Title: Pulse wave velocity during re-feeding and with weight gain in underweight female adolescents with Anorexia Nervosa.

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Anorexia Nervosa (AN) causes harmful underweight and important cardiovascular acute complications however less is known about longer-term cardiovascular risk. We measured carotid femoral pulse wave velocity (PWV) in a group of underweight young women with AN at baseline and weekly as they were refed and gained weight. PWV decreased over time and was negatively associated with increasing BMI and calorific meal content suggesting potential positive cardiovascular benefits for refeeding and weight gain in AN and supports current consensus for the importance of weight gain in underweight young women with AN.

Introduction

Anorexia Nervosa (AN) is a mental disorder characterised by weight and shape concerns leading to harmful levels of starvation and is an important example of a condition where psychological and physical health should be considered together. Underweight in AN frequently leads to acute cardiovascular complications which are considered a key cause of the mortality from AN[1] but less is known about longer-term impact on cardiovascular health. Analysis of population-level data has reported greater cardiovascular disease risk associated with underweight,[2] and a recent systematic review of malnutrition and famine in childhood demonstrated greater cardiometabolic risk in later life.[3] Pulse wave velocity is a well-established measure of arterial stiffness, a risk factor for cardiovascular disease[4] and a cross-sectional study reported greater levels of PWV in underweight adolescents with AN versus healthy weight controls. [5] However, there are no longitudinal studies of arterial stiffness in patients with AN. Weight gain is considered favourable for reducing a range of risk domains in AN and forms a key part of current best practice treatment

recommendations[6] but little is known about how refeeding and weight-gain impacts on arterial stiffness. This is an important question to help understand and potentially limit future cardiovascular disease burden in a patient group already burdened with significant acute cardiovascular risk. We therefore conducted a longitudinal study of PWV (carotid-femoral, cfPWV) in underweight adolescent female patients with AN who were refed in a single inpatient eating disorder unit in the United Kingdom.

Methods

We recruited newly admitted patients with AN to Ellern Mede Eating Disorder Unit (London) between December 2020 and May 2022. Diagnoses of AN were made by a referring community eating disorder team and confirmed by an admitting psychiatrist. Inclusion criteria were: 1) female under 18 years of age; 2) underweight < 85% of median Body Mass Index (BMI) for age. We measured ambulatory cfPWV using Vicorder (Skidmore Medical, UK) with measurements of pulse waveforms at the neck (carotid) and right upper thigh (femoral) following 30 mins rest, supine. Measures were taken at admission (baseline), and approximately weekly to a maximum of 12 additional measurements or until discharge from the unit if earlier. We also recorded at each time point: 1) peripheral systolic and diastolic blood pressures (sBP, dBP) measured using an automated machine immediately prior to PWV measurement (Omron-HEM-907-E7); 2) BMI; 3) calorific content of meal plan. Statistical analysis was performed using Stata (version 17) for graphics R was used. We fitted fixed-effects linear models including a random effects term on the intercept to account for repeated measurements on the participants, to test for: 1) change in PWV, BMI and BP over time; 2) relationships between BMI, daily meal plan content, sBP and dBP with PWV. We

received research ethics approval for the study from the UK Health Research Authority following a London health research ethics committee review (Research Ethics Committee (REC) London Centre: REC reference 20/LO/0084, study specific project ID 259817).

Results

We recruited 16 participants from a total of 18 eligible patients during the time of study (89%). 13 (81%) were Caucasian. 11 (68%) were prescribed antipsychotic medication. Median age was 16.4 years (IQR 5.1). Median time since diagnosis of AN was 1 years (IQR 1.27). At baseline, median (and IQR) for repeated measured variables were as follows: BMI 15.45 Kgm^{-2} (1.62), daily meal plan content 1500 $kcalday^{-1}$ (850), sBP 99 mmHg (8), dBP 62 mmHg (10), cfPWV ms^{-1} 7.47 (0.87). Graphs of changes in participants' cfPWV, BMI, sBP and dBP over time are shown in frames A to D in figure 1 (with linear mixed effects models linear mixed-effects model with 95% prediction confidence intervals overlaid). Linear mixed-effects models for change in cfPWV, BMI, daily meal plan content, sBP and dBP over time; as well as univariable models of repeated measures of BMI, BP and daily meal plan as predictors of cfPWV are shown in tables in frames E and F of figure 1 respectively. In models, over 12 weeks of study, BMI, sBP and dBP all increased (by 2.8 Kgm^{-2} (+ 17.7%); 4 mmHg (+ 7.5%) and 3.8 mmHg (+ 6.1%) respectively); and cfPWV decreased (by 0.6 ms^{-1} (- 8%)).

Discussion

We believe this to be the first study examining longitudinal cfPWV within a group of patients with AN. At baseline, mean PWV in our sample was well above the 90^{th} centile of healthy

young people of a similar age based on several studies using Vicorder.[7] BMI, sBP and dBP increased over the time of study and cfPWV decreased. Increased BMI and calorific meal content were negatively associated with cfPWV, a finding which suggests potential positive cardiovascular benefits for refeeding and weight gain in AN and adds to the rationale for the emphasis upon weight gain in patients with AN who are underweight. Our study also stands in contrast to reported decreases in PWV and BP with loss of weight in overweight adult populations.[8] Interestingly, although dBP and sBP both increased during the study, as is common with weight regain in AN,[1] cfPWV decreased at the same time, and there were no associations between sBP or dBP and cfPWV.

Potential mechanisms for changes in PWV in this context remain to be established, including the observed paradoxical changes in blood pressure over time juxtaposed alongside changes in PWV. There is conflicting evidence on autonomic changes in AN,[9] and although the balance of evidence is consistent with a reduction in sympathetic tone, there is a paucity of studies of vascular in tone in arteries in AN, particularly in central vessels. A common observation in underweight patients with AN is peripheral poor perfusion, appearing as acrocyanosis,[1] suggestive of vasoconstriction at least in some territories; and furthermore these findings appear to recover with weight gain. There is evidence that increased vascular tone increases PWV in other populations,[10] and we speculate that large arterial vasoconstriction may contribute to the increase in PWV in AN, but this hypothesis requires further study to investigate.

Our study is limited by a necessarily small sample size, only female participants, and its unavoidable unblinded and non-randomized methodology. We did not study a healthy

control group for comparison but as stated we were able to compare our baseline distribution of PWV to published normative data in healthy populations,[7] which also demonstrate a gradual increase in PWV with age, (and thus over time) as evidenced by centile distribution, rather than a decrease in PWV as was seen in our sample. Most of the participants were (throughout the study) on antipsychotic medications which are known to have an adverse CVS profile.[11] Our participants were also particularly unwell adolescents with AN and are not necessarily generalisable to all patients with AN. Of importance, our methodology was well tolerated and recruitment unproblematic, which should facilitate future studies of cardiovascular health in adolescents with AN.

In conclusion, we report a fall in cfPWV with refeeding and weight gain in a group of underweight adolescents with AN. Further studies are required to establish if these changes may be favourable for longer term cardiovascular health in young people with AN, however our findings support a continued emphasis for the importance of weight gain in the management of underweight young women with AN.

Data availability statement: Additional data are available from the corresponding author on request

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Figure legend (single figure: Figure 1): Figure 1. Panels A to D: Graphs of changes in participants' cfPWV (panel A), BMI (Panel B), sBP (Panel C) and dBP (Panel D) over time (in weeks) with linear mixed effects models with 95% prediction overlaid. **Panel E**: Table showing linear mixed-effects models for change in cfPWV, BMI, daily meal plan content, sBP and dBP over time. **Panel F**: as well as linear mixed-effects models of individual repeated measures of BMI, BP and daily meal plan as predictors of cfPWV.

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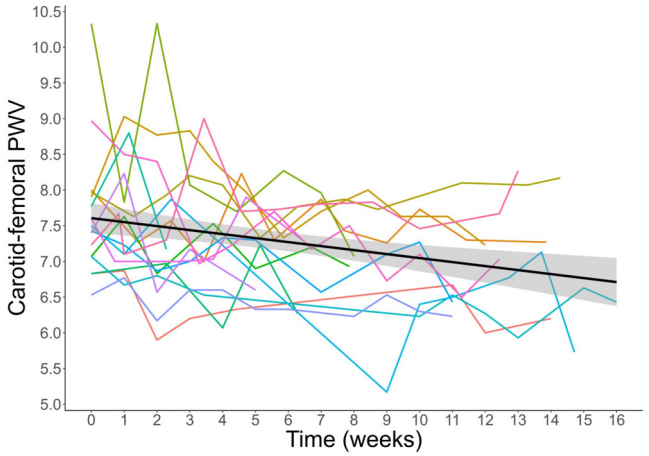
Ethical Approval: We received research ethics approval from a London health research ethics committee.

Competing Interests: None to declare

A



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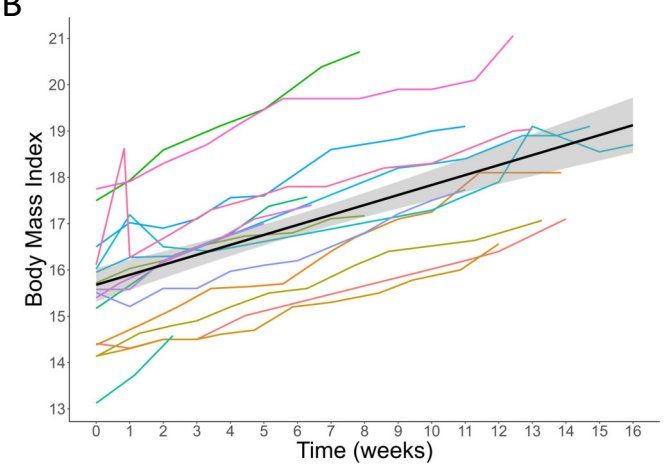

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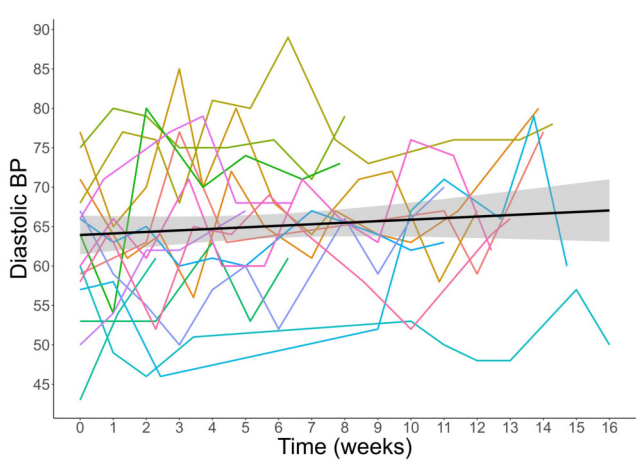

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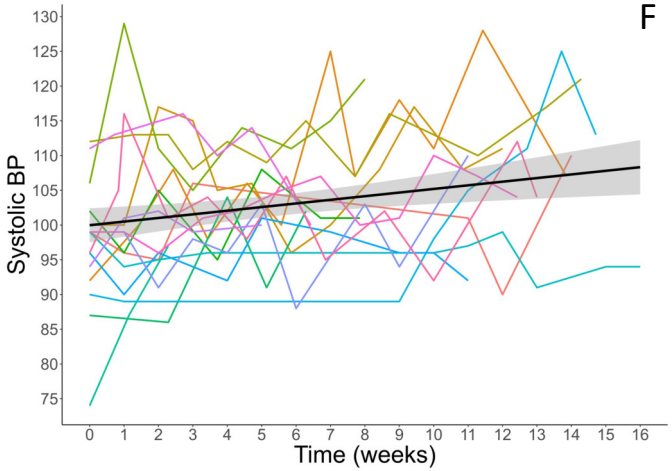

E

Linear mixed effects univariable models of changes in repeated measure variables over time of the study (in weeks)

	Coefficient	95% Confidence Interval Beta	% change over 12 weeks	*p*-value	Intraclass Correlation Coefficient
Pulse Wave Velocity (ms^{-1})	-0.05*	-0.07 to -0.03	- 8.0	<0.001	0.56
Body Mass Index (Kgm^{-2})	0.23*	0.22 to 0.25	+ 17.8	<0.001	0.92
Systolic Blood Pressure (mmHg)	0.61*	0.36 to 0.87	+7.5	<0.001	0.50
Diastolic Blood Pressure (mmHg)	0.32*	0.06 to 0.58	+6.1	0.02	0.51
Meal plan calorific content (Kcal)	38.7	28.7 to 48.7	+ 25	<0.001	0.26

F

Linear mixed effects models for repeated measured variables as predictors of Carotid-Femoral Pulse Wave Velocity (ms^{-1})

	Coefficient	95% Confidence Interval	*p*-value	Intraclass Correlation Coefficient
Body Mass Index (Kgm^{-2})	-0.20 *	-0.28 to -0.12	<0.001	0.57
Meal plan calorific content (Kcal)	- 5.1 x 10^{-3} *	- 8.1 x 10^{-3} to -2.2 x 10^{-3}	<0.001	0.56
Systolic Blood Pressure (mmHg)	-0.01	-0.01 to 0.01	0.89	0.41
Diastolic Blood Pressure (mmHg)	-0.00	-0.01 to 0.01	0.88	0.42