

**Predictive utility of childhood anthropometric measures on adult glucose homeostasis
measures: a 20-year cohort study**

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ABSTRACT

Background/Objectives: Childhood body mass index (BMI) predicts adult glucose homeostasis measures and type 2 diabetes mellitus, but little is known about the predictive utility of other anthropometric measures in childhood. We aimed to identify the anthropometric measure in childhood that best predicts adult glucose homeostasis measures and examine if the combination of additional anthropometric measures further improves predictive utility.

Methods: 20-year follow-up of children participating in the Childhood Determinants of Adult Health Study (n=2345, aged 7-15 years at baseline). Baseline anthropometric measures were waist circumference, waist circumference adjusted for height, weight adjusted for height, hip circumference, waist-hip-ratio, waist-height-ratio, BMI, conicity index, abdominal volume index (AVI), body adiposity index, and a body shape index. Fasting glucose and insulin levels measured at follow-up were used to define insulin resistance (HOMA2-IR), low beta-cell function (HOMA2- β), high fasting insulin, and impaired fasting glucose (IFG).

Results: All child anthropometric measures were significantly associated with HOMA2-IR, HOMA2- β , and high fasting insulin (relative risk=1.12 to 1.55), but not IFG. AVI had the largest area under receiver-operating curve (AUC) in predicting adult HOMA2-IR (AUC, 95% confidence interval: 0.610, 0.584-0.637), HOMA2- β (0.615, 0.588-0.642) and high fasting insulin (0.613, 0.587-0.639). Combining each additional anthropometric measure with AVI did not appreciably increase predictive utility (an increase of 0.001-0.002 in AUC, $p>0.05$ for all).

Conclusions: Anthropometric measures from a single time-point in childhood are associated with insulin-related outcomes 20-years later in adulthood. However, overall predictive utility was low and was not substantially enhanced by combining multiple different child anthropometric measures.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) contributes substantially to worldwide health costs, with the burden expected to rise in future decades¹, particularly in children and young adult populations². This is largely attributed to an increased incidence of obesity in these younger populations³. Furthermore, current evidence suggests that individuals are at increased risk of developing T2DM in adulthood if they had higher levels of adiposity in childhood⁴⁻⁶, but that this risk can be reversed if individuals attain a lower level of adiposity by adulthood⁶ or avoid becoming obese⁷. Therefore, identifying those children and adolescents at higher risk of developing T2DM in adulthood would allow preventive and intervention efforts to be initiated at an earlier life-stage^{8, 9}.

Recent attention has focused on identifying the best child anthropometric measure for determining child and adult cardiometabolic risk^{4-6, 10, 11}. Most longitudinal studies spanning childhood to adulthood have used body mass index (BMI) as the only or main anthropometric measure as it is attained easily. Of note, some other anthropometric measures have been shown to be more strongly associated with the risk of T2DM than BMI. For example, abdominal volume index, estimating overall abdominal volume between symphysis of pubis and xiphoid appendix, has been shown to have a stronger association with impaired glucose tolerance and T2DM than BMI in adults¹². However, it has not yet been determined whether pediatric anthropometric measurements, other than BMI, are better indicators of conditions associated with T2DM^{10, 13}. This is important information to optimise the allocation of public health resources and preventive efforts because greater benefits might be seen in children who are at higher risk of developing diabetes in adulthood if they could be accurately identified at an earlier stage of life using simple anthropometric measures.

Using existing data from a 20-year follow-up of the Childhood Determinants of Adult Health (CDAH) Study, we aimed to identify the anthropometric measure in childhood that has the best predictive utility with adult glucose homeostasis measures (defined by impaired fasting glucose and high insulin resistance, beta-cell function and fasting insulin). We also examined if adding an additional anthropometric measure to the best performing one further improved prediction.

METHODS

Participants

The CDAH study is an adult follow-up of 8498 children and adolescents aged 7 to 15 years who participated in the 1985 Australian Schools Health and Fitness Survey. The sampling frame, and full procedures and methods of the Australian Schools Health and Fitness Survey have been explained previously¹⁴. At the first adult follow-up of the CDAH study, 6840 (81%) of the original participants from the Australian Schools Health and Fitness Survey were traced between 2001-04. Of whom, 817 participants did not respond, 767 refused to participate, and 86 were found to have died. A total of 5170 (61%) participants of the original cohort were enrolled in a follow-up conducted between 2004 and 2006 when participants were aged 26 to 36 years, but 2760 participants were excluded as they did not participate in the follow-up (1205) or attend the follow-up clinics (1555). Finally, 2410 (28% of the original cohort) attended one of 34 CDAH field clinics held across Australia. The analyses for this study are restricted to up to 2345 participants (51% females) who had anthropometric data collected at baseline and provided a fasting blood sample at the CDAH follow-up in adulthood. A flow chart of participation is given in Figure 1. Consent was obtained from both parent and child prior to inclusion in the study at baseline and written informed consent was obtained 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.

Measurements

Childhood anthropometric measures

Standing height was measured to the nearest 0.1 cm using a portable KaWe stadiometer at baseline. Weight was measured to the nearest 0.5 kg using regularly calibrated scales. The data collectors were mostly graduate or undergraduate physical educators with a blend of recent graduates and teachers with some years of experience in schools. To ensure consistency of measurements, each team had a six-day training immediately before testing, which was done by the project director to ensure consistency in the information covered and the instructions given to each team. BMI was calculated as weight (kg)/(height²(m²)). Waist circumference (WC) was measured to the nearest 0.1cm taken at the level of the umbilicus. Hip circumference (HC) was measured horizontally at the level of the greater trochanter. Both waist and hip circumferences were measured using a constant tension tape. Weight adjusted for height and WC adjusted for height were calculated from linear regression analyses, further detailed in the statistical analysis. Waist-hip ratio (WHR) was calculated as waist circumference (cm)/hip circumference (cm), while waist-height ratio (WHtR) was calculated as waist circumference (cm)/ height (cm). A body shape index (ABSI)¹³, was calculated as $ABSI = \frac{WC(m)}{BMI^{\frac{2}{3}} \times Height^{\frac{1}{2}}(m)}$. Abdominal volume index (AVI)¹⁵, was calculated as $AVI = \frac{2cm \times WC^2(cm) + 0.7cm(WC(cm) - HC(cm))^2}{1000}$. Body adiposity index (BAI)¹⁶, was calculated as $BAI = \frac{HC(cm)}{Height^{1.5}(m)} - 18$. Conicity index (C Index)¹⁷ was

117 calculated as $C\ Index = \frac{WC\ (m)}{0.109 \times \sqrt{\frac{Weight\ (kg)}{Height\ (m)}}}$. Tri-ponderal mass index (TMI)¹⁸ was calculated as

118 $TMI = \frac{mass(kg)}{Height^3\ (m^3)}$.

119

120 *Adult glucose homeostasis measures*

121 Blood samples were collected from the antecubital vein after an overnight fast. Study staff

122 confirmed fasting status with the participant prior to the blood draw. Plasma glucose levels were

123 measured enzymatically using the Olympus AU5400 automated analyzer (Olympus Optical,

124 Tokyo, Japan). Impaired fasting glucose (IFG) was defined using the American Diabetes

125 Association cut-off points^{19, 20} as a fasting plasma glucose level ≥ 5.6 but < 6.9 mmol/l

126 (≥ 100 mg/l). Plasma insulin levels were measured by a microparticle enzyme immunoassay kit

127 (AxSYM, Abbot Laboratories, Abbot Park, Illinois, USA) initially (N=224)²¹, but a change in

128 kit was made to measure serum insulin determined by electrochemiluminescence immunoassay

129 (Elecsys Modular Analytics E170; Roche Diagnostics, Mannheim, Switzerland). This is because

130 the laboratory that performed analysis of blood biochemistry for this study was a contract

131 supplier and the assay was changed by the laboratory part-way through our 2-year data collection

132 period, over which we did not have control. As a result of this change in kit, a correction factor

133 was applied to insulin levels from participants assayed using the first methodology to be

134 consistent with levels in participants assayed using the second methodology²². Insulin resistance

135 (HOMA2-IR) and beta-cell function (HOMA2- β) were estimated using the updated homeostasis

136 model assessment (HOMA) index (HOMA2) determined from fasting glucose and fasting insulin

137 data by the pre-formulated program²³, HOMA2 calculator version 2.2.3²⁴. High insulin resistance

138 was defined using a previous WHO²⁵ study where HOMA index was at or above the 75th sex-

specific percentile. For consistency, high beta-cell function and fasting insulin were dichotomized using the 75th sex-specific percentile.

Statistical analysis

Mean (standard deviation, SD) and number (%) were used to describe continuous and categorical variables respectively. Additionally, median (interquartile range) was presented for skewed variables. We used Spearman correlation coefficients to examine the relationship between anthropometric measures in childhood, adjusted for age and sex. Linear regression models were used to predict the estimate of height-adjusted weight and height-adjusted WC indices. Relative risks for associations between childhood anthropometric measures (expressed as per standard deviation increase) and dichotomous glucose homeostasis outcomes in adulthood were computed using log-binomial regression models, adjusting for age and sex. To account for missing data due to loss to follow-up, we conducted the above-mentioned log-binomial regressions weighted by the inverse of participants' estimated probabilities of being observed; ie, of being "not missing". As we only found one instance of a sex*anthropometric measure interaction for one outcome in our analyses (hip circumference*sex with HOMA2- β , $P=0.045$), we present the data for males and females combined. For those adult outcomes that were significantly associated with childhood anthropometric measures, identical logistic regression models were used to obtain area under receiver-operating curve (AUC) values to estimate and compare the predictive utility of each childhood anthropometric measure on each glucose homeostasis outcome (using the measure that had the best predictive capacity as the reference for comparison). We also determined if there was a change in the predictive capacity on the outcomes when a second anthropometric measure was added to the best performing one identified in the above analysis.

162 The AUC is the percentage of randomly drawn pairs (one from positive outcome group, e.g.
163 HOMA2-IR; and one from the negative outcome group, e.g. not HOMA2-IR) for which the
164 person with the more abnormal test result (i.e. poor anthropometric measures) should be the one
165 from the positive outcome group. AUC can range from 0 to 1 where 0.5 represents no utility of
166 the measure to distinguish between those who subsequently develop the outcome vs. those who
167 do not (e.g. flipping a coin), and a value of 1 would indicate perfect prediction of those who do
168 and do not develop the outcome. Although there are no clear cut-offs of what constitutes an
169 acceptable AUC, values in excess of 0.75 are generally considered acceptable for prediction of
170 cardiometabolic outcomes among healthy adult populations. In addition, category-free net
171 reclassification index (NRI) was used as complementary to the AUC to quantify the
172 improvement in predictive capacity when a new marker (i.e. anthropometric measure) was added
173 to the model²⁶. We used NRI to determine if adding an anthropometric measure to the one that
174 had the best predictive capacity increased the predictive capacity on adult glucose homeostasis
175 measures. NRI was calculated using the formula: $NRI = P(\text{up}|\text{event}) - P(\text{down}|\text{event})$
176 $+ P(\text{down}|\text{nonevent}) - P(\text{up}|\text{nonevent})$. “Up” means that the new risk model suggests an increased
177 risk for a person compared with the old model while “down” means the new model gives a lower
178 risk for a person. “Event” means participants who have disease or outcome (e.g., poor HOMA2-
179 IR) and “nonevent” means those who do not have the disease or outcome. Therefore, NRI is the
180 sum of the difference between the proportion of participants who have increased and decreased
181 risk estimated by the new model in participants with “events” and the difference between the
182 proportion of participants who have decreased and increased risk estimated by the new model in
183 participants with “nonevents”. The maximum value of the NRI is 2. All statistical analyses were
184 performed in Stata/IC 14.2. A two-tailed p value < 0.05 was considered statistically significant.

RESULTS

Mean (SD) length of follow-up was 19.9 (0.6) years. **Table 1** shows the childhood (baseline) and adulthood (follow-up) characteristics of the participants by sex. Males were older, taller and heavier and had higher baseline anthropometric measures compared with females except that they had smaller weight adjusted for height, BAI, and TMI ($p < 0.05$ for all). There was no difference in HC and BMI between males and females. In adulthood, males had higher mean levels of glucose, insulin, and HOMA2-IR compared with females, but females had higher HOMA2- β . All childhood anthropometric measures were significantly correlated with each other (**Supplemental Table 1**).

Table 2 provides relative risk estimates for a 1-SD increase in childhood anthropometric measures with adult IFG, HOMA2-IR, HOMA2- β , and fasting insulin. All childhood anthropometric measures were significantly associated with increased risk of developing insulin resistance and having reduced beta-cell function and fasting insulin, but not IFG. In sensitivity analyses, using weighted complete cases did not affect the results (data not shown).

After comparing AVI with all other child anthropometric measures, AVI had the largest AUC in predicting adult HOMA2-IR, HOMA2- β and high fasting insulin though it did not reach statistical significance for a few outcomes (**Table 3**). **Table 4** shows the AUC and category-free NRI for the comparison of predictive capacity between the model with AVI only and models with AVI plus an additional childhood anthropometric measure, adjusted for age and sex. Adding each measure individually to AVI did not increase the predictive capacity.

DISCUSSION

We found that all our studied childhood anthropometric measures were associated with adult HOMA2-IR, HOMA2- β and fasting insulin, but not fasting glucose. Although child AVI had the best predictive utility for adult high HOMA2-IR, HOMA2- β and fasting insulin, the predictive utility was low overall and combining other child anthropometric measures with AVI did not further improve prediction.

The non-significant findings for IFG were unexpected, as previous studies have shown an inverse association between childhood BMI and adult fasting glucose, IFG, or T2DM. For example, Bhargava et al. showed a 36% increase in odds of having impaired glucose tolerance or T2DM in adulthood for a 1-SD increase in childhood BMI²⁷. Moreover, data from the International Childhood Cardiovascular Cohort Consortium found that overweight or obese children, according to international BMI cut-points, had more than twice the risk of developing T2DM in adulthood compared with normal weight peers⁷. During the early developmental stages that lead to T2DM, fasting blood glucose levels remain normal due to compensatory increases in insulin production and hyperinsulinemia as beta cells become insulin resistant²⁸. Our observed associations between child anthropometric measures with adult insulin-related outcomes but not fasting glucose are consistent with the young adult age (26-36 years) and relatively good health of our participants²⁹ – which contrasts with the older average adult age of participants in the aforementioned studies. Thus, future research should endeavor to extend our findings using these novel anthropometric markers in older aged adults where insulin resistance has progressed to IFG, impaired glucose tolerance, and T2DM.

Although our AUC results indicated that the best predictor of HOMA2-IR, HOMA2- β and fasting insulin was AVI in this sample, the predictive utility for all anthropometric measures

examined was poor (AUC ranging from 0.531-0.615). These findings are consistent with previous cross-sectional studies in children (AUCs ranging from 0.55-0.70) and child to adult longitudinal studies using a limited number of anthropometric measures to examine clustered cardiometabolic risk, including insulin^{4, 30}. Specifically, although child anthropometric measures predict important cardiometabolic outcomes later in life, the prediction is insufficient to warrant wide scale assessment and classification of children with increased risk for cardiometabolic outcomes. In particular, these findings suggest that while identifying those with low risk for developing the outcome of interest (specificity) is high, a high proportion of participants identified as being *at-risk* do not go on to develop the outcome (low sensitivity). This has led some authors to suggest classifying this group as being at *unclear* risk and may be a useful proxy for monitoring risk factor levels within this group^{4, 31}. Collectively, however, these observational findings do not provide a strong rationale for the screening of healthy children and adolescents on the basis of anthropometric measures alone – at least in the contexts examined. Interestingly, data from the Bogalusa Heart and Cardiovascular Risk in Young Finns studies found the addition of other risk factors (such as lipids, fasting glucose, blood pressure) to BMI at a single time-point did not improve prediction for those children who develop T2DM, metabolic syndrome, or high carotid intima-media thickness in adulthood (AUCs ranging from 0.563-0.654)⁴, suggesting that other risk factors or a different approach to screening may be needed. By providing information on duration of excess adiposity and rate of change in anthropometric measures over time, it is possible that serial measurements collected throughout childhood and adolescence would improve prediction. For example, data from Arisaka et al. have shown that those who had an earlier adiposity rebound had a more atherogenic lipid profile at age 12 years compared with those who had a later adiposity rebound³², and those with increasing BMI during the typically

stable BMI period from age 1.5-3 years had increased insulin resistance at 12 years of age³³, independent of current BMI status. Moreover, data from the Cardiovascular Risk in Young Finns Study have recently shown that a novel method of detecting divergence in BMI trajectory groups substantially improves prediction of future risk for T2DM compared with BMI measured at a single time-point⁶.

It has been suggested that the combination of different measures of anthropometry and adiposity might improve the classification of obesity-related health risk in pediatric populations^{34, 35}. However, our study showed that the combination of additional child anthropometric measures to AVI did not improve the predictive ability (based on our AUC and NRI values) of adult fasting insulin, insulin resistance, and beta-cell function compared with AVI alone. This might be explained by the high correlation between those anthropometric measurements so that limited additive information would be obtained when they were combined. In addition, a lack of strong association with adulthood outcomes may also in part explain the low predictive utility of the combined childhood anthropometric measurements. Therefore, a higher predictive utility might be achieved when these analyses are conducted with incident diabetes where a stronger association may be observed³⁶. To our knowledge, there have been no previous studies that have examined the combination of these more recently developed anthropometric indices in childhood with other more traditional markers to predict glucose homeostasis measures in adulthood. Meta-analysis of longitudinal and cross-sectional studies in adults aged ≥ 18 years have shown that there was no improved discriminatory capability for predicting T2DM when BMI was combined with abdominal adiposity measures (WC, WHR or WHtR)³⁷. Similar findings were observed for a cardiometabolic risk score in a recent cross-sectional study on 4255 children in the European Youth Heart Study and National Health and

Nutrition Examination Survey³⁸. However, previous cross-sectional data in children from the Bogalusa Heart Study and Kiel Obesity Prevention Study showed the combination of categorical measures of BMI and WC did improve prediction of cardiometabolic risk factors, including fasting insulin^{35 34}. Interestingly, no significant improvement for prediction of insulin levels was observed in the Bogalusa Heart Study when BMI and WC were considered as continuous variables – as all anthropometric measures were considered in our study. We did not consider categories of our measures because there is no population-based reference data for the more recent indices. Moreover, the Bogalusa Study showed improved prediction of insulin levels by considering WC among those who were classified as overweight or obese. As our sample had a low proportion of children who were overweight or obese (n=28, 1.2%), we did not have sufficient power to examine these associations stratified by weight status. Therefore, we are not able to conclude that future combination of these measures using categories would not further improve predictive utility of our study outcomes.

This study has limitations. In 1985, the prevalence of overweight and obesity in Australian children was not as high as in contemporary children³⁹, and changes in body composition in young people aged ≤ 18 years have also been noted over this period⁴⁰. We are therefore unable to be sure that our effect estimates would be the same in a contemporary cohort. We were unable to compare the predictive utility of our measures with the gold standard of hydrostatic weight or dual-energy X-ray absorptiometry because these data were not available. Also, we are unable to discount that more recent or other measures of adiposity and anthropometry such as bioelectrical impedance or neck circumference might provide an improved prediction compared with measures that were available in our study. Also, a one in three subset of our participants had skinfold thickness measurements (bicep, tricep, subscapular,

suprailiac) collected in childhood. Owing to the comparative nature of our analyses, which require the same sample size, we did not include sum of skinfolds as an alternate measurement. In a sub-analysis, sum of skinfolds was a comparable predictor of the insulin-related outcomes as AVI. Although HOMA2 measures are purported to be an improvement from previous HOMA calculations in their correlation with the hyperinsulinemic euglycemic clamp, these are only proxy measures for insulin resistance and beta cell function and markers of future risk of T2DM. We could not examine adult T2DM because of a small number of cases (n=6, 0.3%) in this cohort. Future follow-up of CDAH participants will provide this capability. Lastly, we had loss to follow-up. However, we compared the baseline characteristics between participants who were lost to follow-up and those who were not. Participants who were lost to follow-up were younger and taller and had higher weight. We have accounted for these factors in weighted analyses but the associations remained largely similar. This suggests the impact of missing data is likely to be minor.

This study has several strengths. First, this population-based study had the advantage of a large sample size with a long-term follow-up of approximately 20 years, which provides a unique opportunity to examine the long-term association of childhood exposures with adult outcomes. Second, our study collected measures of anthropometry in childhood other than BMI such as waist and hip circumference. In comparison, most previous long-term studies from childhood that have followed participants into adulthood such as the Cardiovascular Risk in Young Finns, Bogalusa Heart, and Muscatine studies have only collected BMI due to ease of measurement and lack of data at the time of the baseline measurement to include additional anthropometric measures¹⁰.

In conclusion, we found that conventional and more recently developed childhood measures of anthropometry associated with adult fasting insulin, insulin resistance, and beta-cell function, but not IFG. The measure shown to have the best predictive utility was AVI that includes waist and hip circumference as input measures. However, the overall predictive utility from a clinical standpoint was low and we found no evidence to support adding multiple different anthropometric measures from a single time-point in childhood to improve future prediction of insulin-related outcomes in adulthood.

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345 **Conflict of interest**

346 The authors declare no conflicts of interest.

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490 **Figure legend**

491 **Figure 1** Flowchart of study participants