BMJ Open Sport & Exercise Medicine

Cardiovascular effects of exercise training in pregnant people with a high body mass index: secondary results from a randomised controlled trial (ETIP)

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To cite: Moholdt T, Garnæs KK, Vik IP, *et al*. Cardiovascular effects of exercise training in pregnant people with a high body mass index: secondary results from a randomised controlled trial (ETIP). *BMJ Open Sport & Exercise Medicine* 2024;**10**:e002099. doi:10.1136/bmjsem-2024-002099

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjsem-2024-002099).

Accepted 15 October 2024

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ABSTRACT

Objectives We aimed to determine the effectiveness of exercise training during pregnancy on peak oxygen uptake ($\dot{V}O_2$peak), cardiac function and flow-mediated dilatation (FMD) of the brachial artery throughout pregnancy and post partum in individuals with a prepregnancy body mass index (BMI) ≥28 kg/m^2.

Trial design Parallel-group randomised controlled trial (RCT).

Methods The exercise group in the Exercise Training in Pregnancy (ETIP) RCT was offered 3 weekly supervised exercise sessions comprising 35 min of moderate-intensity treadmill walking followed by 25 min of strength exercises. The intervention started in gestational weeks 12–18 and continued throughout pregnancy. We measured $\dot{V}O_2$peak and FMD at baseline, in gestational weeks 34–37 and 3 months post partum and offered echocardiography in gestational weeks 14, 20, and 32, and 6–8 weeks postpartum.

Results Of the 91 participants included in ETIP, 87 participants (age: 31.3±4.2 years, BMI: 34.6±4.3 kg/m^2) provided data on $\dot{V}O_2$peak, cardiac function and/or FMD. There was no statistically significant effect of exercise training on $\dot{V}O_2$peak in gestational weeks 34–37, with an estimated effect of 1.7 mL/min/kg (95% CI −0.4 to 3.7, p=0.112) or post partum (1.6 mL/min/kg, 95% CI −0.2 to 3.4, p=0.079), compared with the control group. There were no statistically significant between-group differences in either FMD or any of the echocardiographic outcomes. Only 50% of the participants in the exercise group fulfilled our prespecified adherence criteria.

Conclusion Offering pregnant individuals with BMI ≥28 kg/m^2, a supervised exercise intervention did not improve cardiorespiratory fitness, cardiac function or FMD.

Trial registration number NCT01243554.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exercise training reduces the risk of cardiovascular diseases in non-pregnant individuals, through exercise-induced improvements in cardiorespiratory fitness, cardiac function and vascular function. The effect of exercise on these measures in pregnant individuals has been less studied.

WHAT THIS STUDY ADDS

⇒ In this randomised controlled trial involving pregnant individuals with overweight/obesity, we demonstrated that regular exercise had little effect on peak oxygen uptake, cardiac function or endothelial function.

⇒ Our study showed that it was difficult for the participants to adhere to regular exercise during pregnancy.

⇒ The cardiorespiratory fitness level was low among our participants, and we uncovered signs of reduced systolic and diastolic function in gestational week 32 and post partum.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The combination of low cardiorespiratory fitness and high burden on the cardiovascular system during pregnancy necessitates preventive strategies for pregnant individuals with overweight/obesity.

⇒ It is important to find strategies to improve adherence to exercise in this population.

INTRODUCTION

Pregnancy is characterised by profound haemodynamic adaptations of the maternal cardiovascular system, including changes in cardiac output, blood volume, systemic blood pressure and systemic vascular resistance.[1] In some instances, the cardiovascular system maladapts, leading to hypertensive disorders of pregnancy. Higher body mass index (BMI) during pregnancy is associated with increased risk of cardiovascular maladaptation,[2] other pregnancy complications,[3] and cardiovascular disease (CVD) morbidity and mortality.[4] A systematic review of observational studies with almost 29 million participants demonstrated that individuals with a broad spectrum of pregnancy complications are at increased

risk of future CVD.[5] As such, pregnancy is a critical period for CVD prevention.

Exercise training is a first-line therapy that reduces CVD risk by beneficial effects on cardiorespiratory fitness, cardiac function and vascular outcomes such as endothelial-dependent dilatation.[6] Exercise-induced cardioprotective effects are mediated by multiple mechanisms, with the greatest benefits attributed to improvements in cardiorespiratory fitness.[6] A systematic review and meta-analysis from 2020 concluded that exercise interventions in pregnancy have a significant and clinically meaningful effect on maximal oxygen uptake ($\dot{V}O_2$max), which is the gold-standard measurement of cardiorespiratory fitness.[7] However, all but one study included in the meta-analysis used protocols that predicted rather than measured $\dot{V}O_2$max. In addition to improving fitness, aerobic exercise training and concurrent aerobic and resistance training increase endothelial function measured as flow-mediated dilatation (FMD) of the brachial artery in non-pregnant individuals with overweight or obesity and in those with type 2 diabetes.[8 9] We have only found two randomised controlled trials (RCTs) investigating the effects of exercise training on FMD in pregnant individuals.[10 11] One study found that FMD increased after exercise training,[11] whereas the other reported no difference in FMD.[10] None of these prior studies focused on participants with high BMI.

Obesity in pregnancy is associated with increased left ventricular (LV) mass, diastolic dysfunction and impaired maternal haemodynamic adaptations.[12] In non-pregnant individuals, aerobic exercise training induces cardiac adaptations, including improvement in diastolic LV function and increased stroke volume (SV). However, studies on the effect of exercise training during pregnancy show unclear effects on maternal cardiac outcomes.[13 14] No prior RCT has determined the effect of exercise training on echocardiographic outcomes in pregnant individuals with obesity. The Exercise Training in Pregnancy (ETIP) trial was an RCT that investigated exercise training during pregnancy for individuals with BMI of ≥28 kg/m^2. The intervention had no effect on gestational weight gain (primary outcome) but reduced the incidence of gestational diabetes, lowered systolic blood pressure in late pregnancy and decreased circulating insulin concentrations 3 months post partum.[15 16] This is a secondary analysis of data from the ETIP trial on cardiovascular outcomes, including $\dot{V}O_2$peak and other exercise testing-related outcomes, cardiac function and FMD of the brachial artery throughout pregnancy and post partum. We hypothesised that exercise training would improve these cardiovascular measurements, compared with the control group.

METHODS

Trial design, randomisation and blinding

ETIP was a single-centre, parallel-group RCT, in which participants were randomly allocated (1:1) to an exercise intervention group or control group. Results have been published previously.[15–20] Details about the method used to generate the random allocation sequence and on blocking are also reported in the main manuscript from the trial.[15] Analyses of echocardiography recordings and FMD data were undertaken by personnel blinded for group allocation. The researchers who measured $\dot{V}O_2$peak were not blinded for group allocation.

Participants

We included pregnant individuals who were ≥18 years, with a self-reported prepregnancy BMI ≥28 kg/m^2, in gestational weeks 12–18, carrying a singleton live fetus. The participants had to live in the Trondheim area and be able to attend assessments and supervised exercise sessions at St. Olavs Hospital. We did not include individuals with a high risk of preterm birth, diseases that could interfere with participation and those who reported exercising twice weekly or more in the period before inclusion. We made some changes to the eligibility criteria after trial commencement, as previously described.[15] The participants signed written informed consents and could withdraw from the trial at any time without giving a reason. In secondary analyses included in this paper, we included participants with data from at least one exercise test, endothelial function assessment and/or echocardiography.

Intervention

Participants in both groups received standard maternity and postpartum care, free of charge. The participants in the exercise group were offered 3 weekly supervised exercise sessions from inclusion in the study until delivery. The exercise programme was designed in accordance with the recommendations for exercise in pregnancy from the American College of Obstetricians and Gynaecologists.[21] A detailed description of the exercise programme has been published previously.[15 22] The exercise sessions consisted of 35 min of moderate-intensity treadmill walking, followed by 25 min of strength exercises. The intensity during the aerobic part was set at approximately 80% of maximal aerobic capacity, corresponding to perceived exertion of 12–15 on the 6–20 Borg scale.[23] Additionally, the participants were encouraged to exercise at home at least once weekly, using the same programme as at the supervised sessions. We registered adherence to the exercise intervention in a training diary. Our prespecified criteria for adherence, and thus inclusion in per-protocol analyses for the trial, were either ≥42 supervised exercise sessions, ≥28 supervised exercise sessions +≥28 home-based exercise sessions or ≥60 home-based exercise sessions.[22] All participants in the trial received a booklet about healthy diet and physical activity during pregnancy. We did not discourage participants in the control group from physical activity or exercise training.

Outcomes

Peak oxygen uptake and other exercise test outcomes

At baseline (in gestational weeks 12–18), in late pregnancy (gestational weeks 34–37) and 3 months post partum, the participants completed a multistage exercise test with measurements of expired gases (Oxycon Pro, Jaeger, Germany). We measured heart rate using heart rate monitors (Polar, Finland) throughout the test. A standard test began with 2–3 min warm-up, followed by walking at 4.5 km/hour at 0% inclination for 4 min. The inclination was elevated 3% at each of the following 4 min stages until the participant reported to be exhausted, the heart rate exceeded 185 beats/min or if systolic and diastolic blood pressure exceeded 200 and 100 mm Hg, respectively. For some participants, we had to modify the test protocol as they were unable to walk at 4.5 km/hour. Between stages, the participants stood on the sides of the treadmill for measurements of blood pressure and lactate (using finger-pricks). The participants also reported their subjective ratings of perceived exertion after each stage on the Borg 6–20 scale.[23] Here, we report the lactate concentrations and perceived exertion at the end of the exercise test. We calculated peak oxygen uptake ($\dot{V}O_2$peak) as the highest consecutive 30 s measured and report absolute (L/min) and relative values (mL/kg/min). The highest heart rate recorded during the test is an estimate of heart rate maximum.[24] As an estimate of SV response to exercise, we calculated the peak oxygen pulse (O_2 pulse) by dividing absolute $\dot{V}O_2$peak by heart rate maximum and report this as mL/beat.[25]

Cardiac function

An echocardiogram specialist (CBI) measured maternal cardiac function in a subset of participants (n=53), all with prepregnancy BMI ≥30 kg/m^2, in gestational weeks 14, 20, and 32, and 6–8 weeks post partum. At these time points, we performed a standardised resting echocardiography.[26] For these measurements, we used a Vivid E9 scanner (GE Vingmed Ultrasound, Norway) with a phased-array transducer. Three cine loops from the parasternal view and three standard apical planes (four-chamber, two-chamber and long-axis) were simultaneously recorded in B-mode and tissue Doppler mode. We obtained conventional Doppler flow parameters and tissue Doppler imaging with pulsed tissue Doppler in the atrioventricular plan (a mean of septal, lateral, inferior and anterior tissue Doppler velocities). Global longitudinal strain and strain rate were performed using a speckle tracking method for left and right ventricle (free wall).[27] We used a customised postprocessing system (GcMat, GE Vingmed, Norway) for automated identification of myocardial segments and analysis.

FMD of the brachial artery

We measured endothelial function (FMD) in a subset of participants (n=36), at baseline, in gestational weeks 34–37 and 3 months post partum. Participants had fasted overnight, abstained from exercise for >24 hours, and from caffeine and smoking for >10 hours. They rested for 10 min before the measurements. We used a Vivid 7 scanner (GE Vingmed Ultrasound, Norway) with a 12 MHz Doppler probe. One operator (KKG) obtained all the ultrasound recordings. The ultrasound probe was placed on the upper arm, perpendicular to the brachial artery. We obtained continuous recordings of the baseline diameter of the brachial artery for 1 min before inflating a pneumatic cuff (300 mm Hg) for 5 min. We recorded the brachial artery diameter for 3 min after deflation of the cuff. We did not include shear rate data in these measurements since we experienced technical difficulties with saving the Doppler velocity assessments. We used an automated edge-detection and wall-tracking software (Brachial Analyzer V.5.9.0, Medical Imaging Application, USA) for diameter analysis. We report average baseline brachial artery diameter (before cuff inflation), peak postocclusion diameter, absolute FMD (in mm) and the percentage change in brachial artery diameter from baseline to peak diameter induced by reactive hyperaemia (FMD%). FMD% was calculated as (peak postocclusion diameter minus baseline diameter)/baseline diameter×100.

Statistical analysis

We calculated the sample size for the ETIP trial based on the trial's primary outcome: gestational weight gain from baseline to delivery.[22] In this calculation, we used a 6 kg difference in weight as a clinically relevant difference, a 5% level of significance and 90% statistical power. For an independent samples t-test, we would need 59 participants in each group. With an estimated drop-out rate of 15%, we aimed to include at least 150 participants. We have not conducted a separate power calculation for the outcomes included in this paper as they were secondary outcomes in the trial.

We have analysed all obtained data irrespective of adherence to the intervention and completeness of outcome measures. To determine the effect of the intervention on the outcomes, we have used linear mixed models that included time and group×time interactions at each time point as fixed effect variables and subject (participant ID) as a random factor, as recommended by Twisk *et al*.[28] We expected no systematic differences between groups at baseline due to the randomised design. We report the estimated effect of exercise compared with the control group with corresponding 95% CIs and p values. To assess the distribution of data, we visually inspected Q-Q plots for the residuals of each outcome measure and performed bootstrapping with 3000 samples and bias-corrected and accelerated CIs in cases of non-normal model residuals. We report the effect of time as the estimated effect in the control group over time. Due to the multiple outcome measures, we considered p values <0.01 as statistically significant. We used IBM SPSS Statistics V.29.0.1.0 for all statistical analyses.

Patient and public involvement

The participants were not involved in the study design, conduct or dissemination of study outcomes.

Table 1 Baseline characteristics for the participants, according to group

	Control (n=43)	Exercise (n=44)
Age, years	31.3 (4.7)	31.4 (3.7)
Weight, kg	98.7 (14.1)	95.5 (13.1)
Body mass index, kg/m^2	35.2 (4.6)	34.0 (3.8)
Systolic blood pressure, mm Hg	124.2 (10.4)	124.4 (14.7)
Diastolic blood pressure, mm Hg	75.9 (8.0)	75.9 (9.1)
Current smoking, number (%)	5 (12%)	4 (9%)

Data are for participants from the Exercise Training in Pregnancy trial who had at least one measurement of peak oxygen uptake, endothelial function and/or echocardiology variables, as average with SD if not otherwise indicated.

RESULTS

Participants and adherence

Recruitment and follow-up were undertaken between September 2010 and March 2015. Table 1 shows the baseline characteristics of the participants. We terminated the trial when we had included 91 participants due to difficulties with recruitment within the project period. Of the 91 participants originally to the control and exercise groups, 87 had data on $\dot{V}O_2$peak, cardiac function and/or endothelial function from at least one time point (figure 1). Only 50% of the participants in the exercise group fulfilled the prespecified adherence criteria. The heart rate during the endurance exercise training was 150 beats/min (SD 13), corresponding to 85% (SD 8) of their heart rate maximum at the initial exercise test. Their rating of perceived exertion was 14.8 (SD 1.2) on the 6–20 Borg scale. There were no adverse events reported during the exercise training or study assessments.

Peak oxygen uptake and other exercise test outcomes

Of the 91 participants originally allocated to the control and exercise groups, 79 participants completed the exercise testing at baseline (figure 1). Four participants in the control group and two in the exercise group were unable to undertake the exercise testing at baseline. In late pregnancy, 19 participants in the control group and 15 participants in the exercise group were unable to undertake exercise testing due to bodily problems (figure 1). The most common reason was pelvic or low-back pain.

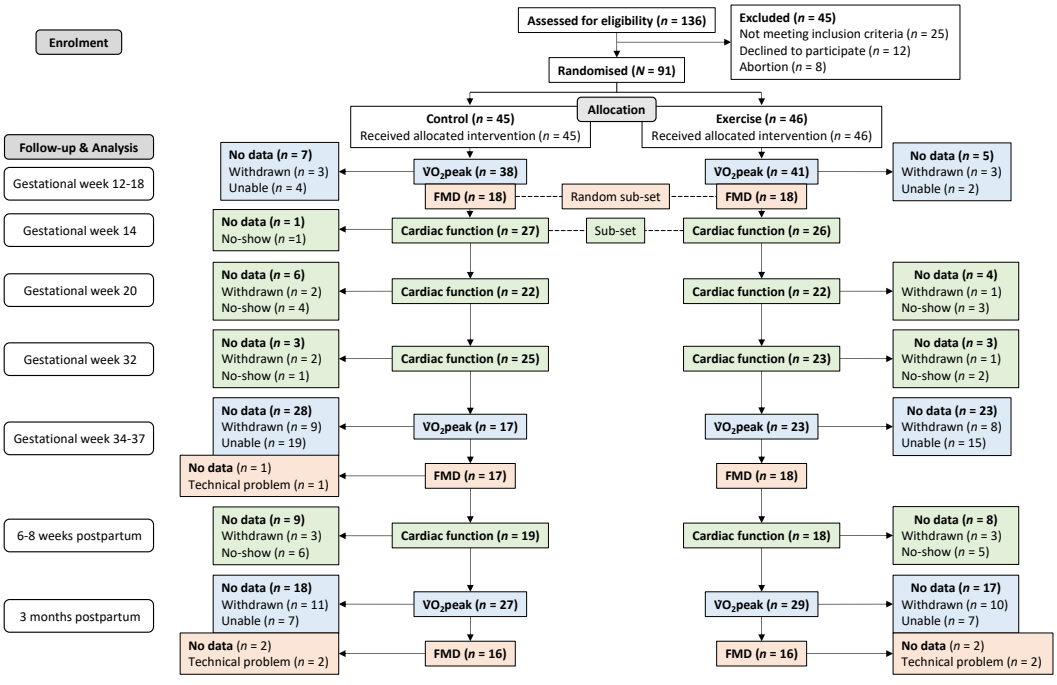

Figure 1 Flow chart of participants included in the analyses. The number of participants who was included in each assessment throughout pregnancy and postpartum. The number of withdrawn participants at each time point is accumulated. The subset of participants included in the cardiac function assessments consisted of those with body mass index ≥30 kg/m^2 who were included in the trial before gestational week 14. FMD, flow-mediated dilatation; $\dot{V}O_2$peak, peak oxygen uptake.

In early pregnancy, three participants in each group had to terminate the test before fatigue due to bodily problems other than exhaustion. Corresponding numbers in late pregnancy were three in the control group and four in the exercise group. We also had to modify the speed in the tests for some participants as they were unable to keep 4.5 km/hour.

There were no statistically significant between-group differences in $\dot{V}O_2$peak, body weight, heart rate maximum, heart rate recovery, O_2 pulse, lactate concentrations at the end of the test or rate of perceived exertion (table 2). Relative $\dot{V}O_2$peak declined by 4.9 mL/kg/min (95% CI 3.3 to 6.6) in late pregnancy, compared with early pregnancy (significant effect of time in the control group, p<0.001) (online supplemental table 1), with an estimated 1.7 mL/kg/min (95% CI −04 to 3.7) lower decline in the exercise group (p=0.112, figure 2). Three months post partum, relative $\dot{V}O_2$peak was not statistically different than in early pregnancy (estimated effect of time in the control group: 1.1 mL/kg/min, 95% CI −0.2 to 2.5, p=0.091) (online supplemental table 1). Post partum, the change in the exercise group was 1.6 mL/kg/min (95% CI −0.4 to 3.7) greater than in the control group (p=0.079). Absolute $\dot{V}O_2$peak declined from early to late pregnancy in the control group (estimated difference −0.3 L/min, 95% CI −0.4 to −0.1, p=0.002) (online supplemental table 1), with no between-group differences (table 2). There were no statistically significant effects of time on body weight, heart rate maximum, heart rate recovery, O_2 pulse, lactate concentrations at the end of the test or rate of perceived exertion (online supplemental table 1).

Cardiac function

The exercise intervention had no statistically significant effects on any of the echocardiographic variables (table 3), but some of the variables changed with progressing pregnancy and/or post partum (figure 3). The following results refer to the effect of time in the control group and should be interpreted as estimated changes that occurred over time in both groups, as there were no statistically significant between-group differences. Online supplemental table 2 shows the estimated main effect of time. Resting heart rate increased significantly in gestational week 32, compared with gestational week 14 (estimated effect 7.3 beats/min, 95% CI 3.1 to 11.5, p<0.001). At the same time point, SV index (SVI), which is SV corrected for body surface area, declined significantly, with an estimated difference of −4.1 mL/m^2 (95% CI −7.3 to −1.0, p=0.009). There was also a tendency of reduced SV at 32 weeks gestation, compared with at 14 weeks (−8.4 mL, 95% CI −15.0 to −1.8, p=0.013). There were also other signs of reduced systolic and diastolic function in gestational week 32, including reduced left ventricular outflow tract velocity time integral (LVOT VTI, estimated effect, −3.4 cm, 95% CI −4.9 to −1.8, p<0.001), reduced early diastolic velocity (E wave) at the mitral valve (E, estimated effect, −0.1 m/s, 95% CI −0.1 to −0.02, p=0.008) and reduced septal and lateral early mitral inflow tissue velocity (e', estimated effect, −1.5 cm/s, 95% CI −2.5 to −0.5, p=0.004). Postpartum, peak systolic tissue velocity (S') declined significantly, compared with gestational week 14, with an estimated effect of time of −1.0 cm/s (95% CI −1.6 to −0.4, p=0.003). Additionally, there was a tendency of reduced e' also post partum (estimated effect, −1.2 cm/s, 95% CI −2.3 to −0.1, p=0.040).

Endothelial function

There were no significant between-group differences in any of the endothelial function variables in late pregnancy or post partum (table 2). Basal brachial artery diameter increased by 0.3 mm (95% CI 0.1 to 0.5) in late pregnancy, compared with early pregnancy (significant effect of time in the control group, p<0.001), and did not differ significantly from early-pregnancy levels 3 months post partum (estimated difference 0.1 mm, 95% CI −0.1 to 0.3, p=0.258) (online supplemental table 1). Peak post-hyperaemia diameter increased from early to late pregnancy (estimated difference 0.3 mm, 95% CI 0.1 to 0.5, p=0.002). There was no statistically significant effect of time for absolute FMD or FMD% (online supplemental table 1).

DISCUSSION

We observed no statistically significant effects of an exercise intervention on $\dot{V}O_2$peak, cardiac function, or FMD in pregnant individuals with BMI ≥28 kg/m^2. These findings may be explained by the low adherence to the exercise programme. There were effects of time for several outcome measures, indicating that progressing pregnancy affected these outcome measures in both the exercise and control groups. Cardiorespiratory fitness, both relative to body mass and absolute, declined between early and late pregnancy, whereas brachial artery diameter, both basal and post-hyperaemia, increased in this interval. In gestational week 32, there were several indications of reduced LV systolic and diastolic function, as a sign of a large load on the cardiovascular system.

The estimated effect of the exercise intervention on $\dot{V}O_2$peak in our trial was 1.7 mL/kg/min in late pregnancy (gestational weeks 34–37). This increase is below what is observed in some other trials. A meta-analysis of exercise intervention RCTs with assessments of cardiorespiratory fitness ($\dot{V}O_2$max, submaximal $\dot{V}O_2$ or $\dot{V}O_2$ at anaerobic threshold) concluded that exercise interventions in pregnancy increased maternal predicted/measured $\dot{V}O_2$max (mean difference 2.77 mL/kg/min, 95% CI 0.32 to 5.21), compared with a no-exercise control group.[7] The main reasons for the non-significant between-group difference in our study can be the low adherence to the exercise programme and low statistical power due to the low number of participants who were able to complete the exercise testing in late pregnancy.

There are relatively few prior RCTs that have investigated the effect of exercise interventions on cardiorespiratory fitness in pregnant individuals with overweight/

Table 2 Exercise testing and endothelial function outcomes

Exercise testing												
	Control (n=38)			Exercise (n=41)			Between-group difference in late pregnancy (GW 34–37)			Between-group difference 3 months post partum		
Outcome	Early pregnancy	Late pregnancy	Post partum	Early pregnancy	Late pregnancy	Post partum	Est. effect	95% CI	P value	Est. effect	95% CI	P value
Weight, kg	98.2 (14.6)	106.4 (15.8)	97.2 (16.9)	95.9 (13.1)	102.7 (13.4)	94.2 (13.0)	0.3	−2.2 to 2.7	0.827	1.4	−1.1 to 3.9	0.271
$\dot{V}O_2$peak, L/min	2.4 (0.4)	2.1 (0.6)	2.5 (0.5)	2.3 (0.4)	2.2 (0.4)	2.6 (0.6)	0.1	−0.1 to 0.3	0.243	0.2	−0.02 to 0.3	0.090
$\dot{V}O_2$peak, mL/kg/min	24.7 (4.4)	20.7 (5.7)	26.2 (4.6)	24.3 (3.8)	22.0 (4.6)	27.7 (3.8)	1.7	−0.4 to 3.7	0.112	1.6	−0.2 to 3.4	0.079
HR max, beats/min	169 (13)	165 (14)	174 (20)	173 (14)	165 (17)	180 (13)	-3	−11 to 5	0.491	3	−4 to 11	0.353
HR recovery, beats	34 (25)	36 (11)	36 (11)	30 (11)	29 (12)	34 (13)	-6	−14 to 3	0.183	0	−7 to 7	0.996
O_2 pulse, mL/beat	14.1 (2.3)	13.1 (3.0)	14.5 (2.5)	13.6 (2.2)	13.6 (2.2)	14.6 (2.3)	0.8	−0.3 to 1.9	0.138	0.9	0.03 to 1.9	0.043
Lactate, mmol/L	4.4 (2.0)	4.0 (2.2)	5.2 (2.5)	4.3 (1.8)	3.9 (2.5)	6.4 (2.5)	−0.3	−1.6 to 1.1	0.698	1.1	−0.0 to 2.3	0.057
RPE, Borg 6–20 scale	17.4 (1.3)	17.6 (1.6)	18.4 (1.0)	17.4 (1.4)	17.3 (1.9)	18.5 (1.0)	−0.5	−1.2 to 0.3	0.250	0.1	−0.6 to 0.7	0.871
Endothelial function												
	Control (n=18)			Exercise (n=18)			Between-group difference, late pregnancy (GW 34–37)			Between-group difference, 3 months postpartum		
	Early pregnancy	Late pregnancy	Post partum	Early pregnancy	Late pregnancy	Post partum	Est. effect	95% CI	P value	Est. effect	95% CI	P value
Basal brachial artery diameter, mm	3.3 (0.3)	3.6 (0.3)	3.4 (0.4)	3.3 (0.4)	3.6 (0.4)	3.3 (0.6)	0.03	−0.2 to 0.3	0.774	−0.07	−0.3 to 0.2	0.553
Peak posthyperaemia diameter, mm	3.6 (0.3)	3.9 (0.3)	3.6 (0.5)	3.6 (0.4)	3.9 (0.4)	3.5 (0.6)	0.03	−0.2 to 0.3	0.796	−0.17	−0.5 to 0.1	0.254
Absolute FMD, mm	0.3 (0.2)	0.3 (0.2)	0.2 (0.2)	0.3 (0.2)	0.3 (0.1)	0.2 (0.1)	−0.01	−0.1 to 0.1	0.901	−0.06	−0.2 to 0.1	0.360
FMD, %	8.4 (5.7)	8.4 (4.9)	6.7 (6.2)	8.6 (5.5)	7.9 (3.2)	5.4 (3.2)	−0.49	−3.8 to 2.8	0.768	−1.34	−5.1 to 2.5	0.486

Observed data at baseline (early pregnancy), in late pregnancy, and 3 months post partum in each group, presented as descriptive mean with SD. The between-group difference (group×time) is the mean change in the exercise intervention group with estimated effect, corresponding 95% CI and p values compared with the control group by linear mixed-model analyses.
Missing data for 26 participants in the control group and 23 participants in the exercise group in late pregnancy, for 18 participants in the control group and 16 participants in the exercise group post partum for exercise testing data. Missing data for one participant in the control group in late pregnancy for endothelial function in late pregnancy, for two participants in each group postpartum, and additionally, three participants in each group with missing data on some of the endothelial function outcomes post partum.
FMD, flow-mediated dilatation; GW, gestational week; HR max, heart rate maximum; O_2 pulse, absolute peak oxygen uptake ($\dot{V}O_2$peak, L/min) divided by heart rate maximum; HR recovery, heart rate at the end of the exercise test minus heart rate 1 min later; RPE, rating of perceived exertion on the 6–20 Borg scale; $\dot{V}O_2$peak, peak oxygen uptake.

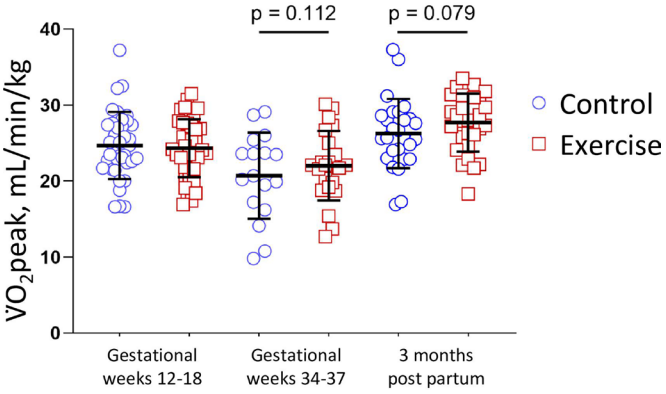

Figure 2 Peak oxygen uptake ($\dot{V}O_2$peak) at baseline (gestational weeks 12–18), in gestational weeks 34–37 and 3 months post partum, according to group. Data are observed values, with each symbol representing one participants and bars representing average and SD. P values for between-group comparisons using linear mixed model. $\dot{V}O_2$peak, peak oxygen uptake.

obesity.[29–31] Consistent with our findings, an RCT from New Zealand showed no improvement in (submaximal) $\dot{V}O_2$peak after a moderate-intensity exercise intervention comprising 67 prescribed sessions of stationary bike cycling.[31] However, in the LiP (Lifestyle in Pregnancy) study from Denmark, the lifestyle intervention marginally increased fitness, compared with the control group.[30] Santos *et al*[29] reported significantly increased $\dot{V}O_2$ at the anaerobic threshold (+2.68 mL/kg/min) after a 12-week supervised exercise intervention similar to the one in our study among pregnant individuals with prepregnancy BMI 25–30 kg/m^2. As in the ETIP study, the adherence rates in the mentioned prior RCTs were low.[29–31] How to encourage pregnant individuals to participate in exercise training remains a challenge. Since prepregnancy physical activity is an important determinant of physical activity during pregnancy, we argue that lifestyle interventions should be initiated before pregnancy in individuals at risk of adverse pregnancy outcomes to improve maternal and offspring health.[32] This is why we have initiated the BEFORE THE BEGINNING trial, in which we will determine the effects of a preconception lifestyle intervention on maternal and offspring cardiovascular and metabolic health.[33]

The cardiovascular system adapts to the metabolic needs of the mother and fetus during pregnancy. Pregnancy induces peripheral vasodilation, which normally leads to a 25%–30% fall in systemic vascular resistance,[34] and to compensate for this, cardiac output increases up to 50% during pregnancy.[35] The increased cardiac output in pregnancy is achieved via an increase in both SV and heart rate.[35] However, in our participants with obesity, we found an increase in heart rate during pregnancy, but tendencies of reduced systolic function, including reduced SVI and LVOT VTI. We also observed a reduction in diastolic function (e') in gestational week 32, which is in line with previous findings.[36 37] These characteristics may render pregnant individuals with obesity more susceptible to develop hypertensive disorders of pregnancy and help explain the high prevalence of such disorders in this population.[38] Reduced systolic function has also been reported during normal pregnancy in healthy (lean) people.[39] Thus far, few studies have compared changes in cardiac function in pregnancy in those with obesity versus healthy weight. Two studies have described cardiac maladaptations in pregnant people with obesity, with significant LV hypertrophy and diastolic dysfunction and impaired deformation (strain and strain rate), compared with lean pregnant individuals.[36 40] Haemodynamic resolution normally occurs post partum.[35] However, we observed a tendency of diastolic dysfunction (reduced e') still evident 6–8 weeks post partum. Others have also reported an increased risk of persistent subclinical myocardial dysfunction in pregnant individuals 6–10 weeks post partum.[40] Since both obesity and diastolic dysfunction increase the risk of heart failure with preserved ejection fraction, these individuals should be followed up also postpartum to prevent CVD.

We found no improvement in FMD after ETIP. This finding is in line with one previous study,[10] but in contrast to another.[11] In both previous studies, the researchers included participants without any criterion for prepregnancy BMI. We observed no indication of increased FMD from early to late pregnancy, but significantly greater basal brachial artery diameter in late pregnancy. Previous research indicates that both FMD and basal brachial artery diameter increase throughout a healthy pregnancy.[41] Our results indicate that individuals with obesity have a maladaptive vascular response to pregnancy, which is consistent with previous findings.[42]

Strengths and limitations of the study

A strength of this RCT is the comprehensive assessments of cardiorespiratory fitness, cardiac function and endothelial function throughout pregnancy and post partum in individuals with overweight/obesity. Our study adds evidence to the scarce knowledge about how exercise training may impact cardiac function throughout pregnancy and post partum. Few previous studies have investigated the effect of exercise training on cardiorespiratory fitness among pregnant individuals with overweight/obesity. There are some limitations of our study. We were unable to undertake the exercise testing blinded for group allocation. The tests at baseline were conducted before allocation to group, but the researchers who undertook the tests in late pregnancy could have been influenced by their knowledge of the participant's group allocation. Another limitation is the large number of participants who were unable to complete the exercise testing, particularly in late pregnancy. Additionally, we were unable to include shear rate data in the endothelial function measurements due to technical difficulties. Furthermore, the findings reported here are secondary outcomes for which we did not calculate statistical power for the analyses.

Table 3 Echocardiographic outcomes

	Control (n=28)				Exercise (n=26)				Between-group difference, GW 20			Between-group difference, GW 32			Between-group difference, 6–8 weeks post partum		
Outcome	GW 14	GW 20	GW 32	6–8 PP	GW 14	GW 20	GW 32	6–8 PP	Est. effect	95% CI	P value	Est. effect	95% CI	P value	Est. effect	95% CI	P value
Heart rate, beats/min	76 (11)	75 (10)	84 (11)	68 (11)	76 (14)	76 (12)	86 (12)	68 (11)	−0.8	−6.7 to 5.1	0.790	1.9	−3.8 to 7.5	0.512	−3.9	−10.2 to 2.4	0.226
Left ventricle																	
EF, %	53.7 (6.8)	57.9 (8.3)	55.6 (10.6)	54.4 (8.8)	60.4 (7.8)	54.1 (9.8)	57.2 (10.3)	54.9 (7.5)	−5.1	−10.3 to 0.1	0.057	0.1	−4.9 to 5.2	0.959	−0.2	−5.9 to 5.4	0.935
EDV, mL	113 (26)	118 (32)	119 (35)	125 (28)	109 (29)	112 (31)	110 (39)	123 (34)	−5.3	−23.2 to 12.7	0.563	−7.0	−24.3 to 10.2	0.423	2.5	−17.0 to 22.0	0.800
EDVi, mL/m^2	53.0 (12.4)	54.5 (14.3)	55.3 (15.5)	58.2 (13.7)	51.7 (12.0)	54.4 (15.4)	53.2 (18.1)	59.8 (15.5)	0.0	−8.9 to 8.0	0.918	−1.9	−10.0 to 6.2	0.641	2.6	−6.5 to 11.8	0.573
ESV, mL	52.4 (12.7)	49.6 (16.4)	51.4 (16.7)	56.4 (15.7)	42.9 (12.9)	51.3 (18.7)	45.8 (15.1)	54.8 (16.2)	3.9	−5.2 to 12.9	0.399	−3.2	−11.9 to 5.5	0.466	1.1	−8.7 to 10.9	0.821
LVOT Vmax, m/sec	1.3 (0.1)	1.3 (0.1)	1.2 (0.2)	1.2 (0.1)	1.3 (0.1)	1.3 (0.2)	1.2 (0.2)	1.2 (0.2)	0.0	−0.1 to 0.03	0.243	0.0	−0.1 to 0.1	0.640	−0.1	−0.1 to 0.03	0.198
LVOT VTI, cm	28.5 (3.1)	28.3 (3.6)	24.9 (3.4)	28.4 (4.2)	28.1 (4.1)	26.6 (4.6)	24.4 (5.0)	26.4 (5.2)	−1.3	−3.5 to 0.9	0.241	−0.2	−2.3 to 1.9	0.839	−0.8	−3.1 to 1.5	0.505
SV, mL	87.0 (17.0)	84.7 (14.5)	79.9 (20.1)	86.2 (16.5)	92.4 (26.2)	85.5 (22.1)	76.9 (21.1)	89.4 (27.9)	−3.7	−13.2 to 5.7	0.436	−5.3	−14.3 to 3.8	0.251	0.4	−9.6 to 10.3	0.940
SVI, mL/m^2	40.5 (7.5)	39.2 (6.3)	37.2 (9.7)	40.1 (7.0)	44.1 (12.0)	41.5 (9.7)	37.3 (9.2)	43.2 (11.8)	−1.1	−5.5 to 3.3	0.629	−2.1	−6.3 to 2.1	0.331	0.7	−4.0 to 5.4	0.760
CO, L/min	6.6 (1.5)	6.3 (1.1)	6.7 (1.9)	5.9 (1.4)	7.0 (2.2)	6.5 (1.9)	6.6 (1.9)	6.0 (2.0)	−0.3	−1.2 to 0.5	0.431	−0.3	−1.1 to 0.6	0.526	−0.4	−1.3 to 0.6	0.436
CI, L/min/m^2	3.1 (0.7)	3.1 (0.9)	2.7 (0.6)	2.9 (0.5)	3.4 (1.0)	3.2 (0.9)	2.9 (0.8)	3.1 (0.9)	−0.1	−0.5 to 0.3	0.711	−0.1	−0.6 to 0.3	0.530	−0.1	−0.5 to 0.3	0.650
S', cm/s	9.6 (1.6)	9.7 (1.0)	10.1 (1.7)	8.7 (1.3)	10.2 (1.7)	10.1 (1.4)	10.2 (1.6)	8.9 (1.5)	0.2	−0.6 to 1.0	0.611	0.1	−0.7 to 0.9	0.790	−0.4	−1.2 to 0.5	0.419
GLS, %	−16.8 (2.9)	−17.5 (3.1)	−16.4 (4.9)	−18.6 (2.6)	−17.7 (3.6)	−17.5 (3.6)	−16.7 (4.4)	−18.3 (3.9)	0.1	−1.8 to 2.1	0.890	0.1	−1.7 to 2.0	0.877	0.4	−1.7 to 2.5	0.684
GLSr, 1/s	−0.8 (0.4)	−1.0 (0.2)	−1.0 (0.2)	−0.9 (0.1)	−0.9 (0.2)	−1.0 (0.2)	−1.0 (0.3)	−0.9 (0.2)	0.0	−0.1 to 0.1	0.889	0.0	−0.1 to 0.1	0.884	0.0	−0.1 to 0.2	0.858
Mitral E, m/s	0.9 (0.2)	0.9 (0.1)	0.9 (0.1)	0.9 (0.2)	0.9 (0.1)	0.9 (0.2)	0.8 (0.1)	0.9 (0.2)	0.0	−0.1 to 0.04	0.313	−0.1	−0.1 to 0.01	0.078	0.0	−0.1 to 0.1	0.923
Mitral E/A ratio*	1.5 (0.3)	1.5 (0.4)	1.4 (0.4)	1.4 (0.4)	1.5 (0.3)	1.4 (0.3)	1.3 (0.3)	1.5 (0.3)	−0.1	−0.3 to 0.1	0.451	−0.1	−0.3 to 0.04	0.387	0.1	−0.1 to 0.03	0.371
e', cm/s	13.9 (1.8)	13.6 (1.9)	12.9 (2.6)	13.1 (2.5)	15.1 (2.5)	13.5 (2.4)	12.8 (2.6)	13.5 (2.2)	−0.5	−1.8 to 0.9	0.472	−0.4	−1.7 to 9.3	0.580	−0.01	−1.5 to 1.4	0.988
E/e'	6.9 (1.4)	6.7 (1.2)	7.0 (1.7)	6.7 (1.0)	6.2 (1.4)	6.6 (1.9)	6.3 (1.6)	6.4 (1.4)	0.1	−0.6 to 0.9	0.728	−0.3	−1.1 to 0.5	0.448	0.1	−0.7 to 0.9	0.798
Right ventricle																	
TAPSE, mm	26.8 (4.4)	26.0 (5.8)	24.8 (5.8)	24.5 (5.9)	25.8 (3.7)	25.5 (4.9)	24.5 (5.4)	25.2 (6.3)	−0.3	−3.3 to 2.7	0.847	0.0	−2.9 to 3.0	0.977	1.6	−1.7 to 4.9	0.327
S', cm/s	16.1 (3.2)	16.0 (3.0)	16.7 (2.7)	15.9 (2.3)	16.3 (2.4)	16.1 (3.5)	16.6 (4.1)	15.3 (2.4)	−0.1	−1.7 to 1.6	0.933	−0.2	−1.8 to 1.3	0.759	−0.3	−2.0 to 1.5	0.779
GLS, %	−19.3 (7.1)	−19.8 (8.1)	−19.3 (6.2)	−18.3 (6.3)	−21.0 (8.4)	−18.3 (7.0)	−18.1 (6.7)	−20.8 (5.0)	2.1	−1.6 to 5.9	0.265	1.9	−1.8 to 5.5	0.318	−2.4	−6.5 to 1.6	0.238
GLSr, 1/s	−1.1 (0.4)	−1.1 (0.5)	−1.3 (0.4)	−1.2 (1.2)	−1.3 (0.4)	−1.1 (0.4)	−1.2 (0.4)	−1.2 (0.3)	0.1	−0.2 to 0.4	0.419	0.1	−0.2 to 0.4	0.339	0.1	−0.3 to 0.4	0.667
Left atrium																	
Left atrial area, cm^2	21.7 (4.5)	24.1 (5.5)	22.9 (5.9)	22.8 (4.9)	22.8 (3.8)	24.0 (4.7)	22.5 (4.9)	25.1 (5.1)	−0.4	−3.2 to 2.5	0.791	−0.8	−3.5 to 1.9	0.560	2.3	−0.8 to 5.3	0.145

Observed data in GW 14, GW 20, GW 32 and 6–8 weeks PP in each group, presented as descriptive mean with SD. The between-group difference (group×time) is the mean change in the exercise intervention group with estimated (Est.) effect, corresponding 95% CI and p values, compared with the control group by linear mixed-model analyses.
Missing data for one participant in the control group in gestational week 14, for six participants in the control group and four participants in the exercise group in gestational week 20, three participants in each group in gestational week 32 and nine participants in each group 6–8 weeks PP.
*95% CI and p values are from bootstrapped analyses with 3000 samples and bias-corrected and accelerated CIs due to non-normal distribution of residuals.
CI, cardiac index; CO, cardiac output; e', septal and lateral early mitral inflow tissue velocity; EDV, end-diastolic volume; EDVi, end-diastolic volume corrected for the body surface area; E/e', ratio of early mitral inflow velocity (E) and early diastolic mitral annulus velocity (e'); EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; GLSr, global longitudinal strain rate; GW, gestational week; LVOT Vmax, left ventricular outflow tract maximum velocity; LVOT VTI, left ventricular outflow tract velocity time integral; Mitral E, early diastolic velocity (E wave) at the mitral valve; MV E/A ratio, ratio of peak velocity blood flow in early diastole (E wave) to peak velocity flow in late diastole caused by atrial contraction (A wave) at the mitral valve (MV); PP, post partum; S', peak systolic tissue velocity; SV, stroke volume; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion.

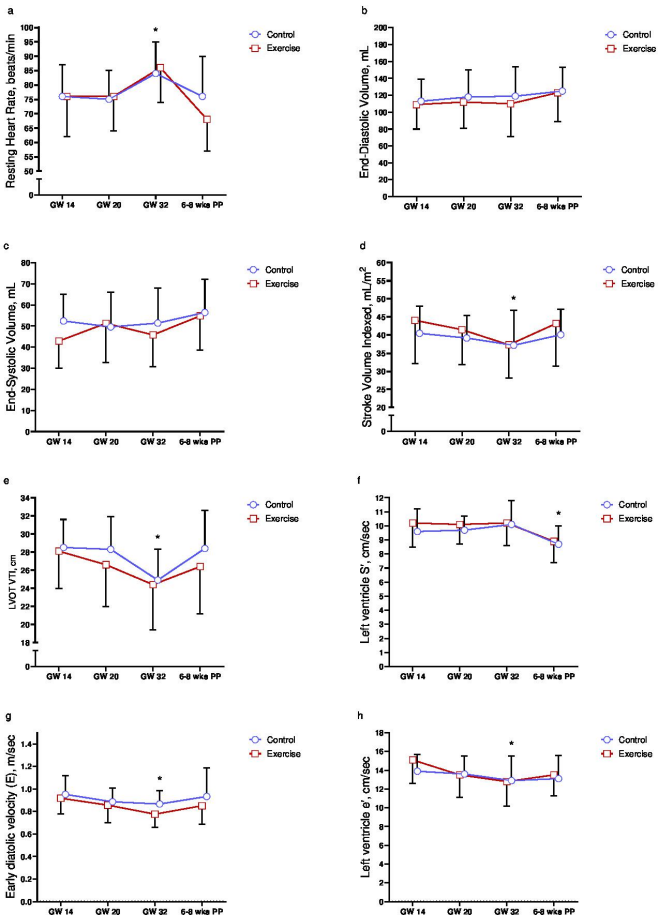

Figure 3 Cardiac function variables in gestational week (GW) 14, GW 20, GW 32 and 6–8 weeks post partum (6–8 weeks PP), according to group. Data are observed values, with symbols representing average per group and bars representing SD. (a) resting heart rate, (b) end-diastolic volume, (c) end-systolic volume, (d) stroke volume corrected for body surface area (indexed), (e) left ventricular outflow tract velocity time integral (LVOT VTI), (f) left ventricular peak systolic velocity (S'), (g) early diastolic velocity (E wave) at the mitral valve, (h) left ventricular septal and lateral early mitral inflow tissue velocity (e'). *Significant (p<0.01) effect of time in the control group.

Clinical implications

Our results suggest a need for alternative or additional interventions to improve long-term cardiovascular health in pregnant individuals with overweight/obesity. In clinical practice, it will be important to find strategies to enhance participant motivation and address barriers to exercise participation. Future studies and clinical practice could benefit from increased patient and public involvement to codesign physical activity interventions for pregnant individuals.[43] To recruit peers acting as trainers from local communities can also be effective in helping people manage their weight and change their health-related behaviour.[44] We strongly believe that guidance about physical activity deserves a prominent place in the clinical care of pregnant individuals. Our findings show that the participants in the ETIP trial had low cardiorespiratory fitness and signs of cardiac dysfunction. The signs of cardiac dysfunction post partum call for further clinical follow-up.

In our trial, the average $\dot{V}O_2$peak was ~27 mL/kg/min 3 months post partum, which is below the 5 percentile lower limit of normal (LLN) for females aged 20–29 (LLN=30.4 mL/kg/min) and for females aged 30–39 (LNN=28.6 mL/kg/min) in a Norwegian reference material.[45] In fact, the cardiorespiratory fitness level of our participants was similar to the average $\dot{V}O_2$peak of Norwegian females aged 70 or above.[45] In line with our findings, Vinter *et al*[30] reported that the majority of the participants in the LiP study had very low fitness. Such poor cardiorespiratory fitness levels in pregnant and postpartum individuals are associated with a markedly increased risk of type 2 diabetes and CVD and call for prevention efforts. Not only are pregnancy complications associated with increased CVD risk later in life, but low cardiorespiratory fitness in young adulthood is associated with increased risk of both CVD and type 2 diabetes.[46] Indeed, the association between hypertensive disorders of pregnancy and future CVD may, at least partly, be mediated by poor cardiorespiratory fitness.[47] Even if the intervention did not influence the cardiovascular outcomes we report here, our previously published data from the ETIP trial showed that the exercise intervention induced other health benefits, including reduced incidence of gestational diabetes, lower systolic blood pressure in late pregnancy and lower circulating insulin concentrations 3 months after delivery.[15 16]

CONCLUSION

There were no statistically significant effects on cardiorespiratory fitness, cardiac function or FMD of offering pregnant individuals with BMI ≥28 kg/m^2 a supervised exercise intervention. The combination of low cardiorespiratory fitness and a high burden on the cardiovascular system, with reduced cardiac function at 32 weeks gestation, calls for cardiovascular prevention in this population. There is a need for strategies to improve adherence to exercise and clinical effectiveness of lifestyle interventions in pregnant people with obesity.

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Acknowledgements We acknowledge personnel at the Clinical Research Facility at the St. Olavs Hospital for data collection and the NeXt Move Core Facility at the Norwegian University of Science and Technology for allowing the use of their laboratories for exercise testing and training. Abstracts containing data included in this paper have previously been presented at the Australian & New Zealand Obesity Society (ANZOS) conference in 2018 and at the European Society of Cardiology (ESC) Preventive Cardiology congress in 2024.[48]

Contributors TM, SM, KS and CBI designed the study. TM, KG, IPV and CBI collected the data. TM, KG, IPV and CBI analysed the data. All authors contributed to the interpretation of the data. TM drafted the manuscript. All authors critically reviewed the manuscript for intellectual content, gave their final approval of the version to be published and agreed to be accountable for all aspects of the work. TM is the guarantor.

Funding Norwegian Fund for Postgraduate Training in Physiotherapy (grant number 7-370-00/08A) and the Liaison Committee for Education, Research and Innovation in Central Norway (grant number 46056728).

Competing interests CBI holds a position at Cimon Medical, a company that develops and manufactures Doppler ultrasound technology for the healthcare sector. The other authors report no conflicts of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The study was approved by the Regional Committee for Medical and Health Research Ethics (REK-midt 2010/1522) and was undertaken at the Norwegian University of Science and Technology (NTNU) and St. Olavs hospital, in Trondheim, Norway.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data underlying this article will be shared on reasonable request to the corresponding author.

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