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# Modest decrease in severity of obesity in adolescence associates with low arterial stiffness

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ABSTRACT

*Background and aims:* Childhood obesity is associated with cardiovascular risk factors (CVRF), subclinical cardiovascular phenotypes (carotid intima-media thickness, cIMT; pulse-wave velocity, PWV; and carotid elasticity), and adult cardiovascular disease (CVD) mortality. In youth with obesity (body mass index, BMI ≥95th centile), we investigated associations between changes in adiposity and CVRF in early adolescence and subclinical cardiovascular phenotypes in late adolescence.

*Methods:* Participants had adiposity measures (the severity of obesity in percentage >95th BMI-centile (%>95th BMI-centile)), waist circumference (WC), percentage total body fat (%BF) and CVRF (systolic blood pressure, SBP; glycoprotein acetyls, GlycA; and low-density lipoprotein cholesterol) assessed in early (mean age 10.2 ± 3.5y) and late (15.7 ± 3.7y) adolescence. Subclinical cardiovascular phenotypes were assessed in late adolescence. Multivariable regression analysis was performed.

*Results:* Decreasing the %>95th BMI-centile was associated with carotid elasticity (0.945%/10 mmHg, $p = 0.002$) in females, and with PWV in males (−0.75 m/s, $p < 0.001$). Changes in all adiposity measures (per 1-unit increase) were associated with carotid elasticity (−0.020 to −0.063%/10 mmHg, $p < 0.005$), and PWV (0.011–0.045 m/s, $p < 0.005$). Changes in GlycA (per 50 μmol-increase) were associated with elasticity (−0.162%/10 mmHg, $p = 0.042$), and changes in SBP (per 10 mmHg-increase) were associated with PWV (0.260 m/s, $p < 0.001$). Adjusted for change in BMI, the coefficient for GlycA was reduced by 46% and for SBP by 12%. Only male sex was associated with cIMT (+34 μm, $p = 0.006$).

*Conclusions:* In youth with obesity, decreasing or maintaining the severity of obesity, and decreasing the levels of SBP and GlycA from early to late adolescence was associated with low arterial stiffness.

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## 1. Introduction

Childhood obesity tracks into adulthood [1] and is associated with premature mortality and morbidity, largely due to cardiovascular disease (CVD) [2]. The duration and severity of obesity throughout childhood predict the acquisition of traditional cardiovascular risk factors (CVRF) [3]. The number and severity of CVRF by early adolescence correlate with adverse subclinical cardiovascular phenotypes, including increased pulse wave velocity (PWV), decreased carotid elasticity, and higher carotid intima-media thickness (cIMT) in mid-adulthood [4,5]. Subclinical cardiovascular phenotypes predict coronary heart disease and stroke [6] and therefore are used as intermediate cardiovascular outcomes in youth [7].

Young subjects with overweight or obesity who regain a normal body mass index (BMI) in adulthood have similar cardiovascular risk to those who had always a BMI of normal weight [8]. However, longitudinal data in adolescencents with obesity are sparse, particularly regarding how change in adiposity and/or CVRF in early adolescence predicts subclinical cardiovascular phenotypes in later adolescence. Over three quarters of children with obesity will become adults with obesity [1] and this group is at high-risk for CVD. Understanding the relationship between adiposity, CVRF and adverse subclinical cardiovascular phenotypes may inform risk prediction and risk-stratification for secondary prevention at an early life.

In this longitudinal study, we aimed to investigate associations between change in the severity of adiposity measures and change in CVRF between early and late adolescence with subclinical cardiovascular phenotypes assessed in late adolescence.

## 2. Patients and methods

### 2.1. Study design, eligibility criteria and sample size estimation

The study population was drawn from the Childhood Overweight Biorepository of Australia (COBRA) cohort study, recruited from the Weight Management Service at The Royal Children's Hospital (Melbourne, Australia) from 2009 to 2018 [9]. The study was approved by the Human Research Ethics Committee at The Royal Children's Hospital (HREC Ref. # 28081P) and conforms to the ethical guidelines of the 1975 declaration of Helsinki. COBRA participants who consented to be re-contacted for subsequent studies were recruited in the current study termed COBRA-Cardiovascular Risk (COBRA-CVR) from June 2017 to January 2019. Inclusion criteria to participate in the longitudinal COBRA-CVR follow-up were: i) age at COBRA participation (baseline) between 3 and 18 years, age at recruitment for COBRA-CVR (follow-up) between 6 and 25 years; ii) an informed consent signed by the legal guardian in case of age <18 years; iii) an obese weight status at baseline (COBRA). Obesity was determined for individuals until 20 years old as a BMI ≥95th centile based on CDC reference criteria [10], and for adults 20 years old and older according to a BMI ≥30 kg/m$^2$ as per CDC recommendations. Exclusion criteria were i) inability to provide informed consent (e.g. due limited language knowledge); ii) glucocorticoid medication within the previous three months; and iii) acute infection requiring hospitalization within the 4 weeks preceding cardiovascular phenotyping (Supplemental Fig. 1). Data were collected at baseline (mean age 10.2 ± 3.5y) and follow-up (15.7 ± 3.7y). An a-priori sample size estimation was based on published correlation coefficients between BMI and BMI z-scores with PWV ranging from 0.22 to 0.31 [11]. Setting $\alpha = 0.05$ and $\beta = 0.2$ (i.e., 80% power), the necessary sample size to detect such correlations ranged from n = 79 to 159.

### 2.2. Exposures: adiposity measures, cardiovascular biomarkers and blood pressure

Adiposity measures were assessed at baseline and follow-up. Measures included BMI, total body fat in percentage (%BF) and waist circumference (WC). BMI z-score and the percentage level of BMI above the obesity threshold (%>95th BMI-centile) were calculated using CDC reference growth charts [10]. At baseline and follow-up, a 6-h fast blood sample was collected. For diabetes risk, fasted glucose and glycated hemoglobin A1c (HbA1c) were analyzed according to standard methods. Glycoprotein acetyls (GlycA) and low-density lipoprotein cholesterol (LDL-C) were derived from a nuclear magnetic resonance (NMR) spectroscopy platform (Nightingale Health, Helsinki, Finland), as previously described [12]. Blood pressure was measured at baseline and follow-up according to standard methods and the updated 2017 clinical guidelines were used to define blood pressure categories and stages according to age, sex and height [13]. See Supplemental Methods 1.

### 2.3. Outcomes: subclinical cardiovascular phenotypes, carotid intima-media thickness, carotid-femoral pulse wave velocity and carotid elasticity

The cIMT was assessed on the right carotid artery by ultrasound in the supine participant with their head turned 45° to the left, according to on-site standardized protocols [14]. Simultaneous electrocardiogram (ECG) gating assessed cIMT at end-diastole (R-wave of ECG) to account for cIMT variation during the cardiac cycle in children [15]. For reliability, a second reader re-analyzed a random sample of 30 de-identified cine loops, using the Bland-Altman method [16]. PWV was determined using the SphygmoCor XCEL (AtCor Medical Pty Ltd., Naperville, USA) in the supine participant after a 5-min rest and the mean out of 3 measures was used for analysis [14,17]. Carotid elasticity was calculated as the percentage change in lumen diameter per $\Delta P$ of 10 mmHg (i.e., %/10 mmHg), as previously described [14]. See Supplemental Methods 1 for methodological details.

### 2.4. Covariates: socioeconomic status, puberty, sex and smoking status

Socioeconomic status (SES, assessed by socio-economic indices for areas, SEIFA [18,33]), age, sex, and pubertal status [19] were considered potential confounders of the association between adiposity measures or CVRF and the subclinical cardiovascular phenotypes outcomes. Accordingly, results for analyses adjusted for sex and pubertal stage are provided (Supplemental Tables 1, 2 and 3). The current smoking status (within the last 30 days) was assessed at follow-up but not included as a confounder.

### 2.5. Statistical analysis

Descriptive statistics for participant characteristics is described at early and late adolescence as mean, standard deviation (SD) and range (min-max) for continuous variables and proportions for categorical variables. To assess the regression coefficient from those decreasing or maintaining, *versus* those increasing their %>95th BMI-centile between visits on the subclinical cardiovascular phenotypes, the %>95th BMI-centile was accordingly dichotomized, and logistic regression analysis was applied. This binary exposure variable was used as exposure, with the subclinical cardiovascular phenotypes at follow-up as outcomes, adjusted for age at baseline and follow-up and SEIFA scores, stratified for sex.

To assess the association between change in adiposity measures from early to late adolescence (exposure) with subclinical cardiovascular phenotypes at late adolescence (outcome), multiple regression analysis was performed, adjusted for the relevant adiposity measure at baseline, for age at both visits, sex, and SEIFA scores. The regression coefficients and model fitness ($R^2$) of the change in adiposity model were compared to the relevant regression outputs from models at baseline *versus* follow-up. BMI z-scores and the %>95th BMI-centile were already considered age and sex adjusted.

To assess the association between change in CVRF from early to late adolescence (exposure) and subclinical cardiovascular phenotypes at late adolescence (outcome), multiple regression analysis was performed,

adjusted for the relevant CVRF measure at baseline, for age at both visits, sex, and SEIFA scores. From a baseline model including age at both visits, sex and SEIFA scores, we provided the regression coefficients for ageing (per 1-year) and sex (males). Subsequently, we separately added change in each CVRF (BMI per 5 kg/m$^2$ increase, SBP per 10 mmHg increase, GlycA per 50 $\mu$mol/l, LDL-C per 0.1 mmol increase and glucose per 0.1 mmol increase) to the baseline model to estimate the total effect from each individual CVRF, as suggested by Westreich and Greenland (Supplemental Table 2 for all results) [20]. If longitudinal change in BMI and CVRFs was associated with a specific subclinical cardiovascular phenotype, we performed a sub analysis that included change in BMI and the relevant CVRF in a multivariable regression model. We compared model coefficients, model fitness, and tested for multicollinearity. Multicollinearity may be introduced when adding change in BMI and change in CVRF to the model (e.g. due to the correlation between change in BMI and change in SBP) that impedes interpretation of collinear predictors because of the overlapping information they share for the outcome of interest [21]. We used Pearson's correlation test (r) and the variance inflation factor (VIF) to test for multicollinearity in multivariable models with potentially collinear predictors (Supplemental Table 4). Commonly, r > 0.8 between predictors and VIF >10 are suggested to detect collinearity, however, there is no universal agreement [21]. R version 3.5 was used for all statistical analysis and figures [22]. The first author had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

## 3. Results

Data were available on 101 participants (52% male). At baseline, all individuals had a BMI >95th centile, and 92 (91%) remained in the BMI-category of obesity at follow-up. During the mean interval of 5.5 years, the mean percentage >95th BMI-centile decreased by 3.8% (Table 1).

### 3.1. Associations for individuals with increasing versus decreasing severity of obesity with subclinical cardiovascular phenotypes

Sixty-four (63%) participants decreased (a total of 29 out of 49 females and 35 out of 52 males) and thirty-seven (37%) increased their severity of obesity from baseline to follow-up. Males who maintained or decreased their severity of obesity from baseline to follow-up according to the %>95th BMI-centile had lower PWV (−0.75 m/s [95% CI -1.137

**Table 1**
Participant characteristics.

| Characteristic | Baseline | | | Follow-up | | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) | Range | n | Mean (SD) | Range |
| Sex, males (%) | 52 | | | 52 | | |
| Age (y) | 101 | 10.2 ± 3.5 | 3.0–16.9 | 101 | 15.7 ± 3.7 | 6.1–24.3 |
| Weight (kg) | 101 | 71.8 ± 29.3 | 19.1–157.7 | 101 | 101.7 ± 30.5 | 40.8–187.7 |
| Height (m) | 101 | 1.49 ± 0.20 | 1.00–1.90 | 101 | 1.67 ± 0.13 | 1.26–1.95 |
| BMI (kg/m$^2$) | 101 | 30.9 ± 6.2 | 18.4–51.8 | 101 | 35.7 ± 7.9 | 18.2–60.9 |
| BMI z-score | 101 | 2.52 ± 0.36 | 1.70–3.90 | 101 | 2.27 ± 0.61 | −0.53–3.39 |
| % >95th BMI-centile | 101 | 135.3 ± 19.2 | 100.5–204.4 | 101 | 131.5 ± 26.4 | 75.6–202 |
| n <100% | | 0 | | | 9 | |
| n ≥ 100% - <120% | | 24 | | | 26 | |
| n ≥ 120% - <140% | | 43 | | | 33 | |
| n ≥ 140% | | 34 | | | 33 | |
| Change in %>95th BMI centile | | | | 101 | −3.8 ± 19.9 | −60.5–46.6 |
| Waist circumference (cm) | 85 | 96.1 ± 17.8 | 54.0–138.0 | 79 | 105.0 ± 16.4 | 66–153 |
| Total body fat % | 73 | 41.7 ± 6.8 | 24.7–58.0 | 99 | 40.6 ± 9.9 | 18.6–67.8 |
| Tanner stage (%) | 96 | | | 101 | | |
| n pre-pubertal | 50 | | | 10 | | |
| n peri-pubertal | 22 | | | 16 | | |
| n post-pubertal | 24 | | | 75 | | |
| SEIFA score | | | | 101 | 1004.21 ± 64.76 | 802–1134 |
| **Cardiovascular risk factors** | | | | | | |
| Smoking status | | | | | | |
| Never smoked | | | | 92 | | |
| Current smoker | | | | 9 | | |
| Systolic BP (mmHg) | 95 | 109 ± 17 | 80–160 | 100 | 126 ± 13 | 96–162 |
| Diastolic BP (mmHg) | 95 | 66 ± 11 | 45–95 | 100 | 69 ± 8 | 50–89 |
| Normal BP | 59 | | | 28 | | |
| Elevated BP | 7 | | | 33 | | |
| Stage I hypertension | 20 | | | 19 | | |
| Stage II hypertension | 9 | | | 20 | | |
| LDL-C (mmol/l) | 67 | 2.54 ± 0.55 | 1.0–4.0 | 98 | 1.76 ± 0.58 | 0.9–4.6 |
| Triglycerides (mmol/l) | 67 | 1.37 ± 0.68 | 0.4–4.6 | 98 | 1.15 ± 0.40 | 0.6–2.5 |
| GlycA (mmol/l) | 67 | 1.11 ± 0.13 | 0.9–1.6 | 98 | 1.11 ± 0.11 | 0.88–1.40 |
| HbA1c (%) | | | | 94 | 5.2 ± 0.4 | 4.1–6.5 |
| Fasting glucose (mmol/l) | 86 | 4.6 ± 0.5 | 3.5–6.1 | 94 | 4.6 ± 0.5 | 3.7–7.1 |
| Diabetes | | 2 | | 8 | | |
| Pre-diabetes | | 12 | | 8 | | |
| **Subclinical cardiovascular phenotypes** | | | | | | |
| Carotid IMT $\mu$m | | | | 100 | 457 ± 62 | 344–608 |
| Carotid-femoral PWV m/s | | | | 98 | 5.32 ± 0.87 | 3.57–7.9 |
| Elasticity %/10 mmHg | | | | 100 | 4.24 ± 1.25 | 1.84–8.40 |

Participant characteristics for baselineand follow-up. Subclinical cardiovascular phenotypes were assessed at follow-up only. n = number of participants with available data.

SD: standard deviation; BMI: body mass index; BP: blood pressure; LDL-C: low-density lipoprotein cholesterol; GlycA: glycoprotein acetyls; IMT: intima-media thickness; PWV: pulse-wave velocity.

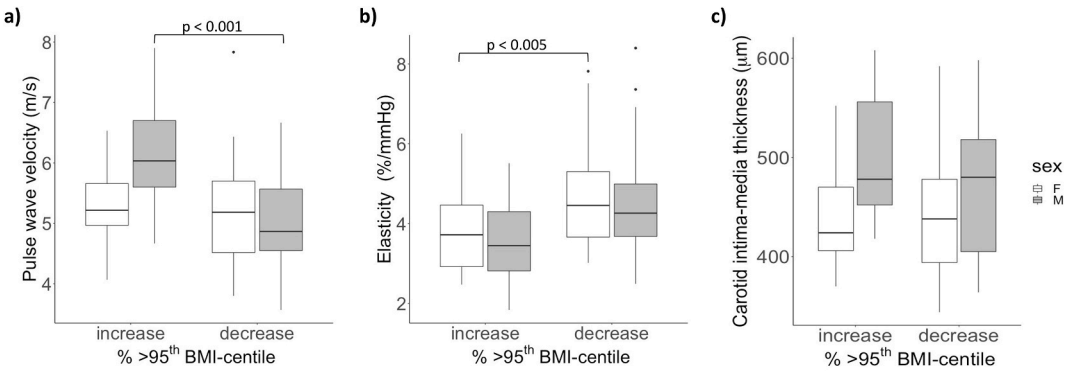


**Fig. 1.** Sex-stratified associations between increasing *vs* decreasing the %>95th BMI-centile from early to late adolescence and subclinical cardiovascular phenotypes at late adolescence.

Boxplots for the association in participants who increased (n = 20 females and 17 males) or decreased (n = 29 females and 35 males) their %>95th BMI-centile between early and late adolescence with subclinical cardiovascular phenotypes. Results for pulse wave velocity, carotid elasticity and carotid intima-media thickness are illustrated in panels A, B and C, respectively. Results are stratified for sex (females n = 49, white; males n = 52, gray). *p*-values for the logistic regression coefficient for the change in the %>95th BMI-centile, adjusted for SEIFA scores and age at both visits are given.

to −0.363, $p < 0.001$]), compared to those with an increase in the severity of obesity. There was no evidence for an association in females with PWV, whether they incrased or decreased their severity of obesity (0.014 m/s [95% CI -0.408 to 0.435, $p = 0.95$]). For carotid elasticity, females who maintained or decreased their %>95th BMI-centile over time had higher carotid elasticity (0.945%/10 mmHg [95% CI 0.365–1.525, $p < 0.005$]), compared to those with an increase in the severity of obesity. There was no evidence for an association in males with carotid elasticity, whether they incrased or decreased their severity of obesity (0.429%/10 mmHg [95% CI -0.214 - 1.073, $p = 0.19$]). There were no associations between the severity of obesity with cIMT in either sex (Fig. 1).

### 3.2. Associations between change in adiposity measures and change in CVRF between baseline and follow-up with subclinical cardiovascular phenotypes at follow up

Increasing change in all adiposity measures was inversely associated with carotid artery elasticity, and increasing change in BMI, %>95th BMI-centile and WC was positively associated with PWV in fully adjusted models. Associations between obesity-measures at baseline, at follow-up, and between change in obesity measures with arterial stiffness measures at follow-up are provided in the Supplemental Table 5. Overall, coefficients for baseline measures were weaker, or even reversed, compared to the equivalent measure at follow-up. The strength of associations (as per the magnitude of the coefficient and the goodness

**Table 2**
Estimated association between change in adiposity measures and subclinical cardiovascular phenotypes.

| Pulse wave velocity (m/s) | | | | |
|---|---|---|---|---|
| Predictors | β-coefficient | 95%CI | *p* | *N* |
| BMI | 0.045 | 0.021–0.068 | <0.001 | 98 |
| % >95th centile | 0.013 | 0.005–0.022 | 0.002 | 98 |
| BMI z-score | 0.072 | 0.045–0.099 | <0.001 | 98 |
| Waist circumference | 0.028 | 0.014–0.042 | <0.001 | 70 |
| % Bodyfat | 0.003 | −0.024–0.030 | 0.812 | 71 |
| **Elasticity (%/10 mmHg)** | | | | |
| Predictors | β-coefficient | 95%CI | *p* | N |
| BMI | −0.063 | −0.100 to −0.026 | <0.001 | 100 |
| % >95th centile | −0.020 | −0.032 to −0.007 | **0.002** | 100 |
| BMI z-score | - 0.098 | −0.135 to −0.060 | <0.001 | 98 |
| Waist circumference | −0.035 | −0.056 to −0.015 | **0.001** | 70 |
| % Bodyfat | −0.052 | −0.087 to −0.017 | **0.004** | 72 |
| Mean carotid intima-media thickness (***µm***) | | | | |
| Predictors | β-coefficient | 95%CI | *p* | N |
| BMI | 0.985 | −1.204–3.174 | 0.374 | 100 |
| % >95th Centile | 0.314 | −0.311–0.940 | 0.321 | 100 |
| BMI z-score | 1.209 | −0.987–3.406 | 0.277 | 100 |
| Waist circumference | 0.216 | −1.092–1.523 | 0.734 | 70 |
| % Bodyfat | 0.030 | −2.323–2.383 | 0.979 | 72 |

Regression coefficients per 1-unit change in predictor (1 kg/m$^2$ for BMI, 1% for %>95th BMI centile, 0.1 z-score for BMI z-score, 1 cm for waist circumference and 1% for body fat) over time, adjusted for age and predictor at baseline, age at follow-up, sex and SEIFA score. BMI: body-mass index; %>95th centile: percentage above the 95th centile for BMI based on CDC growth chart.

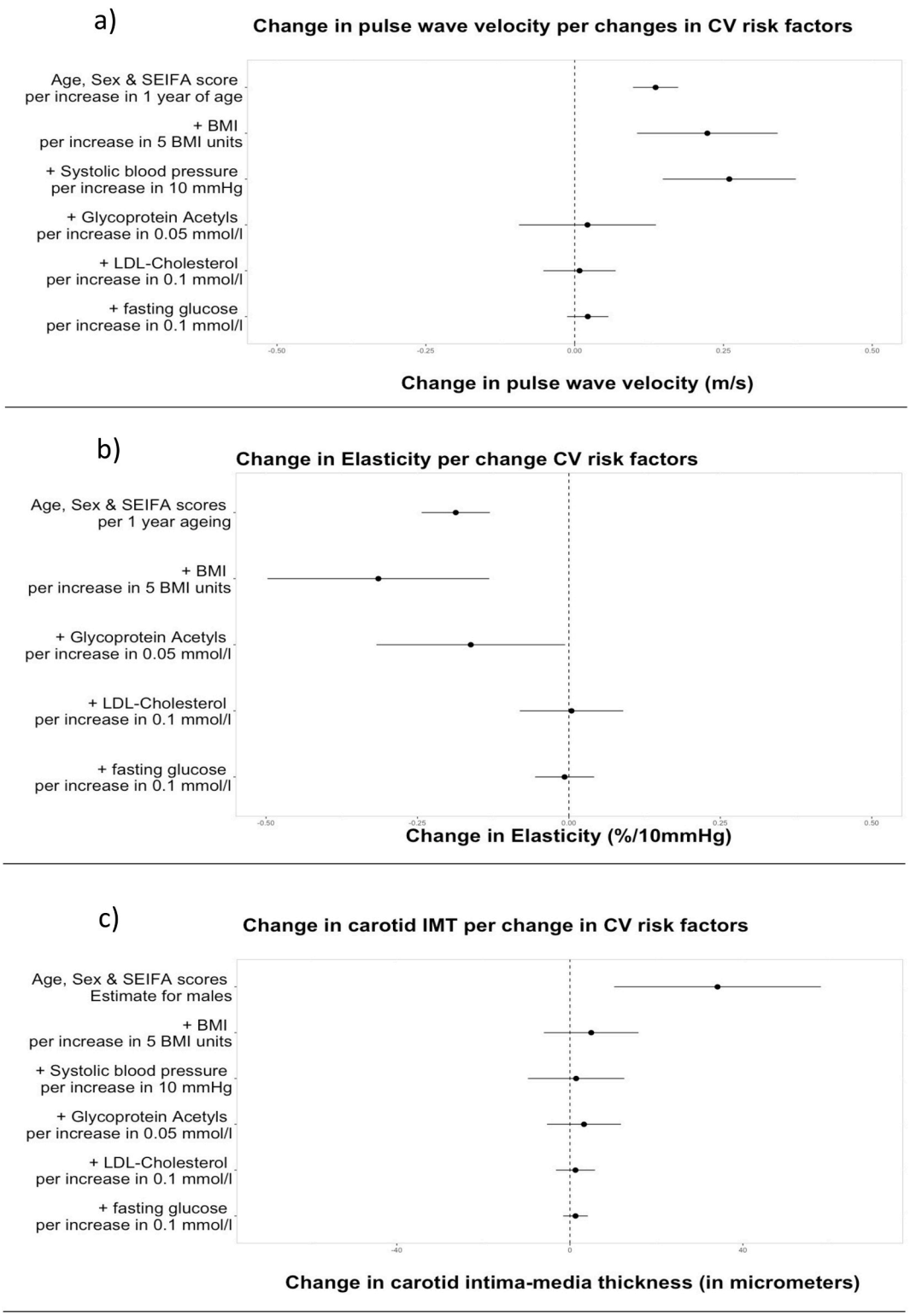


**Fig. 2.** Associations between change in cardiovascular risk factors and subclinical cardiovascular phenotypes in children and adolescents with severe obesity. Regression results on (A) PWV, (B) carotid elasticity and (C) cIMT. Left column lists explanatory variables. From baseline models, the coefficients for ageing per 1 year is given for PWV and elasticity, and for male sex for cIMT. Subsequent models include each cardiovascular risk factor separately from the baseline model. Circle and horizontal line indicate the mean and 95%CI. The dotted vertical line refers to the null hypothesis of no difference.

of fit, $R^2$) for the change in obesity measure over time was at least equivalent or higher compared to the follow-up measure. There was no evidence for an association between change in adiposity measures and cIMT (Table 2). Adjustment for pubertal status did not affect the findings (Supplemental Table 1).

Change in each CVRF was separately added to a baseline model, including age at baseline and follow-up, sex and SEIFA scores. From the baseline model, ageing (per 1-year increase) was associated with higher PWV (0.136 m/s [95% CI 0.098–0.174, $p < 0.001$]), and carotid elasticity (−0.187%/10 mmHg [95% CI -0.243 to −0.130, $p < 0.001$]).

There was no evidence for an association between age and cIMT. Males had higher cIMT compared to females (+34 $\mu$m [95% CI 10–58, $p$ = 0.006]) (Supplemental Table 2Fig. 2). In subsequent models, each CVRF was separately added and the regression coefficient provided: an increase of 5 kg/m$^2$ BMI and 10 mmHg SBP between baseline and follow-up was associated with PWV to a comparable extent (0.223 m/s [95% CI 0.105–0.340, $p < 0.001$] for BMI, and 0.260 m/s [95% CI 0.150–0.370, $p < 0.001$] for SBP). For elasticity, an increase in 5 kg/m$^2$ BMI was associated with carotid elasticity (−0.315%/10 mmHg [95% CI -0.130 to −0.500, $p = 0.001$]) and an increase in GlycA of 50 $\mu$mol/l was associated with carotid elasticity (−0.162%/10 mmHg [95% CI -0.006 to −0.318, $p = 0.042$]). There was no evidence that change in LDL-C or fasting glucose was associated with subclinical cardiovascular phenotypes. Adjustment for pubertal stage did not alter the findings (Supplemental Table 3).

In a multivariable model that included change in BMI and change in SBP for PWV, the regression coefficients reduced for change in BMI (−71%) and systolic BP (−12%) compared to the models with each predictor separately, with change in SBP remaining statistically significant (Supplemental Table 4). The overall model fitness did not improve compared to the model with only change in SBP as predictor ($R^2$ 0.51 *versus* 0.52). In the multivariable model that included change in BMI and change in GlycA for elasticity, the regression coefficients reduced for change in BMI (−21%) and GlycA (−46%) compared to the models with each predictor separately (Supplemental Table 4). The overall model fitness did not improve compared to the model with only change in BMI as predictor ($R^2$ 0.38 *versus* 0.39). There was little evidence for multicollinearity based on correlation coefficients between BMI and SBP (r = 0.65) and between BMI and GlycA (r = 0.37) and with little increase in variance inflaction factors for the relevant coefficients in multivariable linear regression models (Supplemental Table 4).

## 4. Discussion

In this prospective longitudinal study of 101 children and adolescents with obesity, we found that: i) maintaining or decreasing the severity of obesity over 5.5 years from early to late adolescence was associated with higher carotid elasticity in females, and with lower PWV results in males in late adolescence when compared to those who further increased the severity of obesity; ii) ageing and change in all adiposity measures, in SBP and GlycA (inversely) were associated with arterial stiffness; and iii) male sex was the only factor associated with higher cIMT compared to the female counterparts (see Graphical Abstract).

In children and adolescents with obesity, a decrease or maintenance of the percentage level above the 95th BMI-centile (i.e. CDC pediatric obesity threshold) between age 10.2 and 15.7 years was associated with lower PWV in males and higher carotid elasticity in females, even though normal weight targets were not achieved. The difference in PWV in males who improved their severity of obesity was 0.75 m/s when compared to those who further increased their severity of obesity. In adults, each 1 m/s increase in PWV was associated with a 14% increase in risk of CVD events, 15% increase for cardiovascular mortality, and 15% for all-cause mortality [23]. Similar, reported hazard ratios for CVD events and mortality per 1-SD increase in carotid elasticity varied from 1.08 to 1.51, depending on the elasticity measure used [24]. Since the BMI-level for the 95th BMI centile changes throughout childhood due to physiologic growth, our findings suggest that an 11-year old young adolescent with severe obesity who can maintain or increase his/her BMI by no more than ~5 kg/m$^2$ between 11 and 16 years will maintain his/her extent of arterial stiffness in late adolescence. In contrast to measures of arterial stiffness, we found no association with cIMT. This might be because of the young age of the study cohort and the follow-up period of 5.5 years not being sufficient for the subsequent change in adiposity to measurably impact a structural outcome. In line with these arguments, pathology studies have shown the appearance of fatty streaks in the carotid artery after the second decade [25], and long-term BMI trajectory analysis in the International Childhood Cardiovascular Cohort Consortium in adults aged 34–49 years has shown persistently increased risk for higher cIMT, irrespective of an improvement in weight status [8]. Also, our study could not discern those who might have changed early or late within the follow-up period to test for a lag effect. Finally, the time-period investigated in this cohort includes pubertal transition, when the average increase in sitting height (an approximate for the increase in the thoracic arteries length) is ~10 cm [26]. This increase in the longitudinal axis of an elastic artery may limit the detection of more adverse arterial injury (i.e. cIMT), however, this remains hypothetical. In line with the latter argument, including pubertal stage in the analysis had no effect in this study.

The associations between age, male sex and CVRF with high PWV are in keeping with previous reports [27], as is an age- and adiposity-related association for carotid elasticity [28]. However, our findings extend the current literature by simultaneously investigating several adiposity measures, including BMI, BMI z-score, the %>95th BMI-centile, %BF and waist circumference. Also, the study findings suggest that small changes in the majority of the adiposity measures over a relatively short interval may already be associated with clinically relevant arterial stiffness outcomes. Our study is also the first to investigate GlycA and subclinical cardiovascular phenotypes in youth with obesity. In adulthood, GlycA has been associated with future CVD and mortality [29] and is suggested to be a better predictor for CVD risk in adults than high sensitivity C-reactive protein [30]; there are few data in children.

Our findings suggest that changes in the severity of adiposity are a key modifiable factor, associated with cardiovascular health in adolescence. Other than the severity of adiposity, only changes in SBP and GlycA were associated with arterial stiffness in this cohort. Adding change in SBP and change in BMI in a multivariable model for PWV, change in BMI was no longer significantly associated with PWV with the coefficient reducing by 71%. This may be explained by change in SBP being on the pathophysiological pathway between change in BMI and PWV. However, having PWV assessed only once, we could not further investigate the known bi-directional relation between SBP and PWV [31]. Adding change in GlycA and change in BMI to a multivariable model for elasticity as dependent variable, both were no longer significantly associated with elasticity with the coefficients reducing by 46% and 21%, respectively. Though we had a substantially reduced sample size for this analysis, it does suggest that while GlycA might mediate some of the associations between change in BMI and elasticity (reduction in coefficients for BMI), change in BMI is likely a confounder of the change in GlycA-elasticity association. Given our small sample size for this model, and our change analysis not considering temporality, these results need to be confirmed.

Male children and adolescents with obesity had higher cIMT compared to females, which may reflect physiologic reported sex differences as published for healthy children with normal weight [32]. The models used for the analysis were adjusted for preceding values of each exposure, suggesting that changes in adiposity measures are proximal on the causal pathway to adverse cardiovascular health. However, the methodology used does not allow to establish causality.

The strengths of the study include the comprehensiveness of repeated measurements of adiposity and cardiovascular risk factors, allowing adjustment for common confounders and assessment of intra-individual change, in contrast to cross-sectional designs. Finally, the subclinical cardiovascular phenotypes are valuable intermediate outcomes in adolescence due to their predictive capacity for CVD events and mortality in adulthood. Limitations include the modest sample size, missing information on physical activity and nutritional intake, a limited generalizability in a predominantly Caucasian study population and the assessment of the subclinical cardiovascular phenotypes at only one time-point; however, they findings are derived from and are relevant to the clinical care of children and adolescents with obesity.

### 4.1. Conclusion

In youth with obesity, improving or maintaining the severity of obesity from early to late adolescence – even without attaining normal weight status - was associated with lower arterial stiffness. Besides change in adiposity, ageing and change in SBP and GlycA (inversely) were associated with arterial stiffness. Male sex was the only factor associated with high carotid intima-media thickness. If replicated in other settings, our findings in adolescents with obesity highlight the importance of weight management and suggest that males with obesity warrant targeted CVD prevention.

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## CRediT authorship contribution statement

**Christoph Saner:** Conceptualization, Formal analysis, Writing – original draft, conceptualized the study, collected the data, performed the statistical analysis, interpreted the results, and wrote/revised manuscript, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Tomi T. Laitinen:** Writing – original draft, interpreted the study results and critically reviewed the manuscript for important intellectual content, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Joel Nuotio:** Writing – original draft, interpreted the study results and critically reviewed the manuscript for important intellectual content, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Sarah J. Arnup:** Formal analysis, Writing – original draft, assisted with generation and performance of the statistical analysis plan and provided support in interpreting the results, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Brooke E. Harcourt:** Writing – original draft, collected data and critically revised the manuscript, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Siroon Bekkering:** Writing – original draft, generated the figure abstract and critically reviewed the manuscript for important intellectual content, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Zoe McCallum:** Writing – original draft, collected data and critically revised the manuscript, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Kung-Ting Kao:** Writing – original draft, collected data and critically revised the manuscript, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Marco Janner:** Writing – original draft, interpreted the study results and critically reviewed the manuscript for important intellectual content, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Costan G. Magnussen:** Writing – original draft, Formal analysis, assisted with generation and performance of the statistical analysis plan and provided support in interpreting the results, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Matthew A. Sabin:** Writing – original draft, Conceptualization, Supervision, conceptualized/designed the study, supervised the data collection, interpreted reults and revised the manuscript for important intellectual content, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Markus Juonala:** interpreted the results and revised the manuscript for important intellectual content, All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **David P. Burgner:** Writing – original draft, Conceptualization, Supervision, conceptualized/designed the study, supervised the data collection, the data analysis, supported the results interpretation and critically revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.09.013.

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