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ORIGINAL ARTICLE

Weight reduction and aortic stiffness in obese children and adolescents: a 1-year follow-up study

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Little is known about the effect of weight reduction on aortic stiffness and especially so in the young. The present study investigates whether weight reduction influences aortic stiffness in obese children and adolescents. Carotid–femoral pulse wave velocity (cfPWV) and augmentation index at heart rate 75 (AIx@HR75) were measured in 72 obese patients aged 10–18 years at baseline and after 1-year of lifestyle intervention (follow-up). We found that although the degree of obesity decreased (Δbody mass index *z*-score: -0.24 ± 0.45, $P < 0.0001$), cfPWV was higher at follow-up (ΔcfPWV: 0.27 ± 0.47 m s^{-1}, $P < 0.0001$), which was explained by the increase in age ($\beta = 0.12$ ms^{-1} per year, 95% confidence interval (CI) 0.07–0.17, $P < 0.0001$) and partly by changes in mean arterial pressure and heart rate. Changes in cfPWV were not related to changes in obesity measures. No significant change was found in AIx@HR75 (ΔAIx@HR75: 2.10 ± 9.73%, $P = 0.072$), but changes in AIx@HR75 were related to changes in abdominal fat (Δwaist/height ratio: $\beta = 50.3$, 95% CI 6.7–94.0, $P = 0.02$) and changes in total body fat percent by dual energy X-ray absorptiometry scan (Δtotal body fat (%): $\beta = 0.7$, 95% CI 0.1–1.3, $P = 0.02$) when adjusted for gender and relevant baseline confounders. In conclusion, no clear effect of weight reduction was found on aortic stiffness, although changes in AIx@HR75 were associated with changes in both abdominal fat and total body fat percent. The higher cfPWV at follow-up was related to the older age.

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INTRODUCTION

Aortic stiffness and obesity are independent risk factors of cardiovascular disease.[1,2] Obesity has been associated with reduced aortic stiffness in children and adults until middle-age.[3–5] In middle-aged and older adults, weight reduction has been related to a reduction in aortic stiffness.[6,7] Little is known about the effect of weight reduction on aortic stiffness and especially so in children and adolescents. Information about vascular stiffness in obese children may shed light upon the pathophysiology of obesity associated elevated blood pressure (BP).

Carotid–femoral pulse wave velocity (cfPWV) is known as the gold standard for evaluating aortic stiffness.[8] Peripheral reflected BP waves measured by augmentation index (AIx) is regarded as an indirect measure of aortic stiffness.[9,10] The noninvasive methodologies used in adult studies are typically adopted in pediatrics.[10,11] Measurements of BP, aortic stiffness and body mass index (BMI) uses universal cutoff ranges for adults and are recognized by clinicians. However, these biological measures are complicated by growth and development in children and adolescents. Standardization into *z*-scores in respect to gender, age and height to standard normal populations enables comparisons of estimates across gender and age.[12] Waist circumference—a surrogate for abdominal fat—can be indexed by height representing growth when comparing measurements over time.[13,14]

In a recent publication,[5] we found that the newly recommended distance measure of the cfPWV measurement[8,15] did not introduce systematic error when young obese patients were compared with normal weighted control individuals. Further, changes in obesity measures were associated with changes in ambulatory BP.[16]

The objective of the present study is to investigate the impact of weight reduction on aortic stiffness in obese children and adolescents after 1-year of lifestyle intervention.

MATERIALS AND METHODS

Design and patients

Inclusion criteria were an age of 10–18 years in newly referred patients to the Children's Obesity Clinic.[17] Lifestyle intervention was based on a family-centered approach involving behavior-changing techniques as given in the clinic's treatment protocol.[17] In this protocol, 90 advices are defined aimed at nutrition, activity, obesity-related eating disorders and more. The treatment plan typically includes 12–20 advices that are given in writing at the first consultation. Patients are offered follow-up consultations by dieticians and nurses where the treatment plan is optimized.[17]

Baseline examination was no >60 days before or after the first visit to the clinic. Childhood overweight is defined as a BMI *z*-score >1, whereas obesity is defined as a BMI *z*-score >2.[18] Primary treatment end point was change (Δ) in BMI *z*-score; responders having a ΔBMI *z*-score <0 and nonresponders having a ΔBMI *z*-score >0.[17]

In a repeatability substudy including 25 patients, the day-to-day variation of the aortic stiffness measures was evaluated in respect to the possible long-term effect of weight reduction on these parameters. These 25 patients had three visits: baseline (day 1), follow-up 1 year later (day 2) and the day after the follow-up visit (day 3). The day-to-day repeatability (days 2 and 3) was investigated, as well as the year-to-year difference (day 1 minus day 2).

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The study was declared to ClinicalTrials.gov (NCT01310088), The Danish Data Agency and approved by The Scientific Ethical Committee of Region Zealand. Written informed consent was obtained from parents and individuals aged 18 years according to the Helsinki Declaration.

Anthropometry and obesity measures

Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg wearing light indoor clothes without shoes using an integrated calibrated weight and stadiometer (ADE, Modell MZ10023, Hamburg, Germany). BMI (kg m^{-2}) was calculated into BMI *z*-scores in respect to a Danish standard population with the same age and gender.[19] Waist circumference was measured to the nearest 0.1 cm with subjects standing using a stretch-resistant tape. Waist/height ratio was calculated.

Total body fat percentage was measured by dual energy X-ray absorptiometry (DXA) scanning (Lunar iDXA, GE Healthcare, enCore version 13.20.033, Madison, WI, USA). The DXA scan was part of the treatment protocol at The Children's Obesity's Clinic's. Only DXA scans performed <60 days before or after study days were included in the analyses. Fifty-nine (82%) patients had a DXA scan at both baseline and at follow-up.

Peripheral and central hemodynamic measures

Patients were asked to refrain from eating and smoking 3 h before examination. All hemodynamic measures were obtained after a rest of minimum 10 min in supine position.

Clinic brachial BP was measured with the oscillometric device Omron 705IT (Omron Healthcare Europe, Gl Hoofddorp, The Netherlands) validated in children and adolescents[20] using cuff sizes as recommended by the manufacturer; small (arm circumference <22 cm), medium (22–32 cm) and large ($\geqslant 32$ cm). Mean of the last two out of three BP measurements was reported and calculated into *z*-scores according to an American standard population based on individuals' gender, age and height.[12] A *z*-score value of zero is equal to the expected mean in relation to the given reference population. The 95th percentile equals to a *z*-score of 1.645 and is arbitrarily defined as the cutoff level in the BP classification.[12]

Aortic stiffness was measured as cfPWV and AIx noninvasively by applanation tonometry using the SphygmoCor 9.0 device (AtCor Medical, Sydney, NSW, Australia).[8,9]

CfPWV was calculated as the pulse wave travel distance divided by transit time. Travel distance was measured with a caliper (infantometer) being 80% of the direct distance from the carotid artery to the femoral artery.[5] Transit time was determined from carotid and femoral artery waveforms recorded consecutively with an electrocardiographic-gated signal simultaneously recorded. CfPWV was reported as mean of at least two measurements and calculated into *z*-scores according to an Hungarian–Italian–Algerian standard population based on individuals' gender and age, and gender and height.[21]

The quality of the carotid and femoral artery waveforms was evaluated with pulse transit time s.d. and regarded as acceptable when $<10\%$ as given in the manufacturer's manual. No significant difference was found between baseline and follow-up (pulse transit time s.d.; median 7.8 (interquartile range: 6.6–9.7)% at baseline vs 7.7 (6.2–8.8)% at follow-up, $P=0.07$).

A central BP waveform was collected from the radial artery. AIx is the augmentation pressure expressed as a percentage of the pulse pressure, where augmentation pressure is the difference between the second and first systolic peaks from the reflected BP waves. The central waveform obtained from the radial measurement was calibrated to the brachial systolic and diastolic BP using a generalized transfer function.[22] AIx was corrected for a standard heart rate of 75 b.p.m. (AIx@HR75) by the AtCor software. AIx@HR75 was reported as mean of at least two measurements. Three patients had only one AIx measurement: two patients at baseline owing to difficulties in obtaining the measurements and one patient at follow-up owing to a software error.

The quality of the central BP waveforms was evaluated with operator index, a composite quality control parameter in the SphygmoCor software and regarded as acceptable when >80 on a scale 0–100 as given in the manufacturer's manual. No significant difference was found between baseline and follow-up (operator index; 90.0 (83.5–93.5) at baseline vs 87.5 (83.0–91.0) at follow-up, $P=0.06$).

The corresponding author performed all anthropometric and hemodynamic measurements.

Statistics

Statistical analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA). Results were reported as mean ± s.d. or median (interquartile range) dependent on whether data were normally distributed.

Differences in measurements between baseline and follow-up were investigated with paired Student's *t*-tests or Wilcoxon signed rank tests dependent on whether differences were normally distributed or not. Differences in response rates between genders were investigated with a χ^2-squared test.

In linear regression analyses, we investigated whether measures of aortic stiffness were related to age at baseline and follow-up. In mixed model analyses, we tested whether the linear regression equations between cfPWV and age at baseline and follow-up differed, in order to evaluate whether a potential difference in the level of cfPWV at follow-up was merely ascribed to the higher age, or whether gender and hemodynamic differences (mean arterial pressure and heart rate) contributed.

We investigated whether changes in aortic stiffness were related to changes in obesity measures using linear regression analyses. In multiple regression analyses, the potential relationship between changes in obesity measures and changes in cfPWV were adjusted for gender and baseline confounders: age, mean arterial pressure, heart rate, the obesity measure and cfPWV. The potential relationship between changes in obesity measures and changes in AIx@HR75 were adjusted for gender and baseline confounders: age, the obesity measure and AIx@HR75. In additional analyses, the potential relationship between the constituents of waist/height ratio (changes in both height and waist circumference) and changes in AIx@HR75 were investigated. In order to pool data from the two genders, we tested for a possible interaction of gender with the explanatory variable of interest (the change in the obesity or anthropometric measure).

The day-to-day repeatability of the aortic stiffness measures was investigated with paired (one sample) *t*-tests for possible systematic differences, Bland–Altman plots for possible differences in the magnitude of the measurements and Pearson's correlation coefficients as intraclass correlation coefficients as indexes of reliability.

The year-to-year differences (day 1 minus day 2) vs the numeric day-to-day differences (|day 2 minus day 3|) of the aortic stiffness measures were investigated with paired Student's *t*-test.

RESULTS

Characteristics of the study population

Seventy-two overweight and obese Caucasian patients (girls: 37 (51%)) were included in the present study. Median age was 12.5 (interquartile range: 11.2–14.6) years at baseline and the follow-up time was 364 (363–371) days.

Initially, 104 patients (71% of invited patients) were investigated at baseline and 74 patients (71% of patients investigated at baseline) were evaluated at follow-up 1 year later. No data was collected on reasons for patients dropping out. Two patients were excluded from the analyses owing to either a chronic kidney disease or onset of influenza symptoms at follow-up. None of the remaining patients were diagnosed as having secondary hypertension.

Eleven patients used medication: four due to asthma or allergy, three for gastro-intestinal symptoms, two took hormonal supplementation (one due to hypothyroidism taking a thyroid hormone analog and one due to nocturnal enuresis taking a synthetic antidiuretic hormone), three used birth control medication and one used a not-specified drug. Use of medication had not changed at follow-up. Two patients were smokers throughout the study.

Changes in anthropometric and obesity measures

Fifty-three (74%) patients experienced a reduction in their BMI *z*-score (responders) with no significant difference between genders (girls 24 (64%) vs boys 29 (83%), $P=0.08$). BMI *z*-score, waist/height ratio and DXA total body fat percentage were significantly lower at follow-up despite an increased height and weight, and no change in BMI or waist circumference (Table 1).

Table 1. Anthropometrics and obesity measures at baseline and follow-up

	Baseline, N = *72*	*Follow-up,* N = *72*	*Difference (Δ)*	P-*value*
	Mean ± s.d. or median (IQR)	*Mean ± s.d. or median (IQR)*	*Mean ± s.d. or median (IQR)*	
N (girls/boys)	37/35	37/35		
Height (cm)	159.5 ± 11.6	164.5 ± 10.2	5.0 ± 3.5	< 0.0001
Weight (kg)	66.7 (57.1–89.7)	72.1 (61.9–61.9)	4.1 ± 5.9	< 0.0001
BMI (kg m^{-2})	27.0 (24.0–31.7)	26.5 (22.8–32.0)	− 0.08 ± 2.06	0.74
BMI *z*-score	2.75 ± 0.62	2.51 ± 0.87	− 0.24 ± 0.45	< 0.0001
Waist (cm)	96.9 ± 15.0	97.2 ± 17.0	0.38 ± 6.61	0.63
Waist/height ratio	0.60 ± 0.07	0.58 ± 0.09	− 0.02 ± 0.04	0.004
DXA total body fat (%)	44.2 ± 4.7	41.0 ± 7.3	− 3.3 ± 4.3	< 0.0001

Abbreviations: BMI, body mass index; DXA, dual energy x-ray absorptiometry; IQR, interquartile range. Data are presented in mean ± s.d. or median (IQR). Twelve (17%) patients at baseline and one (1%) patient at follow-up lacked a DXA scan, comparison of DXA total body fat percent is based on 59 (82%) patients having a DXA scan at both baseline and follow-up.

Table 2. BP and aortic stiffness at baseline and follow-up

	Baseline, N = *72*	*Follow-up,* N = *72*	*Difference (Δ)*	P-*value*
	Mean ± s.d.	*Mean ± s.d.*	*Mean ± s.d.*	
Brachial systolic BP (mm Hg)	110.7 ± 8.9	112.5 ± 8.1	1.9 ± 8.3	0.06
Brachial systolic BP *z*-score	1.50 ± 1.13	1.84 ± 1.00	0.33	0.0009
Brachial diastolic BP (mm Hg)	62.1 ± 5.7	61.3 ± 6.2	− 0.8 ± 5.5	0.25
Brachial diastolic BP *z*-score	0.44 ± 0.61	0.44 ± 0.66	0.004 ± 0.49	0.94
Brachial pulse pressure (mm Hg)	48.6 ± 7.9	51.2 ± 7.9	2.6 ± 6.5	0.001
Central systolic BP (mm Hg)	93.2 ± 7.6	94.5 ± 6.6	1.3 ± 7.6	0.14
Central diastolic BP (mm Hg)	63.1 ± 5.9	62.7 ± 6.1	− 0.5 ± 5.8	0.51
Central pulse pressure (mm Hg)	30.0 ± 5.6	31.8 ± 5.8	1.8 ± 4.7	0.002
Heart rate (b.p.m.)	67.1 ± 9.7	65.3 ± 10.0	− 1.8 ± 8.4	0.08
AIx@HR75	− 1.03 ± 10.39	1.07 ± 9.15	2.10 ± 9.73	0.07
CfPWV (m s^{-1})	4.84 ± 0.57	5.11 ± 0.60	0.27 ± 0.47	< 0.0001
CfPWV *z*-scores$_{gender\text{-}age}$	− 0.04 ± 0.80	0.19 ± 0.78	0.23 ± 0.71	0.007
CfPWV *z*-scores$_{gender\text{-}height}$	− 0.26 ± 0.81	− 0.05 ± 0.78	0.21 ± 0.68	0.01

Abbreviations: AIx@HR75, augmentation index at heart rate 75; BP, blood pressure; cfPWV, carotid–femoral pulse wave velocity. Data are presented in mean ± s.d. Mean brachial BP in mmHg was calculated into BP *z*-scores in respect to an American standard population based on individuals' gender, age and height.[12] CfPWV (m s^{-1}) was reported as mean of at least two measurements and calculated into *z*-scores according to an Hungarian–Italian–Algerian standard population based on individuals' gender and age, and gender and height.[21]

Changes in BPs and aortic stiffness

Clinic brachial and central systolic and diastolic BP's in mmHg did not differ between baseline and follow-up (Table 2). Likewise, no change was found in clinic brachial diastolic BP *z*-scores between baseline and follow-up, whereas clinic brachial systolic BP *z*-scores, clinic brachial pulse pressure and central pulse pressure, as well as cfPWV's in m s^{-1} and *z*-scores, were higher at follow-up. No significant change was found for AIx@HR75.

In linear regression, cfPWV was equally related to age at baseline ($\beta = 0.13$ m s^{-1} per year, 95% confidence interval (CI) 0.08–0.18, $R^2 = 0.252$, $P < 0.0001$) and follow-up ($\beta = 0.13$ m s^{-1} per year, 95% CI 0.07–0.19, $R^2 = 0.237$, $P < 0.0001$; Figure 1), and the regression slopes did not differ in mixed model analysis ($P = 0.97$). In further mixed model analysis, cfPWV was still strongly related to age ($\beta = 0.12$ m s^{-1} per year, 95% CI 0.07–0.17, $P < 0.0001$) but the values were higher at follow-up ($\beta = 0.17$ m s^{-1} higher at follow-up, 95% CI 0.28–0.05, $P = 0.005$) when adjusted for heart rate ($\beta = 0.01$ m s^{-1} per b.p.m., 95% CI 0.004–0.02, $P = 0.005$), mean arterial pressure ($\beta = 0.01$ m s^{-1} per mm Hg, 95% CI 0.0009–0.03, $P = 0.04$) and gender ($\beta = 0.06$ m s^{-1} higher in girls, 95% CI − 0.15 to 0.27, $P = 0.60$). In this respect, the higher cfPWV at follow-up was predominantly explained by the increase in age and partly by changes in BP and heart rate.

AIx@HR75 was not related to age at baseline ($\beta = -0.62$, 95% CI − 1.71 to 0.47, $R^2 = 0.018$, $P = 0.26$) or at follow-up ($\beta = -0.02$, 95% CI − 0.99 to 0.95, $R^2 = 0.00002$, $P = 0.97$).

Associations between changes in obesity measures and changes in aortic stiffness

Changes in cfPWV were not associated with changes in obesity measures in linear or multiple regression analyses (Table 3). Changes in AIx@HR75 tended to be linear associated with changes in BMI *z*-score ($\beta = 4.32$, 95% CI − 0.71 to 9.35, $R^2 = 0.040$, $P = 0.09$), waist/height ratio ($\beta = 48.01$, 95% CI − 2.94 to 98.96, $R^2 = 0.048$, $P = 0.06$) and DXA total body fat percent ($\beta = 0.57$, 95% CI − 0.04 to 1.17, $R^2 = 0.058$, $P = 0.07$). In multiple regression analyses, changes in AIx@HR75 were associated to changes in waist/height ratio ($\beta = 50.32$, 95% CI 6.67–93.97, $P = 0.02$, model: $R^2 = 0.430$, $P < 0.0001$) and changes in DXA total body fat percent ($\beta = 0.70$, 95% CI 0.11–1.29, $P = 0.02$, model: $R^2 = 0.415$, $P < 0.0001$) but not significantly to changes in BMI when adjusted for gender and relevant baseline confounders.

Changes in AIx@HR75 were related to changes in waist in linear ($\beta = 0.36$, 95% CI 0.02–0.70, $R^2 = 0.059$, $P = 0.04$) and multiple regression analyses ($\beta = 0.36$, 95% CI 0.08–0.64, $P = 0.01$, model: $R^2 = 0.423$, $P < 0.0001$). Changes in AIx@HR75 were not related to

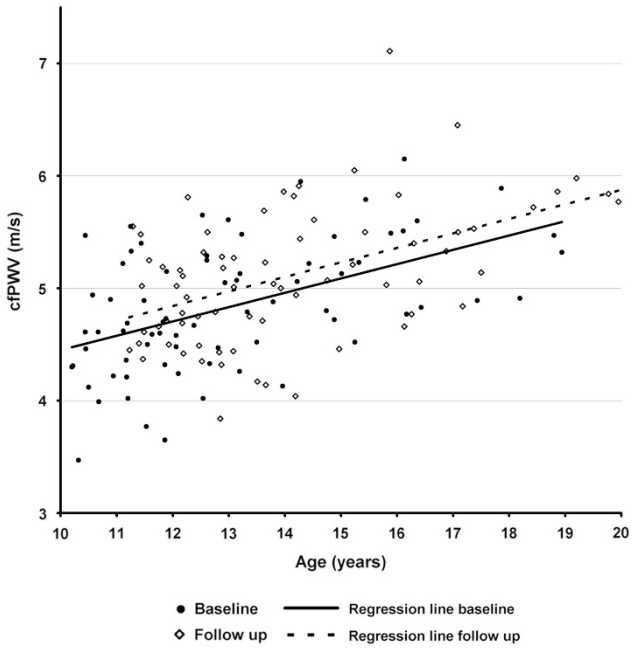

Figure 1. Carotid–femoral pulse wave velocity (cfPWV) in relation to age at baseline and follow-up.

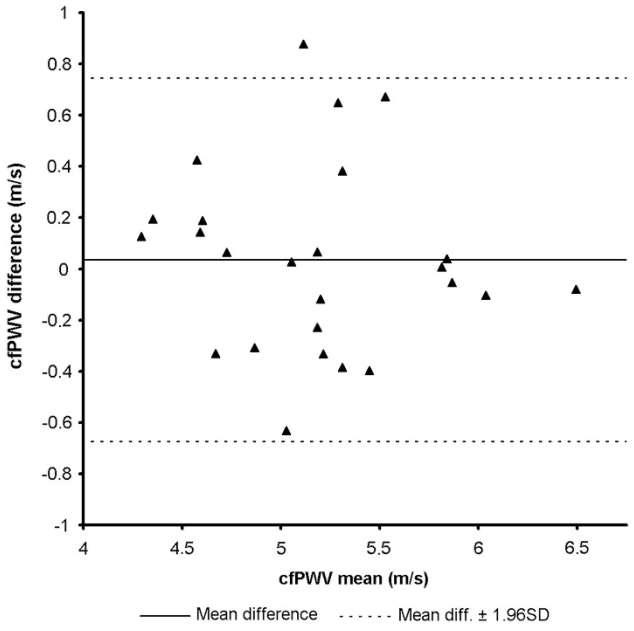

Figure 2. Bland–Altman plot of the day-to-day variability of carotid–femoral pulse wave velocity (cfPWV; $N = 25$).

Table 3. Relationship between changes in obesity measures and changes in aortic stiffness

	ΔcfPWV		*ΔAIx@HR75*	
	Unadjusted	*Adjusted*	*Unadjusted*	*Adjusted*
ΔBMI *z*-score ($N = 72$)	0.08 (0.52)	0.08 (0.57)[a]	4.32 (0.09)[a]	3.33 (0.17)[b]
ΔWaist/height ratio ($N = 72$)	−0.62 (0.62)	−0.73 (0.57)[a]	48.01 (0.06)[a]	50.32 (0.02)[b]
ΔDXA total body fat (%; $N = 59$)	0.01 (0.71)	0.006 (0.72)[a]	0.57 (0.07)[a]	0.70 (0.02)[b]

Abbreviations: Δ AIx@HR75, change in augmentation index at heart rate 75; BMI, body mass index; ΔcfPWV, change in carotid–femoral pulse wave velocity; DXA, dual energy x-ray absorptiometry. Results are *β*-coefficients (*P*-values) of regression analyses of Δ aortic stiffness (outcome) in relation to Δ obesity measure (explanatory variable), that is, ΔBMI *z*-score, Δ waist/height ratio or ΔDXA total fat percent. Unadjusted analyses are simple linear regression. Adjusted analyses are multiple regression analyses. ΔcfPWV are adjusted for gender and baseline confounders: age, mean arterial pressure, heart rate, cfPWV as well as the corresponding obesity measure, that is, the baseline measure of BMI *z*-score, waist/height ratio or DXA total fat percent. ΔAIx@HR75 are adjusted for gender and baseline confounders: age, AIx@HR75 as well as the corresponding obesity measure. No interactions of gender with the obesity measure were found in the multiple regression analyses. [a]Denotes a model trend: $P < 0.10$. [b]Denotes a highly significant model: $P < 0.0001$.

changes in height in linear ($\beta = 0.09$, 95% CI −0.57 to 0.75, $R^2 = 0.001$, $P = 0.78$) or multiple regression analyses ($\beta = 0.46$, 95% CI −0.31 to 1.24, $P = 0.24$, model: $R^2 = 0.377$, $P < 0.0001$). None of the multiple regression models had an interaction with gender and change in the obesity or anthropometric measure of interest.

Repeatability of aortic stiffness

The 25 patients (35% of the included patients) included in the repeatability substudy did not differ at baseline in respect to gender, age, height, weight and BMI *z*-score from those without the repeatability measurements (data not shown).

CfPWV had no systematic difference (0.03 ± 0.36 m s^{-1}, $P = 0.64$), was not dependent on the magnitude of the cfPWV measurement (Figure 2) and had an intraclass correlation coefficient of 0.80 ($P < 0.0001$) the 2 days in between. The year-to-year difference of cfPWV was higher than the day-to-day difference (0.25 ± 0.46 m s^{-1}, $P = 0.01$).

AIx@HR75 had no systematic difference (-2.46 ± 7.19%, $P = 0.11$), was not dependent on the magnitude of the AIx@HR75 measurement (Figure 3) and had an intraclass correlation coefficient of 0.68 ($P = 0.0002$) the 2 days in between. No difference was found between the year-to-year difference and the numeric day-to-day difference (-2.07 ± 13.31%, $P = 0.45$).

DISCUSSION

The present study suggests that weight reduction across 1 year did not have a clear impact on aortic stiffness in obese children and adolescents. In fact, cfPWV was higher at follow-up, although changes in AIx@HR75 were associated with changes in abdominal fat and also changes in total body fat percent. The higher cfPWV at follow-up may be explained by the increased age and changes in BP and heart rate, as cfPWV was equally related to age at baseline and follow-up.

Previous studies have investigated associations between obesity and aortic stiffness in children and adolescents.[3–5] However, knowledge is lacking on the effect of weight reduction on aortic stiffness.

There are methodological considerations when assessing aortic stiffness noninvasively, as no validation studies exist in children and adolescents. In adults, the distance measure of cfPWV is validated in a magnetic resonance imaging study.[15] We would not expect systematic errors in the distance measure by the changing

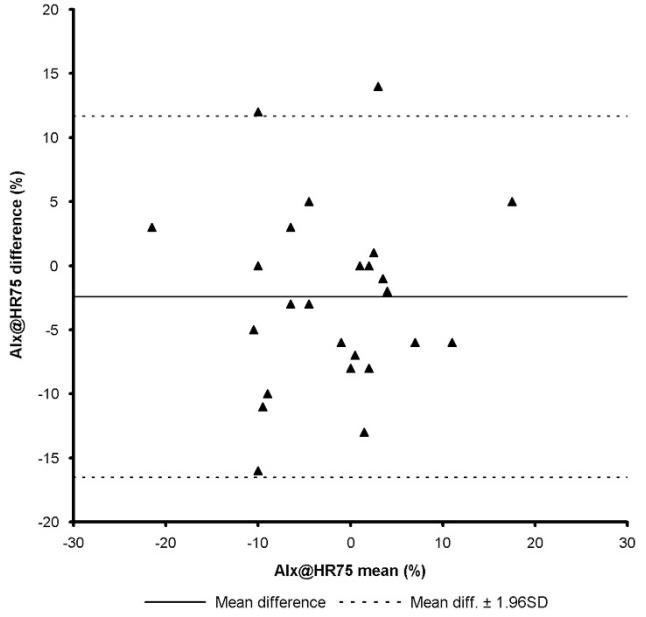

Figure 3. Bland–Altman plot of the day-to-day variability of AIx@HR75 ($N = 25$). AIx@HR75, augmentation index at heart rate 75.

degree of obesity at follow-up when using the same distance method.[5] Several normative populations have been established for standardization of cfPWV into *z*-scores.[21,23,24] All uses different distance measures compared with the present study. The material by Reusz *et al*.[21] was chosen as cfPWV was obtained by applanation tonometry, but the use of a different distance measure possibly influence the accuracy of the calculated *z*-scores, which might explain the observed difference between baseline and follow-up.[5] Another consideration is the day-to-day variation of cfPWV and AIx@HR75 vs the expected long-term effect of weight reduction on these parameters. CfPWV had a small daily variation and was related to age, as also found in adults,[25,26] rather than to weight changes.

The general transfer function used in the computation of AIx from the brachial BP is validated in adults in an invasive study.[22] Invasive validation of central BP and AIx in children is generally difficult.[11] In healthy adults, the week-to-week variation of AIx@HR75 is acceptable,[27] as we also found for the day-to-day variation. However, the day-to-day variation of AIx@HR75 did not differ from the year-to-year variation, and AIx@HR75 did not change at follow-up. Despite this variation and that no difference in AIx@HR75 was found, a potential mechanism for the association between changes in abdominal obesity (waist/height ratio) and changes in AIx@HR75 could be the linkage between abdominal obesity and resistance artery function.[28–30]

In adults aged 21–46 years, weight reduction after 6 and 12 months of lifestyle intervention was accompanied with a reduction in cfPWV,[31,32] but the changes in cfPWV were not related to changes in weight.[32] In these studies, the distance measure of cfPWV was measured with tape by a subtracted technique. This might lead to bias as a subtracted distance measure overestimated the distance and hence the cfPWV at baseline.[5] Abdominal obesity likely contributes to this bias even further when the distance is measured with a tape.[33,34] Possibly, a significant weight reduction can lead to a smaller subtracted distance, when measured with a tape, and therefore a decreased cfPWV.

Previous studies indicate that no damage to the central vasculature exists in obese children and adolescents.[3–5] In this respect, it has been found that overweight children who recover their normal weight have similar risk of cardiovascular outcomes in adulthood, as individuals having a normal weight consistently from childhood to adulthood.[35]

Contrary to expected,[36] no reduction was found in clinic brachial and central BP at follow-up despite the significant weight reduction in the obese patients. However, not all patients were responders, and recently we have found that the obese patients in the present study have a relationship between changes in obesity measures (BMI and waist/height ratio) and changes in 24-h BP.[16] In the present study, the noninvasive measures of aortic stiffness were obtained in the same resting conditions as the clinic brachial BP. BP is closely related to aortic stiffness, and changes in BP are related to changes in weight. In this respect, changes in BP could be an indirect mechanism between changes in the obesity measures and aortic stiffness. As the actual BP, that is, clinic brachial BP, did not change, this might explain that no relationship was found between changes in obesity and aortic stiffness.

The strengths of the present study are that patients experienced a significant weight reduction similar to earlier published treatment results of the Children's Obesity Clinic—although still obese at follow-up.[17] Implications of the effect of the yearly aortic stiffness measurements were evaluated in respect to the random daily variation in a subsample of the patients. Patients were their own controls and although few used medication and smoked a potential bias herein will most probably have the same impact at baseline and follow-up.

There are also limitations in the present study. First, ~30% patients dropped out, and loss in statistical power made it difficult to detect small differences between baseline and follow-up. Second, no control group was included in the present study. However, not all patients were responders, and the mixture of patients reducing and gaining weight might have influenced arterial stiffness differently. Nevertheless, no relationship was found when changes in cfPWV were related to changes in obesity measures, that is, evaluated as a continuum. Third, no puberty and physical activity measures were collected, and these might influence aortic stiffness.[37] However, measurements were standardized into *z*-scores, enabling comparisons of estimates across gender and age. Fourth, waist/height ratio is a composite measure of waist and height. Hence, the association between this composite measure and an outcome in a regression model might merely be the effect of one of the composite constituents, that is, either waist or height alone. Potentially, the association between waist/height ratio and changes in AIx@HR75 was merely ascribed to the higher height at follow-up, as waist did not change. However, we found that changes in AIx@HR75 were related to changes in waist but not to changes in height in separate analyses. In this respect, changes in abdominal fat seem to influence aortic stiffness when evaluated as AIx. Fifth, the participants represent a selected population having a BMI *z*-score >2 for gender and age. Therefore, it is uncertain whether the hemodynamic findings of the present study are applicable in a more moderate overweight range.

In conclusion, our data suggest that no clear effect of weight reduction was found on measures of aortic stiffness in obese children and adolescents after 1 year of lifestyle intervention. We found a higher aortic stiffness when assessed as cfPWV at follow-up, which was partly due to the increased age and changes in BP and heart rate. At the same time, an association between changes in abdominal obesity and changes in AIx, as well as an association between changes in total body fat percent and changes in AIx were observed.

In perspective, it seems that no damage to the central vasculature exists in obese children and adolescents.[5,35] Early treatment and prevention of childhood obesity should be recognized because it might ameliorate increases in BP,[16] and most importantly, it can be introduced before irreversible damage to the cardiovascular system occurs.[35]

What is known about topic

- Aortic stiffness and obesity are independent risk factors of cardiovascular disease.
- Obesity has been associated with reduced aortic stiffness in children and adults until middle-age.

What this study adds

- Knowledge on the effect of weight reduction on aortic stiffness in children and adolescents.
- This information about vascular stiffness in obese children may shed light upon the pathophysiology of obesity associated elevated blood pressure.

CONFLICT OF INTEREST

KNH received LEO Pharma's Travel Grant during data collection of the present study. The remaining authors declare no conflict of interest.

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REFERENCES

1 Mitchell GF, Hwang S-J, Vasan RS, Larson MG, Pencina MJ, Hamburg NM *et al.* Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010; **121**: 505–511.
2 Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; **67**: 968–977.
3 Corden B, Keenan NG, de Marvao ASM, Dawes TJW, Decesare A, Diamond T *et al.* Body fat is associated with reduced aortic stiffness until middle age. *Hypertension* 2013; **61**: 1322–1327.
4 Lurbe E, Torro I, Garcia-Vicent C, Alvarez J, Fernández-Fornoso JA, Redon J. Blood pressure and obesity exert independent influences on pulse wave velocity in youth. *Hypertension* 2012; **60**: 550–555.
5 Hvidt KN, Olsen MH, Holm J-C, Ibsen H. Aortic stiffness in obese children and adolescents: comparison of two distance measures of carotid-femoral pulse wave velocity. *Artery Res* 2013; **7**: 186–193.
6 Rider OJ, Tayal U, Francis JM, Ali MK, Robinson MR, Byrne JP *et al.* The effect of obesity and weight loss on aortic pulse wave velocity as assessed by magnetic resonance imaging. *Obesity (Silver Spring)* 2010; **18**: 2311–2316.
7 Dengo AL, Dennis EA, Orr JS, Marinik EL, Ehrlich E, Davy BM *et al.* Arterial destiffening with weight loss in overweight and obese middle-aged and older adults. *Hypertension* 2010; **55**: 855–861.
8 Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T *et al.* Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012; **30**: 445–448.
9 Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D *et al.* Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; **27**: 2588–2605.
10 Stoner L, Lambrick DM, Faulkner J, Young J. Guidelines for the use of pulse wave analysis in adults and children. *J Atheroscler Thromb* 2013; **20**: 404–406.
11 Urbina EM, Williams RV, Alpert BS, Collins RT, Daniels SR, Hayman L *et al.* Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. *Hypertension* 2009; **54**: 919–950.
12 National High Blood Pressure Education Program Working Group on High Blood Pressure in Adolescents andressure in Children. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; **114**: 555–576.
13 McCarthy HD, Ashwell M. A study of central fatness using waist-to-height ratios in UK children and adolescents over two decades supports the simple message--'keep your waist circumference to less than half your height'. *Int J Obes (Lond)* 2006; **30**: 988–992.
14 Nambiar S, Truby H, Abbott RA, Davies PSW. Validating the waist-height ratio and developing centiles for use amongst children and adolescents. *Acta Paediatr* 2009; **98**: 148–152.
15 Huybrechts SAM, Devos DG, Vermeersch SJ, Mahieu D, Achten E, de Backer TLM *et al.* Carotid to femoral pulse wave velocity: a comparison of real travelled aortic path lengths determined by MRI and superficial measurements. *J Hypertens* 2011; **29**: 1577–1582.
16 Hvidt KN, Olsen MH, Ibsen H, Holm J-C. Effect of changes in BMI and waist circumference on ambulatory blood pressure in obese children and adolescents. *J Hypertens* 2014; **32**: 1470–1477.
17 Holm J-C, Gamborg M, Bille DS, Grønbæk HN, Ward LC, Faerk J. Chronic care treatment of obese children and adolescents. *Int J Pediatr Obes* 2011; **6**: 188–196.
18 WHO BMI-for-age (5-19 years) [Internet]. 2012. Available at http://www.who.int/growthref/who2007_bmi_for_age/en/index.html (accessed 18 April 2013).
19 Nysom K, Mølgaard C, Hutchings B, Michaelsen KF. Body mass index of 0 to 45-y-old Danes: reference values and comparison with published European reference values. *Int J Obes Relat Metab Disord* 2001; **25**: 177–184.
20 Stergiou GS, Yiannes NG, Rarra VC. Validation of the Omron 705 IT oscillometric device for home blood pressure measurement in children and adolescents: the Arsakion School Study. *Blood Press Monit* 2006; **11**: 229–234.
21 Reusz GS, Cseprekal O, Temmar M, Kis E, Cherif AB, Thaleb A *et al.* Reference values of pulse wave velocity in healthy children and teenagers. *Hypertension* 2010; **56**: 217–224.
22 Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J* 1993; **14**: 160–167.
23 Hidvégi EV, Illyés M, Benczúr B, Böcskei RM, Rátgéber L, Lenkey Z *et al.* Reference values of aortic pulse wave velocity in a large healthy population aged between 3 and 18 years. *J Hypertens* 2012; **30**: 2314–2321.
24 Fischer D-C, Schreiver C, Heimhalt M, Noerenberg A, Haffner D. Pediatric reference values of carotid-femoral pulse wave velocity determined with an oscillometric device. *J Hypertens* 2012; **30**: 2159–2167.
25 Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA *et al.* Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 2004; **43**: 1239–1245.
26 Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR *et al.* Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens* 1998; **16**: 2079–2084.
27 Papaioannou TG, Karatzis EN, Karatzi KN, Gialafos EJ, Protogerou AD, Stamatelopoulos KS *et al.* Hour-to-hour and week-to-week variability and reproducibility of wave reflection indices derived by aortic pulse wave analysis: implications for studies with repeated measurements. *J Hypertens* 2007; **25**: 1678–1686.
28 Christou DD, Pierce GL, Walker AE, Hwang M-H, Yoo J-K, Luttrell M *et al.* Vascular smooth muscle responsiveness to nitric oxide is reduced in healthy adults with increased adiposity. *Am J Physiol Heart Circ Physiol* 2012; **303**: H743–H750.
29 Pierce GL, Beske SD, Lawson BR, Southall KL, Benay FJ, Donato AJ *et al.* Weight loss alone improves conduit and resistance artery endothelial function in young and older overweight/obese adults. *Hypertension* 2008; **52**: 72–79.
30 Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX *et al.* Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arterioscler Thromb Vasc Biol.* 2006; **26**: 968–976.
31 Cooper JN, Buchanich JM, Youk A, Brooks MM, Barinas-Mitchell E, Conroy MB *et al.* Reductions in arterial stiffness with weight loss in overweight and obese young adults: potential mechanisms. *Atherosclerosis* 2012; **223**: 485–490.
32 Hughes TM, Althouse AD, Niemczyk NA, Hawkins MS, Kuipers AL, Sutton-Tyrrell K. Effects of weight loss and insulin reduction on arterial stiffness in the SAVE trial. *Cardiovasc Diabetol* 2012; **11**: 114.
33 Levi-Marpillat N, Desamericq G, Akakpo S, Affes-Ayadi H, Tropeano A-I, Millasseau S *et al.* Crucial importance of using a sliding calliper to measure distance for carotid-femoral pulse wave velocity assessment. *J Hypertens* 2013; **31**: 940–945.
34 Hvidt KN, Olsen MH, Holm J-C, Ibsen H. Carotid–femoral pulse wave velocity in obese children and adolescents: The potential bias of tape distance measuring. *Artery Res* 2013; **7**: 234–237.
35 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**: 1876–1885.
36 Rocchini AP, Katch V, Anderson J, Hinderliter J, Becque D, Martin M *et al.* Blood pressure in obese adolescents: effect of weight loss. *Pediatrics* 1988; **82**: 16–23.
37 Ahimastos AA, Formaosa M, Dart AM, Kingwell BA. Gender differences in large artery stiffness pre- and post puberty. *J Clin Endocrinol Metab* 2003; **88**: 5375–5380.