Associations of Childhood and Adult Obesity with Left Ventricular Structure and Function

Hong Yang, BMed*[1]; Quan L Huynh BMD, PhD*[1], Alison J Venn, PhD[1]; Terrence Dwyer, PhD[2], Thomas H. Marwick MBBS, PhD, MPH[1, 3]

Menzies Institute for Medical Research, Hobart, Australia [1], The George Institute, Oxford, UK[2] and Baker-IDI Heart and Diabetes Institute, Melbourne[3], Australia

Running title: Cardiac dysfunction in childhood and adulthood obesity

Corresponding Author: Prof Thomas H. Marwick

Baker-IDI Heart and Diabetes Institute

75 Commercial Road

Melbourne, 3004, Australia

Phone: +61-3-8532-1550

Fax: +61-3-8532-1160

Email: Tom.Marwick@bakeridi.edu.au

*Hong Yang and Quan L Huynh are joint first authors of this work

Abstract: 247 words; text: 2950 words (43 references; 3 tables, 3 figures)

Author disclosures. HY is supported by a Health Professional Scholarship from the National Heart Foundation of Australia (100307). None of these agencies had any role in design, analysis, or interpretation of this study.

Abstract

Background: Overweight and obesity are associated with left ventricular (LV) dysfunction. We sought whether echocardiographic evidence of abnormal adult cardiac structure and function was related to childhood or adult adiposity.

Methods: This study included 159 healthy individuals aged 7-15 years and followed until age 36-45 years. Anthropometric measurements were performed both at baseline and follow-up. Cardiac structure (indexed left atrial volume [LAVi], left ventricular mass [LVMi]) and LV function (global longitudinal strain [GLS], mitral e') were assessed using standard echocardiography at follow up. Conventional cut-offs were used to define abnormal LAVi, LVMi, GLS and mitral annular e'.

Results: Childhood body mass index (BMI) was correlated with LVMi ($r=0.25$, $p=0.002$), and child waist circumference was correlated with LVMi ($r=0.18$, $p=0.03$) and LAVi ($r=0.20$, $p=0.01$), but neither were correlated with GLS. One standard deviation (by age and sex) increase in childhood BMI was associated with LV hypertrophy (RR: 2.04 [95% CI: 1.09, 3.78]) and LA enlargement (RR: 1.81 [95% CI: 1.02, 3.21]) independent of adult BMI, but the association was not observed with impaired GLS or mitral e'. Cardiac functional measures were more impaired in those who had normal BMI as child but had high BMI in adulthood ($p<0.03$), and not different in those who were overweight or obese as a child and remained so in adulthood ($p>0.33$).

Conclusions: Childhood adiposity is independently associated with structural cardiac disturbances (LVMi and LAVi). However, functional alterations (GLS and mitral e') were more frequently associated with adult overweight or obesity, independent of childhood adiposity.

Keywords: childhood adiposity, adulthood adiposity, asymptomatic cardiac dysfunction, myocardial deformation

Abbreviations and Acronyms

2D:	two dimensional
BMI:	body mass index
CDAH:	childhood determinants of adult health
CRP:	C-reactive protein
CVD:	cardiovascular disease
DecT:	E wave deceleration time
e':	tissue d0ppler mitral annular early diastolic velocity
E:	mitral inflow Peak early diastolic velocity
GLS:	global longitudinal strain
HDL:	high density lipoprotein
IOTF:	International Task Force reference for child BMI
LA:	left atrial
LAE:	left atrial enlargement
LAVi:	left atrial volume index
LDL:	low density lipoprotein
LV:	left ventricular
LVH:	left ventricular hypertrophy
LVMi:	left ventricular mass index
STE:	speckle-tracking echocardiography
VVI:	velocity vector imaging
WC:	waist circumference

Introduction

The obesity epidemic is a relatively recent health problem, with more than doubling of the prevalence of obesity from 1962 to 2000 in the United States and worldwide[1, 2]. More than one in three adults in the United States and more than one in four in Australia are obese[3]. The prevalence among children and adolescents has also increased and continues to do so[3, 4]. In addition to its impact on childhood health, a major concern about childhood obesity is that it may adversely affect health in adulthood[5]. The longitudinal progression of adiposity and associated adult risk of cardiovascular disease (CVD) has been established in large population studies[6-9], which have mainly focused on cardiovascular risk factors and morphologic changes including carotid intima-media thickness (IMT) and left ventricular (LV) mass index (LVMi). However, the independent relationship between childhood obesity and adult CVD risk is controversial. The risk of CVD among overweight or obese children who became non-obese by adulthood is similar to those who were never obese[10], while those who were normal or at the lower end of the weight scale in childhood and became obese as an adult have the worst CVD outcome[11]. Thus, while there is clearly a need to control childhood obesity, the development of obesity over the life course also needs attention. Indeed, our previous results suggested that large artery stiffness appeared to be dependent primarily on current adiposity and magnitude of adiposity gain from childhood[12]. The importance of the development of obesity is demonstrated in another of our previous studies to assess LVMi[13].

In addition to changes in morphology, obesity may cause functional disturbances, independent of structural changes[14, 15], and to which conventional echocardiographic measures (eg. left ventricular ejection fraction, LVEF) are insensitive[16]. Myocardial strain is a sensitive and robust echocardiographic marker of myocardial deformation that has been used to detect subtle myocardial impairment in patients with hypertension[17], diabetes[18], obesity and metabolic syndrome[19] in the presence of normal LVEF. As asymptomatic LV dysfunction is associated with progression to heart failure (HF), the independent risk of childhood adiposity for cardiac functional alterations is a key research question. In the light of our previous work on obesity and LV dysfunction,[20] we hypothesized that current obesity is the main problem linked with cardiac *functional* changes. If this were the case, early myocardial dysfunction would be likely to be associated more with adult

adiposity and less by childhood adiposity. We sought to investigate whether childhood adiposity was associated with adult subclinical myocardial dysfunction.

Methods

Study population. This work was performed in a follow-up substudy of subjects enrolled in the Childhood Determinants of Adult Health (CDAH) study, a prospective, nationwide cohort of Australian children aged 7-15 years (n=8498), who participated in the 1985 Australian Schools Health and Fitness Survey (ASHFS).[21] The sampling method for the original study has been described elsewhere.[22] In this exploratory substudy of adult participants who first participated in the ASHFS in 1985, we selected 159 subjects at two sites for detailed myocardial function analysis. We anticipated that 52 patients would provide an 80% power to show a 10% difference in LV mass index (the main LV structural endpoint) from the expected 55±7 $g/m^{1.7}$ with $p<0.05$, and that 126 patients would provide an 80% power to show a 10% difference in LV global longitudinal strain (the main LV functional endpoint) from the expected 20±3 $g/m^{1.7}$ with $p<0.05$.

The study was approved by the Tasmanian Human Ethics Committee, and all individuals gave written informed consent.

Body size or adiposity. Weight, height, waist and hip circumference were measured in childhood and adulthood.[23] Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Body surface area was measured as $[\text{weight (kg)} \times \text{height (cm)}/3000]^{0.5}$. Waist circumference (WC) in childhood was measured at the level of the umbilicus to the nearest 0.1 cm. WC in adulthood was measured at the narrowest point between the lower costal border and the iliac crest to the nearest 0.5 cm. Waist-to-hip and waist-to-height ratios were calculated as waist (cm)/hip (cm) and waist (cm)/height (cm) respectively. Childhood body habitus was classified as healthy weight, overweight or obese using IOTF (International Task Force) age- and gender-specific cut-offs.[24] Adult adiposity was classified as normal weight ($BMI<25$ kg/m^2), overweight ($25\leq BMI<30$ kg/m^2) and obese ($BMI\geq30$ kg/m^2). Blood pressure was measured from the right brachial artery three times using a digital automatic blood pressure monitor (Omron HEM907, Omron Healthcare Inc, Japan), after participants had been

sitting for at least 5 minutes. The mean of the three measurements was used. High blood pressure was defined as systolic blood pressure (SBP)/diastolic blood pressure (DBP) >140/90 mmHg.

Echocardiographic study. Standard transthoracic 2D and Doppler echocardiographic studies were performed using standard equipment (Siemens SC2000, Siemens Healthcare, Mountain View, CA) and transducers (4V1c, 1.25-4.5 MHz; 4Z1c, 1.5-3.5 MHz), and measured in accordance with the American Society of Echocardiography (ASE) guidelines, by an observer blinded to other data.[25, 26] Left ventricular (LV) dimensions during diastole and systole and wall thicknesses were measured according to the recommended criteria. [25] LV mass was indexed to body height using LVM/height$^{1.7}$.[27] LV hypertrophy (LVH) was defined as LVM index >75 g/m$^{1.7}$ in men and >57 g/m$^{1.7}$ in women[27]. LV and left atrial (LA) volumes were calculated by the Simpson biplane method,[25] and LA volume was indexed to body surface area, with LA enlargement (LAE) defined as LAVi≥34 ml/m^2.[25] Mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, E wave deceleration time (DecT) were measured for diastolic function assessment.[26] Tissue Doppler mitral annular early diastolic velocity (e') was assessed at septal and lateral, averaged e' <10 was used as cut-off.[26] Averaged E/e'>14 was defined as cutoff for abnormal.[26] LV peak longitudinal strain measurements were obtained from gray scale-recorded images in the apical 4-chamber, 2-chamber and long-axis views. Strain was analyzed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions). GLS was measured by averaging strain from the regional of interest in the apical 4-chamber, 2-chamber and long-axis views. Impaired GLS was defined using cut-off of <18 %.[28]

Biomarkers. A 30 ml blood sample was taken from the antecubital vein after at least 8 hours of fasting. Fasting glucose, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol were analyzed. C-reactive protein (CRP) level was also obtained. Biomarkers were collected only in a subgroup of children at baseline.

Statistical analysis. Child BMI was converted to z-score specific to each sex and year of age by subtracting from each measurement the mean for that sex and age category and dividing by its standard deviation (SD). Data are presented as mean±SD after testing for normal distribution (Shapiro-Wilk test). Data deviating from normality are expressed as median (inter-quartile range [IQR]). Categorical variables are expressed as percentages. For differences among groups, the Mann-

Whitney U test was used for continuous variables and X^2 tests or Fisher's exact test for categorical variables. Associations between variables were assessed with Pearson or Spearman correlation coefficients. Multi-group comparison was performed by the analysis of variance with Bonferroni post hoc analysis when data showed a normal distribution. Otherwise, the Kruskal-Wallis test was used for comparison of non-normally distributed variables. Linear regression analysis was used to examine the associations between body size or adiposity and echo variables. Logistic regression was used to examine the association of adult adiposity with abnormal cardiac measures using conventional cut-offs. Statistical analyses were performed using a standard statistical software package (SPSS software 22.0, SPSS Inc., Chicago, IL). Two-sided comparisons were used and statistical significance was defined by $p< 0.05$.

Code availability. Details may be obtained from the authors.

Results

Baseline characteristics. The mean follow-up time among the total 159 participants (age 40.2±2.8, range 36-45 years, 47% male) was 28.9±0.1 years. **Table 1** summarizes the participants' characteristics at baseline and at follow-up. Men generally had higher BMI at baseline and follow-up.

Progression of overweight and obesity. According to IOTF age- and gender-based cut-offs at baseline, 18 (11.3%) children were classified as ≥overweight and 2 (1.3%) was obese. During follow-up, 93 (59%) adults were categorized as ≥ overweight and 29 (18%) were obese. 55% (78/141) of children of normal weight had progressed to either overweight (38%, 53/141), or obese (18%, 25/141) while 94% (15/16) of overweight children remained overweight (11/16) or obese (4/16) into adulthood. Of the 2 obese child at baseline, one became normal weight and one became overweight (**Appendix F1,** supplementary information).

Echocardiographic characteristics. Cardiac structure and function at follow-up are summarized in **Table 1**. Using conventional cut-offs, the prevalence of LA enlargement (LAE), LV hypertrophy (LVH), impaired GLS and abnormal e' were 16%, 19%, 16%, 6.3% respectively. None had abnormal E/e' by conventional cut-off. The detailed correlations of various body size metrics (including height,

weight, BMI, WC, Hip, Waist-height ratio, Waist-hip ratio) as child and as adult with adult cardiac structural (including LAVi, LVMi) and functional (including mitral e', E/e' and GLS) measures are summarized in **Appendix T1** (Supplementary information). Childhood body BMI was correlated with LVMi (r=0.25, p=0.002), and child WC was correlated with LVMi (r=0.18, p=0.03) and LAVi (r=0.20, p=0.01), but neither were correlated with mitral e' and E/e', nor with GLS. Of all adult body size metrics, BMI and WC showed stronger association with both structural and functional measures including LVMi, mitral e', E/e' and GLS. **Figure 1** shows the correlation of GLS with adult BMI and WC, not with childhood BMI, nor with child WC. The relationship of GLS with childhood WC and BMI demonstrated a non-linear pattern. In addition, the association of adult WC with GLS seemed to be stronger (r=-0.362, p<0.001) than that of BMI (r=-0.164, p=0.39) (**Figure 1**).

Association of change in body habitus with cardiac structure and function. Table 2 shows the estimated response of adult cardiac changes to one standard deviation (SD) increase in childhood BMI and WC before and after adjustment of adult BMI and WC. Of the structural measures, increase in child BMI was associated with age and gender–specific increase of LVMi, independent of adult systolic blood pressure and other cardiovascular risk factors including glucose, insulin and blood lipids. However, these associations substantially attenuated after adjustment for adult BMI. In contrast, adult BMI and WC remained significant associations with or without the presence of childhood weight metrics. Of the functional measures, adult BMI and WC were significantly associated with adverse diastolic functional measure (e') independent of child BMI and WC. Adult BMI and WC were not associated with systolic functional measure (GLS). Childhood WC demonstrated a positive association with e' and GLS. However, in the presence of adult BMI and WC, these positive association became more prominent and statistically significant, suggesting the increased body weight gain from childhood was positively associated with systolic and diastolic functional measures **(Table 2).**

One standard deviation (SD) (by age and gender) increase in childhood BMI (2.4 g/m^2) was associated with greater risk of adult LAE (RR: 1.81 [95% CI: 1.02, 3.21]) and LVH (RR: 2.04 [95% CI: 1.09, 3.78]), one SD (by age and gender) increase of child WC (7.6 cm) was associated with greater risk of LAE (RR: 2.05 [1.26, 3.34]) independent of adult BMI and WC **(Appendix T2**).

Participants were then divided into three groups according to results of progression of BMI status from childhood and adulthood; normal child and adult BMI (Child-/Adult-, n=63); normal child but high adult BMI (Child-/Adult+, n=78) and high child and adult BMI (Child+/Adult+, n=15). Only 3 participants had abnormal child but normal adult BMI and were not included for further study. **Table 3** presents the clinical, cardiac and biomarker findings of the three groups. Child-/Adult+ had significantly higher blood pressure and more adult hypertension, relatively more impaired cardiac functional measures including mitral e', higher E/e' and more LVH. Child+/Adult+ group had similar functional measures compared to Child-/Adult- but more impaired structural changes. Results of biomarkers were similar between Child-/Adult- and Child+/Adult+, but more abnormal in Child-/Adult+.

To further demonstrate the magnitude of weight gain on cardiac changes, we further separated Child-/Adult+ into two subgroups based on overweight (Child-/Adult overweight) and obese (Child-/Adult obese) and compared cardiac changes with controls (Child-/Adult-) and with (Child+/Adult+). **Figure 2** emphasizes the role of adult overweight and obesity as a driver of LVH and diastolic dysfunction, rather than systolic impairment. These findings parallel the presence of metabolic disturbance and inflammation in overweight and obese adults **(Figure 3).**

Discussion

In this longitudinal study over almost 30 years, we assessed the association of current and past adiposity with adult cardiac structure and function. The findings showed: 1) adult overweight and obesity were associated with adverse cardiac function independent of childhood weight status, 2) childhood adiposity was associated with adult structural cardiac disturbances independent of adult adiposity, 3) disturbances of cardiac function were most pronounced in those who had increased adiposity in adulthood, and seem to parallel the severity of their metabolic disturbance.

Association of LV structure and function with obesity. Obesity is linked with alterations of LV structure and function in adults[29] and children.[30, 31] Functional alterations often precede and accompany structural changes, and may lead to the clinical syndrome of obesity cardiomyopathy.

Studies investigating obesity-related cardiac dysfunction has shown a number of features. First, abnormalities of cardiac structure and function do not require morbid obesity (BMI >35). Application of new imaging markers including tissue velocity (e' and E/e') and speckle tracking echocardiography (GLS) have shown myocardial alterations in overweight (BMI, 25 to 30) and mildly obese (BMI, 30 to 35) individuals,[29, 32] perhaps because these markers are more sensitive to subtle myocardial damages than are conventional markers[33]. The assessment of subtle cardiac dysfunction using tissue Doppler and speckle tracking has mostly been performed in cross sectional studies. In contrast, this study uses a longitudinal population sample to address the importance of functional alterations because early cardiac dysfunction is a precursor stage of overt heart failure and may lead to adverse outcome. The longitudinal sample allowed us to assess adiposity change from childhood and the magnitude of adiposity gain to be important predictors. Our results are in agreement to other studies using tissue Doppler imaging that showed depressed diastolic function in obese young adults[29, 34]. In addition, we showed a positive association of child BMI and WC with e' and GLS in the presence of increased adult BMI and WC. This suggests that increased gain of adipose tissue is associated with both systolic (GLS) and diastolic (tissue Doppler e') alterations. Second, the effects of obesity on the heart varies from asymptomatic LV dysfunction to overt dilated cardiomyopathy. These abnormal findings can be found in individuals who are otherwise young (<40 year) and healthy[34] and with no evidence of hypertension, diabetes, metabolic disturbance and inducible coronary artery disease by stress testing.[29] In the current study cohort of young (≤ 45 year) and healthy individuals with no known history of diabetes, hypertension and coronary artery disease, the prevalence of structural abnormalities using guideline-recommended cut-offs[25] was 16% by LAE, 19% by LVH, 16% by impaired GLS and 6.3% by impaired e'. These observations support the notion that depressed LV function is already present in relatively young, overweight/obese people even if clinical features of common comorbidities and other associated disease are not evident. Third, the effect of weight loss on cardiac functional improvement has been variable, which implies that cardiac impairment may not be completely reversible. Many factors contribute to outcomes, mostly the magnitude and duration of obesity as well as the magnitude and duration of cardiac damage, and both may worsen with the development of codominant comorbidities.[35, 36]

The potential implications of change of obesity with time. Obese children are at risk of being obese as adults[37, 38] which leads to an increased risk of cardiac structural and functional impairment. The prognostic implications of childhood obesity has been studied in large population studies.[10] Although most evidence has been based on obesity-related metabolic disturbance,[8] the impact of childhood obesity in the development of adult left ventricular hypertrophy has been demonstrated[39, 40]. However, no studies have assessed the impact of childhood obesity on adult cardiac function. In our study, there was not enough evidence to demonstrate the independent association of childhood body size. We suspect a few possible contributing factors: 1) a relatively "healthy childhood population" with only 11.3% overweight and 1.3% obese children; 2) a possible non-linear relationship between childhood BMI and functional measures; 3) adult cardiac functional changes are more associated with adult body adiposity and characteristics. Cardiac functional impairment in adulthood is an indication of adverse outcome and disease progression.

Whether childhood obesity is an independent predictor of adverse adult outcome has been challenged in the recent literature. In a systematic review by Lloyd, evidence indicated that children with low BMI but overweight in adulthood[11] had the highest risk of CVD. In another systematic review and meta-analysis, Llewellyn and Simmonds challenged the conventional view of using childhood BMI predicting adult morbidity.[41 38] The authors concluded that childhood obesity is associated with moderately increased risk of adult morbidity but that the association was not strong enough to predict outcome. This was due to the fact that most weight-related morbidities occurred in individuals who were of healthy weight as a child. . In our study, after adjustment for adult body size, the magnitude of adiposity change seemed to be associated with alteration of both GLS and e'. It likely that the duration of obesity is an important determinant of cardiac function changes and subsequent adverse outcomes, but we were unable to gather this information in our study[42]. Further research is needed to explore the effects of the time course of weight change.

The mechanism of cardiac dysfunction and metabolic disturbance. The progression of cardiac dysfunction in obese individuals is influenced by a variety of determinants including genetic and environmental influences.[43] In adulthood, obesity often coexists with weight-related comorbidities, mostly diabetes and hypertension, which further complicates the cardiac manifestations. First,

cardiac preload is increased in obese individuals due to increased metabolic demand[44, 45]. In the absence of myocardial dysfunction, this may explain the observation of increased or supernormal LV ejection fraction.[20] Second, cardiac afterload is also increased due to alterations of arterial resistance and stiffness.[20] Obesity related insulin resistance plays an important role by causing arterial wall smooth muscle cell damage (which alters stiffness and resistance), and myocardial cell apoptosis and cardiac dysfunction.[46] Third, a combination of inflammatory, metabolic and neurohormonal changes lead to myocardial fibrosis, causing both cardiac systolic and diastolic dysfunction.[19] The presence of metabolic disturbance in this cohort is demonstrated by the subgroup of child-/adult+, who had the highest insulin, glucose and triglyceride levels (**Figure 3**). C-reactive protein was significantly higher in all three groups with increased adult weight as compared with normal adult weight, reflecting the inflammatory process associated with obesity. Functional measures in child+/adult+ were relatively preserved and similar to those of child-/adult- (**Figure 2**), suggestive of functional cardiac changes are associated with adiposity gain. Interestingly, this subgroup had lower levels of metabolic and inflammatory markers than other obese and overweight patients (**Figure 3**), indicating that adiposity gain may be the key determinant.

Limitations. This study has several limitations. First, it comprises a small study population, obtained from two sites (Tasmania and Victoria), which we thought likely to be representative of the rest. The influence of progression of body weight at populational level, i.e. socio-economic and environmental factors cannot be excluded. Echocardiographic assessment of cardiac function needs to be further explored in the full cohort in all sites. Second, at baseline in 1985, this study cohort was relatively healthy, only 11% classified as overweight and 1.3% obese. This has limited our ability to track changes of cardiac function in relation to their weight status. Third, echocardiography was not performed at baseline. Fourth, the duration of obesity and adiposity gain was not available. Fifth, baseline blood pressure and biochemistry was not adjusted as potential confounders due to the limited data points available at follow-up. These are potential independent risk factors affecting adult cardiac function, and the potential impact needs to be further explored. Finally, there was a change in the protocol for measurement of waist circumstance between baseline (at umbilicus) and at follow up

(minimum waist level). Although this difference was minor and unlikely to invalidate the results, it could still be responsible for some variations observed in echocardiographic parameters.

Conclusion. Childhood adiposity is independently associated with structural cardiac disturbance (LVMi and LAVi). However, cardiac functional alterations (abnormal GLS and mitral e') were more frequently associated with adult overweight/obese independent of childhood adiposity.

Acknowledgements. The CDAH study was funded by the Australian National Health and Medical Research Council, the Australian National Heart Foundation, the Tasmanian Community Fund and Veolia Environmental Services, and the contributions of the CDAH's project manager, Marita Dalton, all other project staff and volunteers, and the study participants.

Conflict of Interest: HY is supported by a Health Professional Scholarship from the National Heart Foundation of Australia (100307). None of these agencies had any role in design, analysis, or interpretation of this study.

Supplementary information is available at International Journal of Obesity's website

References

1. WHO. Global Health Observatory (WHO) data - Obesity situation and trends. *http://www.who.int/gho/ncd/risk_factors/obesity_text/en/*.

2. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *Jama* 2002; **288**(14)**:** 1723-7.

3. (OECD) TOfEC-oaD. Obesity Update-OECD. *www.oecd.org/health/obesity-update.htm* 2014.

4. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *Jama* 2006; **295**(13)**:** 1549-55.

5. McCrindle BW. Will childhood obesity lead to an epidemic of premature cardiovascular disease? *Evidence-based cardiovascular medicine* 2006; **10**(2)**:** 71-4.

6. Berenson GS. Childhood risk factors predict adult risk associated with subclinical cardiovascular disease. The Bogalusa Heart Study. *Am J Cardiol* 2002; **90**(10c)**:** 3l-7l.

7. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation* 2001; **104**(23)**:** 2815-9.

8. Magnussen CG, Raitakari OT, Thomson R, Juonala M, Patel DA, Viikari JS *et al.* Utility of currently recommended pediatric dyslipidemia classifications in predicting dyslipidemia in adulthood: evidence from the Childhood Determinants of Adult Health (CDAH) study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study. *Circulation* 2008; **117**(1)**:** 32-42.

9. Raitakari OT, Juonala M, Kahonen M, Taittonen L, Laitinen T, Maki-Torkko N *et al.* Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *Jama* 2003; **290**(17)**:** 2277-83.

10. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA *et al.* Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med* 2011; **365**(20)**:** 1876-85.

11. Lloyd LJ, Langley-Evans SC, McMullen S. Childhood obesity and adult cardiovascular disease risk: a systematic review. *Int J Obes (Lond)* 2010; **34**(1)**:** 18-28.

12. Huynh Q, Blizzard L, Sharman J, Magnussen C, Schmidt M, Dwyer T *et al.* Relative contributions of adiposity in childhood and adulthood to vascular health of young adults. *Atherosclerosis* 2013; **228**(1)**:** 259-64.

13. Tapp RJ, Venn A, Huynh QL, Raitakari OT, Ukoumunne OC, Dwyer T *et al.* Impact of adiposity on cardiac structure in adult life: the Childhood Determinants of Adult Health (CDAH) study. *BMC Cardiovasc Disord* 2014; **14:** 79.

14. Iacobellis G, Ribaudo MC, Leto G, Zappaterreno A, Vecci E, Di Mario U *et al.* Influence of excess fat on cardiac morphology and function: study in uncomplicated obesity. *Obesity research* 2002; **10**(8)**:** 767-73.

15. Pascual M, Pascual DA, Soria F, Vicente T, Hernandez AM, Tebar FJ *et al.* Effects of isolated obesity on systolic and diastolic left ventricular function. *Heart* 2003; **89**(10)**:** 1152-6.

16. Wang TJ, Levy D, Benjamin EJ, Vasan RS. The epidemiology of "asymptomatic" left ventricular systolic dysfunction: implications for screening. *Ann Intern Med* 2003; **138**(11)**:** 907-16.

17. Hensel KO, Jenke A, Leischik R. Speckle-tracking and tissue-Doppler stress echocardiography in arterial hypertension: a sensitive tool for detection of subclinical LV impairment. *BioMed research international* 2014; **2014:** 472562.

18. Holland DJ, Marwick TH, Haluska BA, Leano R, Hordern MD, Hare JL *et al.* Subclinical LV dysfunction and 10-year outcomes in type 2 diabetes mellitus. *Heart* 2015; **101**(13)**:** 1061-6.

19. Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, Mysiak A, Marwick TH. Fibrosis and cardiac function in obesity: a randomised controlled trial of aldosterone blockade. *Heart* 2013; **99**(5)**:** 320-6.

20. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiological reviews* 2008; **88**(2)**:** 389-419.

21. Venn AJ, Thomson RJ, Schmidt MD, Cleland VJ, Curry BA, Gennat HC *et al.* Overweight and obesity from childhood to adulthood: a follow-up of participants in the 1985 Australian Schools Health and Fitness Survey. *Med J Aust* 2007; **186**(9)**:** 458-60.

22. SL G, K J, K S, T D, A V. The childhood determinants of adult health study: a profile of a cohort study to examine the childhood influences on adult cardiovascular health. *Australas Epidemiol* 2009; **16:** 35-39.

23. Schmidt MD, Dwyer T, Magnussen CG, Venn AJ. Predictive associations between alternative measures of childhood adiposity and adult cardio-metabolic health. *Int J Obes (Lond)* 2011; **35**(1)**:** 38-45.

24. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *Bmj* 2000; **320**(7244)**:** 1240-3.

25. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L *et al.* Recommendations for cardiac chamber quantification by echocardiography in

adults: an update from the american society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr* 2015; **28**(1)**:** 1-39 e14.

26. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T *et al.* Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; **29**(4)**:** 277-314.

27. Chirinos JA, Segers P, De Buyzere ML, Kronmal RA, Raja MW, De Bacquer D *et al.* Left ventricular mass: allometric scaling, normative values, effect of obesity, and prognostic performance. *Hypertension* 2010; **56**(1)**:** 91-8.

28. Yingchoncharoen T, Agarwal S, Popovic ZB, Marwick TH. Normal ranges of left ventricular strain: a meta-analysis. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2013; **26**(2)**:** 185-91.

29. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 2004; **110**(19)**:** 3081-7.

30. Labombarda F, Zangl E, Dugue AE, Bougle D, Pellissier A, Ribault V *et al.* Alterations of left ventricular myocardial strain in obese children. *Eur Heart J Cardiovasc Imaging* 2013; **14**(7)**:** 668-76.

31. Mangner N, Scheuermann K, Winzer E, Wagner I, Hoellriegel R, Sandri M *et al.* Childhood obesity: impact on cardiac geometry and function. *JACC Cardiovasc Imaging* 2014; **7**(12)**:** 1198-205.

32. Lauer MS, Anderson KM, Kannel WB, Levy D. The impact of obesity on left ventricular mass and geometry. The Framingham Heart Study. *Jama* 1991; **266**(2)**:** 231-6.

33. Russo C, Sera F, Jin Z, Palmieri V, Homma S, Rundek T *et al.* Abdominal adiposity, general obesity, and subclinical systolic dysfunction in the elderly: A population-based cohort study. *Eur J Heart Fail* 2016; **18**(5)**:** 537-44.

34. Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Barzilai B *et al.* Alterations in left ventricular structure and function in young healthy obese women: assessment by echocardiography and tissue Doppler imaging. *J Am Coll Cardiol* 2004; **43**(8)**:** 1399-404.

35. Wong C, Marwick TH. Obesity cardiomyopathy: diagnosis and therapeutic implications. *Nat Clin Pract Cardiovasc Med* 2007; **4**(9)**:** 480-90.

36. Karimian S, Stein J, Bauer B, Teupe C. Impact of Severe Obesity and Weight Loss on Systolic Left Ventricular Function and Morphology: Assessment by 2-

Dimensional Speckle-Tracking Echocardiography. *Journal of obesity* 2016; **2016:** 2732613.

37. Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ. Tracking of childhood overweight into adulthood: a systematic review of the literature. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2008; **9**(5)**:** 474-88.

38. Simmonds M, Burch J, Llewellyn A, Griffiths C, Yang H, Owen C *et al.* The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: a systematic review and meta-analysis. *Health Technol Assess* 2015; **19**(43)**:** 1-336.

39. Li X, Li S, Ulusoy E, Chen W, Srinivasan SR, Berenson GS. Childhood adiposity as a predictor of cardiac mass in adulthood: the Bogalusa Heart Study. *Circulation* 2004; **110**(22)**:** 3488-92.

40. Kharod AM, Ramlogan SR, Kumar S, Raghuveer T, Drake W, Dai H *et al.* Childhood obesity increases left-ventricular mass irrespective of blood pressure status. *Pediatr Cardiol* 2014; **35**(2)**:** 353-60.

41. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2016; **17**(1)**:** 56-67.

42. Hu Y, Bhupathiraju SN, de Koning L, Hu FB. Duration of obesity and overweight and risk of type 2 diabetes among US women. *Obesity (Silver Spring)* 2014; **22**(10)**:** 2267-73.

43. Cote AT, Harris KC, Panagiotopoulos C, Sandor GG, Devlin AM. Childhood obesity and cardiovascular dysfunction. *J Am Coll Cardiol* 2013; **62**(15)**:** 1309-19.

44. Chinali M, de Simone G, Roman MJ, Lee ET, Best LG, Howard BV *et al.* Impact of obesity on cardiac geometry and function in a population of adolescents: the Strong Heart Study. *J Am Coll Cardiol* 2006; **47**(11)**:** 2267-73.

45. Giordano U, Ciampalini P, Turchetta A, Santilli l A, Calzolari F, Crino A *et al.* Cardiovascular hemodynamics: relationships with insulin resistance in obese children. *Pediatr Cardiol* 2003; **24**(6)**:** 548-52.

46. Wong C, Marwick TH. Obesity cardiomyopathy: pathogenesis and pathophysiology. *Nat Clin Pract Cardiovasc Med* 2007; **4**(8)**:** 436-43.

Figure Legends.

Figure 1. Comparison of correlations of global longitudinal strain (GLS) with adult and child waist circumference (WC) and body mass index (BMI). The correlation coefficients and p values are also listed in Appendix T2. The findings show that GLS correlates with adult waist circumference better than with BMI, but not with childhood waist circumference and BMI. The correlation of GLS with childhood waist circumference and body mass is non-linear.

Figure 2. Comparison of cardiac structure and function between participants cross-classified by child and adult BMI status. Among adults of overweight/obesity, no differences were detected in their cardiac structure and function between who were normal in childhood versus who were overweight/obese in childhood (labels in red). Among those who were normal in childhood, those who became overweight/obese in adulthood had structural and function cardiac abnormalities (labels in blue). Abnormal structural (normal functional) change was detected in those who were abnormal in childhood as compared to who were normal (labels in green). Overall p values obtained from ANOVA, with pairwise comparisons.
Group 1 (open circle, n=63, normal adult, normal child BMI);
Group 2 (close circle, n=53, overweight adult, normal child BMI);
Group 3 (close circle, n=25, obese adult, normal child BMI);
Group 4 (square, n=15, overweight/obese adult, overweight/obese child BMI).

Figure 3. Comparison of biomarkers between participants cross-classified by child and adult BMI status. Comparing group 4 versus 3&2 (red), no differences were observed except for insulin level, indicating most biomarker were elevated in overweight/obese adult regardless of their childhood obesity history. Comparing group 1 versus the rest (blue), indicating the development of overweight/obese is associated with significantly increased biomarkers. Comparing group 1 versus 4 (green), CRP was significantly higher in group 4 indicating the presence of inflammatory status although no difference was detected in their insulin, glucose and triglyceride levels. Comparing group 2 and 3 (purple), no difference was observed between adult overweight versus obese except for obese individual had higher insulin levels. Overall p values obtained from ANOVA, with pairwise comparisons.
Group 1 (open circle, n=63, normal adult, normal child BMI);
Group 2 (close circle, n=53, overweight adult, normal child BMI);
Group 3 (close circle, n=25, obese adult, normal child BMI);
Group 4 (square, n=15, overweight/obese adult, overweight/obese child BMI).