/m ²	2362	18.1 (2.7)	18.2 (2.8)
Waist circumference, cm	2363	64.7 (8.3)	62.1 (7.9)
Adulthood (follow-up)			
Fasting plasma glucose, mmol/L	2360	5.17 (0.48)	4.83 (0.40)
Fasting plasma insulin, mU/L	2179	6.08 (4.21, 9.04)	5.80 (4.29, 8.10)
HOMA2-IR	2176	0.85 (0.61, 1.23)	0.77 (0.59, 1.08)
HOMA2-β, %	2176	87.19 (33.59)	93.80 (31.95)

* Statistics are mean (standard deviation) for normally distributed data or median (interquartile range) for skewed data.

Abbreviations: VO₂ max, maximal oxygen consumption; BMI, body mass index; HOMA2-IR, Homeostasis Model Assessment 2 – Insulin Resistance; HOMA2-β, Homeostasis Model Assessment 2 – Beta cell function; SD, standard deviation.

Table 2. Multivariable association between childhood muscular strength and muscular power and measures of glucose homeostasis in adulthood.

		Model 1*		Model 2†		Model 3‡	
	n§	Beta (95% CI)	<i>p-value</i>	Beta (95% CI)	<i>p-value</i>	Beta (95% CI)	<i>p-value</i>
Muscular strength							
Males							
Fasting glucose, mmol/L	362	-0.03 (-0.05, 0.00)	0.05	-0.02 (-0.05, 0.01)	0.14	-0.02 (-0.05, 0.01)	0.20
Fasting insulin, mU/L	359	-0.60 (-0.83, -0.38)	<0.001	-0.40 (-0.64, -0.15)	0.002	-0.34 (-0.61, -0.07)	0.02
HOMA2-IR	331	-0.07 (-0.09, -0.05)	<0.001	-0.05 (-0.07, -0.03)	<0.001	-0.05 (-0.07, -0.02)	0.001
HOMA2-β, %	331	-3.86 (-5.32, -2.41)	<0.001	-2.62 (-4.31, -0.93)	0.002	-2.34 (-4.10, -0.58)	0.009
Females							
Fasting glucose, mmol/L	378	-0.02 (-0.04, 0.01)	0.15	0.00 (-0.02, 0.03)	0.83	0.01 (-0.02, 0.04)	0.35
Fasting insulin, mU/L	375	-0.39 (-0.63, -0.16)	0.01	-0.22 (-0.49, 0.05)	0.11	-0.13 (-0.42, 0.16)	0.39
HOMA2-IR	344	-0.03 (-0.05, -0.01)	0.01	-0.02 (-0.04, 0.01)	0.31	-0.01 (-0.04, 0.02)	0.72
HOMA2-β, %	344	-1.92 (-3.67, -0.17)	0.03	-1.45 (-3.57, 0.68)	0.18	-0.89 (-3.06, 1.28)	0.42
Muscular power							
Males and females combined							
Fasting glucose, mmol/L	2197	0.00 (-0.02, 0.02)	0.85	0.02 (0.00, 0.04)	0.05	0.03 (0.00, 0.05)	0.02

Fasting insulin, mU/L	2183	-0.43 (-0.59, -0.27)	<i><0.001</i>	-0.15 (-0.34, 0.04)	<i>0.11</i>	-0.04 (-0.23, 0.15)	<i>0.67</i>
HOMA2-IR	2027	-0.05 (-0.07, -0.04)	<i><0.001</i>	-0.03 (-0.05, -0.01)	<i>0.006</i>	-0.02 (-0.04, 0.00)	<i>0.09</i>
HOMA2-β, %	2027	-3.68 (-4.81, -2.55)	<i><0.001</i>	-2.50 (-3.81, -1.20)	<i><0.001</i>	-1.85 (-3.17, -0.54)	<i>0.006</i>

* Model 1 is adjusted for childhood age, sex and length of follow up.

† Model 2 is adjusted for model 1 covariates and additionally for childhood cardiorespiratory fitness.

‡ Model 3 is adjusted for model 2 covariates and additionally for childhood waist circumference.

§ Muscular strength was measured only in children aged 9, 12 or 15 years, therefore a lower n is observed for analyses where muscular strength is a primary exposure or covariate.

Abbreviations: CI, confidence intervals; HOMA2-IR, Homeostatic Model Assessment 2 – Insulin Resistance; HOMA2-β, Homeostatic Model Assessment 2 – Beta cell function.

Table 3. Multivariable association between childhood muscular endurance and CRF and measures of glucose homeostasis in adulthood.

Table S7. Multivariable association between childhood muscular endurance and CVD and measures of glucose homeostasis in adulthood							
		Model 1*		Model 2†		Model 3‡	
	n§	Beta (95% CI)	<i>p-value</i>	Beta (95% CI)	<i>p-value</i>	Beta (95% CI)	<i>p-value</i>
Muscular endurance							
Males and females combined							
Fasting glucose, mmol/L	2191	0.01 (-0.01, 0.02)	0.56	0.01 (-0.01, 0.03)	0.20	0.02 (-0.00, 0.04)	0.14
Fasting insulin, mU/L	2177	-0.39 (-0.54, -0.24)	<0.001	-0.27 (-0.43, -0.11)	0.001	-0.19 (-0.35, -0.03)	0.02
HOMA2-IR	2022	-0.05 (-0.06, -0.03)	<0.001	-0.03 (-0.05, -0.02)	<0.001	-0.03 (-0.04, -0.01)	0.005
HOMA2-β, %	2022	-3.33 (-4.43, -2.23)	<0.001	-2.73 (-3.85, -1.61)	<0.001	-2.24 (-3.37, -1.11)	<0.001
Cardiorespiratory fitness							
Males and females combined							
Fasting glucose, mmol/L	740	-0.06 (-0.10, -0.02)	0.002	-0.06 (-0.10, -0.01)	0.01	-0.05 (-0.09, 0.00)	0.07
Fasting insulin, mU/L	734	-0.93 (-1.16, -0.69)	<0.001	-0.73 (-1.02, -0.44)	<0.001	-0.57 (-0.93, -0.21)	0.002
HOMA2-IR	675	-0.09 (-0.12, -0.06)	<0.001	-0.06 (-0.10, -0.03)	<0.001	-0.04 (-0.08, -0.00)	0.05
HOMA2-β, %	675	-4.64 (-6.43, -2.86)	<0.001	-3.06 (-5.14, -0.97)	0.004	-1.98 (-4.44, 0.48)	0.12
HOMA2-S, %	675	13.44 (8.65, 18.22)	<0.001	9.08 (3.74, 14.42)	0.001	5.62 (-0.20, 11.44)	0.06
* Model 1 is adjusted for childhood age, sex and length of follow up.							

† Model 2 is adjusted for model 1 covariates and additionally for childhood cardiorespiratory fitness or muscular strength.

‡ Model 3 is adjusted for model 2 covariates and additionally for childhood waist circumference.

§ Muscular strength was measured only in children aged 9, 12 or 15 years, therefore a lower n is observed for analyses where muscular strength is a primary exposure or covariate.

Abbreviations: CI, confidence intervals; HOMA2-IR, Homeostatic Model Assessment 2 – Insulin Resistance; HOMA2- β , Homeostatic Model Assessment 2 – Beta cell function.

Online-only supplement

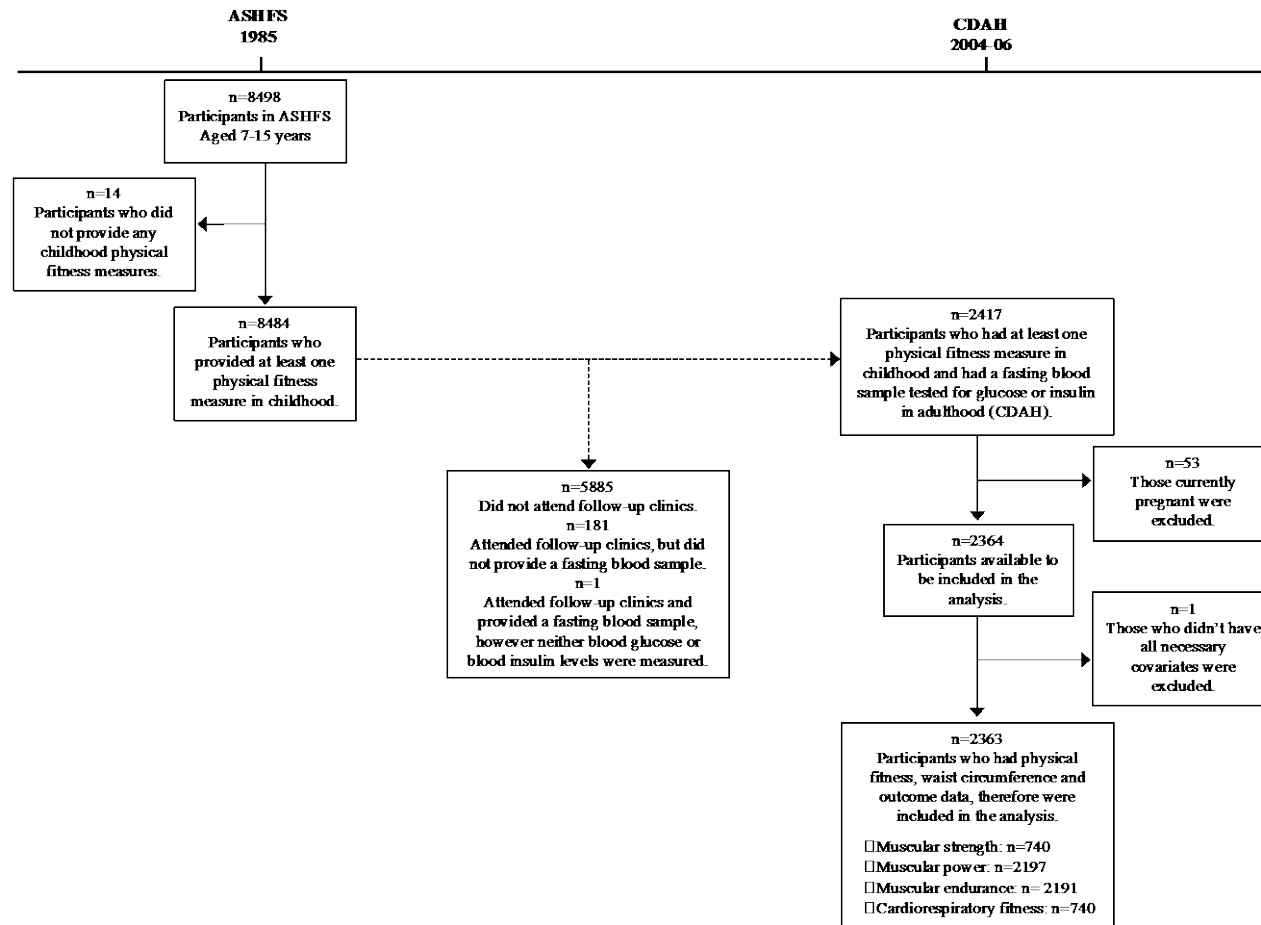


Figure S1. Participant flow chart. Abbreviations: ASHFS, Australian Schools Health and Fitness Survey; CDAH, Childhood Determinants of Adult Health Study.

Table S1. Mean (SD) values of each muscular fitness measure not attributable to body weight for each age and sex.

Muscular fitness measure	Male	Female
	Mean (SD)	Mean (SD)
Right grip strength, kg		
9 years	24.28 (3.57)	19.54 (2.96)
12 years	23.98 (5.06)	21.48 (4.06)
15 years	27.71 (6.14)	22.20 (4.53)
Left grip strength, kg		
9 years	23.84 (3.44)	18.91 (2.86)
12 years	23.66 (4.95)	20.52 (3.82)
15 years	27.17 (6.05)	21.21 (4.32)
Shoulder extension, kg		
9 years	16.79 (3.37)	12.87 (2.91)
12 years	16.23 (5.00)	13.72 (3.84)
15 years	19.50 (7.21)	15.41 (4.99)
Shoulder flexion, kg		
9 years	19.25 (4.34)	16.11 (4.16)
12 years	17.85 (7.30)	18.14 (5.85)
15 years	23.97 (10.06)	20.22 (6.93)
Leg strength, kg		
9 years	107.02 (23.30)	76.81 (18.31)
12 years	111.34 (31.93)	85.60 (25.39)
15 years	127.20 (38.94)	88.35 (29.59)
Standing long jump, cm		
7 years	138.21 (18.80)	120.01 (17.47)
8 years	141.07 (19.59)	128.55 (18.51)
9 years	145.67 (20.43)	132.94 (19.98)
10 years	151.54 (20.82)	138.25 (19.85)
11 years	149.96 (24.65)	140.14 (22.38)
12 years	150.81 (25.64)	140.58 (23.00)
13 years	156.18 (26.11)	140.25 (22.80)
14 years	159.45 (24.84)	142.11 (21.49)
15 years	163.09 (25.51)	139.48 (22.32)
Push-ups		

7 years	12.05 (4.67)	6.22 (4.90)
8 years	12.64 (5.33)	7.36 (5.33)
9 years	12.14 (5.36)	7.21 (4.98)
10 years	13.53 (5.87)	8.11 (5.00)
11 years	12.56 (6.41)	7.65 (5.25)
12 years	12.57 (6.26)	7.67 (5.47)
13 years	13.66 (6.17)	7.71 (4.92)
14 years	15.64 (6.24)	8.86 (5.44)
15 years	16.71 (6.41)	7.64 (4.92)
Estimated VO ₂ max, ml/min/kg		
7 years	47.66 (2.96)	44.72 (2.55)
8 years	48.79 (3.42)	45.08 (2.83)
9 years	49.58 (3.87)	45.15 (3.58)
10 years	50.62 (3.97)	45.23 (3.46)
11 years	50.44 (4.58)	44.95 (4.13)
12 years	50.56 (4.69)	44.64 (3.91)
13 years	50.95 (4.86)	43.71 (3.93)
14 years	51.66 (4.43)	43.65 (3.71)
15 years	52.02 (4.24)	42.70 (4.89)

Abbreviations: SD, standard deviation; VO₂ max, maximal oxygen consumption.

Table S2. Multivariable association between childhood muscular strength phenotypes and adult measures of glucose homeostasis for males.

		Model 1*		Model 2†		Model 3‡	
	n	Beta (95% CI)	<i>p-value</i>	Beta (95% CI)	<i>p-value</i>	Beta (95% CI)	<i>p-value</i>
Right grip strength							
Fasting glucose, mmol/L	370	-0.06 (-0.10, -0.02)	0.005	-0.06 (-0.10, -0.01)	0.01	-0.06 (-0.10, -0.01)	0.02
Fasting insulin, mU/L	367	-0.85 (-1.26, -0.44)	<0.001	-0.59 (-1.01, -0.16)	0.006	-0.52 (-0.96, -0.07)	0.02
HOMA2-IR	338	-0.10 (-0.14, -0.07)	<0.001	-0.08 (-0.12, -0.04)	<0.001	-0.08 (-0.12, -0.03)	<0.001
HOMA2-β, %	338	-5.19 (-8.01, -2.38)	<0.001	-3.45 (-6.47, -0.44)	0.03	-3.05 (-6.19, 0.08)	0.06
Left grip strength							
Fasting glucose, mmol/L	368	-0.04 (-0.08, -0.00)	0.04	-0.04 (-0.08, 0.01)	0.11	-0.03 (-0.08, 0.01)	0.17
Fasting insulin, mU/L	365	-0.76 (-1.10, -0.42)	<0.001	-0.45 (-0.82, -0.08)	0.02	-0.37 (-0.77, -0.03)	0.07
HOMA2-IR	337	-0.08 (-0.11, -0.05)	<0.001	-0.05 (-0.09, -0.01)	0.008	-0.05 (-0.09, -0.00)	0.03
HOMA2-β, %	337	-4.33 (-6.78, -1.87)	<0.001	-2.41 (-5.21, 0.39)	0.09	-1.92 (-4.87, 1.03)	0.20
Shoulder flexion							
Fasting glucose, mmol/L	364	-0.03 (-0.08, 0.01)	0.16	-0.02 (-0.07, 0.03)	0.36	-0.02 (-0.07, 0.03)	0.44
Fasting insulin, mU/L	361	-0.69 (-1.08, -0.29)	0.001	-0.32 (-0.78, 0.14)	0.18	-0.23 (-0.71, 0.26)	0.36
HOMA2-IR	333	-0.07 (-0.11, -0.03)	<0.001	-0.04 (-0.08, -0.01)	0.12	-0.03 (-0.08, 0.02)	0.21
HOMA2-β, %	333	-4.12 (-6.84, -1.39)	0.003	-1.74 (-4.84, 1.35)	0.27	-1.21 (-4.46, 2.04)	0.47
Shoulder extension							
Fasting glucose, mmol/L	365	-0.01 (-0.06, 0.04)	0.67	0.00 (-0.05, 0.06)	0.94	0.00 (-0.05, 0.06)	0.86
Fasting insulin, mU/L	362	-0.81 (-1.24, -0.38)	<0.001	-0.43 (-0.91, 0.05)	0.08	-0.38 (-0.88, -0.12)	0.14
HOMA2-IR	334	-0.10 (-0.14, -0.06)	<0.001	-0.07 (-0.11, -0.02)	0.007	-0.06 (-0.11, -0.01)	0.02
HOMA2-β, %	334	-6.31 (-8.88, -3.74)	<0.001	-4.20 (-7.27, -1.13)	0.007	-3.92 (-7.07, -0.77)	0.02

Leg strength

Fasting glucose, mmol/L	367	-0.02 (-0.06, 0.02)	<i>0.39</i>	-0.01 (-0.06, 0.04)	<i>0.62</i>	-0.01 (-0.06, 0.04)	<i>0.73</i>
Fasting insulin, mU/L	364	-0.54 (-0.88, -0.20)	<i>0.002</i>	-0.25 (-0.63, 0.14)	<i>0.21</i>	-0.18 (-0.57, 0.22)	<i>0.39</i>
HOMA2-IR	336	-0.06 (-0.10, -0.02)	<i>0.001</i>	-0.03 (-0.07, 0.01)	<i>0.13</i>	-0.03 (-0.07, 0.02)	<i>0.23</i>
HOMA2- β , %	336	-3.70 (-6.23, -1.17)	<i>0.004</i>	-1.88 (-4.67, 0.91)	<i>0.19</i>	-1.50 (-4.31, 1.30)	<i>0.29</i>

* Model 1 is adjusted for childhood age and length to follow up.

† Model 2 is adjusted for model 1 covariates and additionally for childhood cardiorespiratory fitness.

‡ Model 3 is adjusted for model 2 covariates and additionally for childhood waist circumference.

Abbreviations: CI, confidence intervals; HOMA2-IR, Homeostatic Model Assessment 2 – Insulin Resistance; HOMA2- β , Homeostatic Model Assessment 2 – Beta cell function.

Supplementary methods

Childhood socioeconomic status

Using the Australian Bureau of Statistics Socio-economic Index for Areas (SEIFA) and 1981 census data, childhood socioeconomic status was derived from residential postcode. Additional detail has been outlined previously¹. These postcodes were classified into four categories: low, medium-low, medium-high and high.

Childhood smoking status

Smoking status in childhood was ascertained from self-report in isolation from parents and teachers. Children were asked “How long have you been smoking regularly? (Regularly means 1 or more times a week)”. Children were defined as non-smokers if they indicated “I don’t smoke” and defined as smokers if they indicated any of the remaining responses (just started, 1-6 months, 7-12 months, 1-2 years, 2-4 years, >4 years).

Childhood dietary guideline index

In childhood, the dietary guideline index (DGI) was calculated according to servings of food and beverage items recorded in a 24-hour food diary. This score was based on the 2013 Australian Dietary Guidelines². The DGI was calculated from nine individual components, where a score from each component was summed to provide an overall DGI score. The individual DGI components included diet variety, vegetable intake, fruit intake, breads/cereals/wholegrains intake, meat intake, dairy intake, total fluid intake, discretionary (energy dense, nutrient poor) food intake and healthy fat intake. The maximum DGI score is 100, where a larger DGI reflects a healthier diet.

Adult muscular fitness

Using the same protocols as those used in childhood, muscular strength and muscular power was measured in adults. Additional methodological detail has been described elsewhere³. Muscular endurance was not measured in adulthood.

Right grip strength, left grip strength, shoulder extension, shoulder flexion and leg strength were measured using isometric dynamometers (Smedley's Dynamometer, TTM, Tokyo, Japan). Each strength measure was performed twice, with the maximum of two attempts used in analyses. Right and left grip strength was measured as participants held the dynamometer in the required hand and supported the dynamometer on their opposite shoulder. The participants then gripped the dynamometer with maximum force. Shoulder strength (flexion and extension) was measured as participants held the dynamometer in front of their chest with both hands parallel to the ground and pulled (extension) or pushed (flexion) with maximum force. Leg strength was measured as participants stood on the leg-back dynamometer with their body flat against a wall. Participants held a bar with an overhand grip and flexed their knees at an angle of 115° . At this point, the bar was attached to the dynamometer by a chain. Ensuring their body remained in contact with the wall behind them, the participant then pulled the bar up as far as possible by moving their body upwards. A combined muscular strength score was created incorporating each of the five individual muscular strength measures via principal component analysis⁴.

Adult muscular power was measured by the distance of standing long jump. This standing long jump required a two footed take off. Each participant was allowed two attempts, with the best resulting distance used in the analysis.

To create adult measures of muscular fitness not attributable to body weight, body weight was regressed on each muscular fitness measure and the residuals were used⁴. All muscular fitness measures were standardised for age and sex.

Adult cardiorespiratory fitness

Adult cardiorespiratory fitness was measured as physical work capacity at a heart rate of 170 beats per minute (PWC_{170}). This test followed a standardised protocol and used a Monark cycle ergometer pedaled at 60 revolutions per minute. The PWC_{170} test was made up of three-four minute workloads, with heart rate being recorded during the last 20 seconds of each workload. PWC_{170} was estimated by

extrapolating the line of best fit from the heart rates recorded at each workload. To create a measure of CRF not attributable to lean body mass, lean body mass was regressed on PWC_{170} and the residuals were used⁴.

Lean body mass was calculated from body density and percent body fat equations that used measures of skinfold thickness⁵. Tricep, bicep, subscapular and suprailiac skin folds were measured using Slim Guide Calipers to the nearest 0.5mm. Sum skinfolds was created via summing each site-specific skin fold score. Calculations of body fat were made from body density using the Siri formula⁵ and lean body mass was estimated by subtracting fat mass from total body mass.

Adult waist circumference

Using a constant tension tape, adult waist circumference was measured at the narrowest point between the lower costal border and iliac crest to the nearest 0.1 cm.

References:

1. Jose KA, Blizzard L, Dwyer T, et al. Childhood and adolescent predictors of leisure time physical activity during the transition from adolescence to adulthood: a population based cohort study. *Int J Behav Nutr Phys Act*. 2011;8:54.
2. National Health and Medical Research Council. Eat for Health: Australian Dietary Guidelines. Canberra, Australia: National Health and Medical Research Council; 2013.
3. Fraser BJ, Schmidt MD, Huynh QL, et al. Tracking of muscular strength and power from youth to young adulthood: Longitudinal findings from the Childhood Determinants of Adult Health Study. *J Sci Med Sport*. 2017;20(10):927-31.
4. Quan HL, Blizzard CL, Sharman JE, et al. Resting heart rate and the association of physical fitness with carotid artery stiffness. *Am J Hypertens*. 2014;27(1):65-71.
5. Siri W. Gross composition of the body. New York: Academic Press; 1956.