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## Cardiorespiratory fitness in women after severe pre-eclampsia

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### ABSTRACT

**Aims:** To objectively study cardiorespiratory fitness (CRF) and physical activity (PA) and to evaluate limiting factors of exercise intolerance associated with poor CRF after severe pre-eclampsia.

**Methods:** In this single-centre, cross-sectional study, CRF was measured as peak oxygen uptake ( $VO_{2peak}$ ) during a cardiopulmonary exercise test (CPET) on a treadmill in women 7 years after severe pre-eclampsia. Ninety-six patients and 65 controls were eligible to participate. Cardiac output (CO) was measured by impedance cardiography. PA was measured using accelerometers.

**Results:** In 62 patients and 35 controls (mean age  $40 \pm 3$  years), the  $VO_{2peak}$  (in  $mL \cdot kg^{-1} \cdot min^{-1}$ ) values were  $31.4 \pm 7.2$  and  $39.1 \pm 5.4$ , respectively ( $p < 0.01$ ). In the patients, the  $CO_{peak}$  was ( $9.6 L \cdot min^{-1}$ ), 16% lower compared to controls ( $p < 0.01$ ). Twelve patients (19%) had a cardiac limitation to CPET. Twenty-three (37%) patients and one (3%) control were classed as unfit, with no cardiopulmonary limitations. The patients demonstrated 25% lower PA level (in counts per minute;  $p < 0.01$ ) and 14% more time being sedentary ( $p < 0.01$ ), compared with the controls. Twenty-one patients (34%) compared with four (17%) controls did not meet the World Health Organization's recommendations for PA ( $p = 0.02$ ). Body mass index and PA level accounted for 65% of the variability in  $VO_{2peak}$ .

**Conclusion:** Significantly lower CRF and PA levels were found in patients on long-term follow-up after severe pre-eclampsia. CPET identified cardiovascular limitations in one third of patients. One third appeared unfit, with adiposity and lower PA levels. These findings highlight the need for clinical follow-up and exercise interventions after severe pre-eclampsia.

### ARTICLE HISTORY

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### KEYWORDS



Preeclampsia; hypertension; left ventricular dysfunction; cardiopulmonary exercise testing; physical activity

## Introduction

Preeclampsia occurs in up to 4% of all pregnancies in the industrialized world (1). Women with a history of pre-eclampsia have an increased risk of cardiovascular disease (CVD) later in life (2,3). Studies suggest the CVD risk profile to be different in two different subgroups of pre-eclampsia, i.e., early-onset preeclampsia (onset before 34 weeks of gestation) and late-onset preeclampsia (onset at or after 34 weeks of gestation) (4). Systematic reviews demonstrate an approximately doubled risk of ischemic heart disease, cerebrovascular incidents, and CVD mortality after preeclampsia (5). Preeclampsia with severe features in the clinical presentation (severe hypertension, thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, severe new-onset headache) (6) influence the long-term outcome, and seem to double the odds risk of future CVD (7). Observational echocardiographic studies demonstrate reduced left ventricular (LV) diastolic and systolic function at long-term follow-up in women after previous preeclampsia (8,9).

Cardiorespiratory fitness (CRF) refers to the capability of the circulatory and respiratory systems to supply oxygen to skeletal muscle mitochondria for energy production needed during sustained physical activity (PA). CRF is an important marker of physical fitness and correlates well with overall health status. A cardiopulmonary exercise test (CPET) can express CRF and is the gold-standard measurement of peak oxygen uptake ( $VO_{2peak}$ ) and gas exchange variables during incremental exercise (10,11). To our knowledge, only one study has characterized CRF after preeclampsia at long-term follow-up by a CPET (12).

We hypothesized that women with a history of severe preeclampsia would have poor CRF and low PA levels compared with healthy controls. Accordingly, the primary aim of this study was to characterize CRF and PA levels in women after severe preeclampsia, compared with healthy controls. The secondary aims were to evaluate limiting factors of poor CRF, including the evaluation of LV function by echocardiography.

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## Materials and methods

### Design and study population

This cross-sectional, single-center study was conducted at Oslo University Hospital from October 2013 to January 2016. After a review of the hospital's database, women diagnosed with severe preeclampsia between 2005 and 2010, defined as the index pregnancy, were invited to participate. Inclusion criteria for the patient group were previous severe preeclampsia with early and late-onset disease and giving birth at the Department of Obstetrics at Oslo University Hospital, Rikshospitalet. The control group consisted of women randomly recruited from a database of women with previous healthy pregnancies giving birth at the same hospital between 2008 and 2009. The inclusion criteria for the control population were earlier healthy pregnancies. Exclusion criteria for the patient and the control group were any physical inability to perform CPET, ongoing pregnancy, breastfeeding, assisted reproductive technology therapy, neoplastic disease therapy, or debilitating psychiatric illness.

Data from the pregnancy and clinical follow-up of the study populations, including the patient and controls groups, have recently been published (9).

The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK Southeast, No. 2013-585b) and the local institutional board at Oslo University Hospital. Written informed consent was obtained from all study participants following the Declaration of Helsinki (13).

### Patient and public involvement

This research was approved by the Data Protection Officer at Oslo University Hospital, required to safeguard the research participant's privacy, interest, and rights.

### Clinical characteristics and registrations

Severe preeclampsia was defined as a new onset of severe hypertension, with systolic blood pressure (SBP)  $\geq 160$  mmHg or diastolic blood pressure (DBP)  $\geq 110$  mmHg, and one or more severe features (thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or severe new-onset headache) (6). The diagnosis of preeclampsia included previous criteria from The International Society for the Study of Hypertension in Pregnancy (ISSHP), including proteinuria defined as  $\geq 30$  mg·mmol<sup>-1</sup> albumin in a urine spot sample from a creatinine assay or  $\geq 1+$  on a repeat dipstick test (14). Early-onset preeclampsia

was defined as occurring at  $<34$  weeks of gestation and late-onset at  $\geq 34$  weeks of gestation, according to the previous ISSHP guidelines (14). Maternal and fetal data were obtained through a standardized participant interview and review of the medical records. Any family history of CVD was defined from reporting it in first-degree relatives. Hypertension was defined as any use of antihypertensive medication.

### Measurements

Clinical tests, blood sampling, pulmonary function, CPET, and questionnaires were undertaken on two days. In addition, objective measures of PA were registered. All tests were performed by the same physician (LG) and an exercise physiologist.

### Echocardiography

Echocardiography was performed using an ultrasound scanner (Vivid E9, GE, Horten, Norway) 3–6 months before CPET. EchoPac version 13.1 (GE, Horten, Norway) was used for analysis. LV end-diastolic volume and ejection fraction (EF) were calculated using Simpson's modified biplane method (15). The LV mass was calculated from LV dimensions (16). The mitral peak early (E), late (A) diastolic flow, and peak early (e') velocities were measured (17). LV global longitudinal strain (GLS) was measured by two-dimensional speckle tracking echocardiography.

### Pulmonary function tests

Pulmonary function was assessed by spirometry, maximal voluntary ventilation, and the diffusing capacity of the lungs for carbon monoxide (DLco) (Viasys, Wurzburg, Germany) following the recommendations of the American Thoracic Society/European Respiratory Society task force (18,19).

### Cardiopulmonary exercise testing

CPET was performed on a treadmill (Woodway PPS Med, Germany) using a stepwise modified Balke protocol until exhaustion (20). Gas exchange and exhaled volumes were measured directly, breath by breath (Vyntus CPX Metabolic Cart, CareFusion Corporation, Hochberg, Germany). Blood pressure (BP) was measured at rest, during and after CPET (Tango Stress Test Monitor, SunTech Medical Instruments, Morrisville, NC, USA). Heart rate (HR) was recorded, and a 12-lead electrocardiogram (ECG) (Custo cardio 100, CustoMed, Ottobrunn, Germany) was used.

Percutaneous oxygen saturation was measured by finger pulse oximetry (NONIN 8600, Medical Inc., Minneapolis, MN, USA). The rating of perceived exertion (21) was assessed using the Borg scale<sub>6-20</sub> (22). Post-exercise capillary blood lactate and hemoglobin concentrations (ABL 700 series, Radiometer, Copenhagen, Denmark) were measured within 60 s after exercise (23). Before each CPET, a complete volume and gas calibration was performed, and all underwent treadmill familiarization before starting.

### Cardiac output monitoring

Stroke volume (SV), HR, and cardiac output (CO) were monitored continuously at rest and throughout the CPET by impedance cardiography with an integrated 6-lead electrocardiogram using the PhysioFlow Q-link device (Manatec Biomedical, Paris, France). This technology applies the cyclic variations in transthoracic impedance during the cardiac cycle to estimate SV and has been validated against the direct Fick method (24,25).

### Physical activity assessment

For the objective assessment of PA, all participants wore an accelerometer (ActiGraph GT1M, LLC, Pensacola, FL, USA) on their right hip for seven consecutive days. Accelerometer data were extracted from the vertical axis records in 10-s epochs and were re-analyzed to produce PA and sedentary time variables using KineSoft (version 3.3.20, Saskatchewan, Canada; <http://www.kinesoft.org>). Data were included in the analysis if the subject had a least 10 hours of valid activity recordings per day, for at least 4 days (26). Steps per day, count per minute, sedentary time, and time spent in moderate to vigorous physical activity (MVPA) were registered.

### Data handling

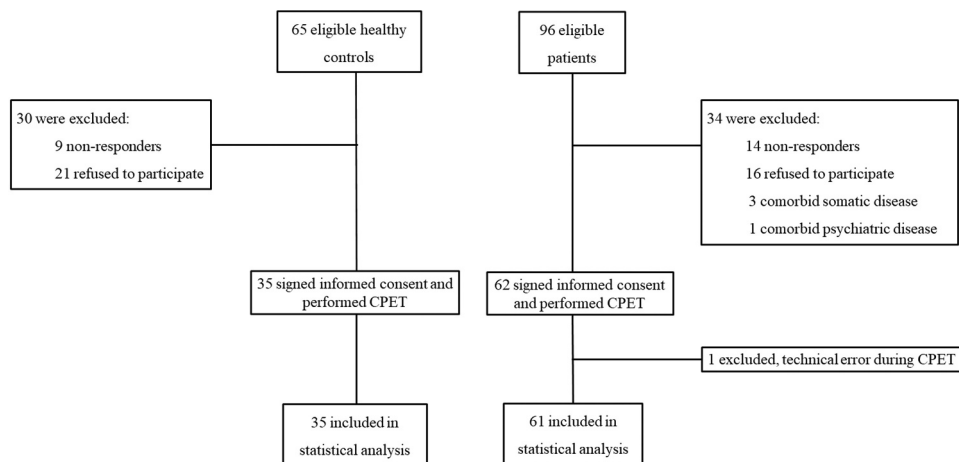
Being overweight was defined as a body mass index (BMI)  $\geq 25 \text{ kg}\cdot\text{m}^{-2}$ , and obesity was defined as BMI  $\geq 30 \text{ kg}\cdot\text{m}^{-2}$ , according to the World Health Organization (WHO) classification (27). The predicted values for spirometry were calculated using the Global Lung Function Initiative equations (28,29). The highest  $\text{VO}_2$  sampled over 30 s was defined as  $\text{VO}_{2\text{peak}}$ . Reference values for  $\text{VO}_{2\text{peak}}$  values were used from a large Norwegian population of 759 healthy adults who successfully completed CPET using the same treadmill protocol as in the present study (20). Low CRF was defined as  $\text{VO}_{2\text{peak}} < 85\%$  of that predicted

(30). Ventilatory threshold was determined by the ventilatory equivalent method. A ventilatory limitation was defined as a breathing reserve  $\leq 15\%$  or  $11 \text{ L}\cdot\text{min}^{-1}$ , and a gas exchange limitation was defined as a  $\text{VE}/\text{VCO}_2$  slope  $\geq 34$  (31). CPET end criteria defining maximal effort were respiratory exchange ratio ( $\text{RER} \geq 1.10$ ) or RPE on Borg scale<sub>6-20</sub>  $\geq 17$  (22).

Cardiac limitation was defined as an oxygen pulse  $< 80\%$  of the predicted, an  $\text{HR}_{\text{peak}} < 90\%$  of the age-predicted  $\text{HR}_{\text{peak}}$ , and an HR reserve  $< 15$  beats/min in the absence of pulmonary limitations (32). Hypertensive response to exercise (HRE) was defined as  $\text{SBP}_{\text{peak}} > 196$  during maximal effort (33). Deconditioning was defined as poor  $\text{VO}_{2\text{peak}}$  ( $\text{VO}_{2\text{peak}} < 85\%$  of expected) in the absence of cardiac or pulmonary limitations. Participants were classified as physically active if they performed  $\geq 150$  min of moderate to vigorous PA per week in  $\geq 10$ -min bouts (34).

### Statistical analysis

Standard statistical analyses were performed using IBM SPSS Statistics (v. 25; IBM Corp., Armonk, NY, USA). Results are presented as the mean  $\pm$  standard deviation of the mean (SD). Differences between patients and controls and between groups of early vs late-onset preeclampsia were analyzed using Student's *t* test and ANOVA for normally distributed data. The Mann – Whitney nonparametric *U* test was used for non-normally distributed data. Categorical variables between the groups were compared using the chi-squared test or Fisher's exact test as appropriate. Simple linear regression analyses were used to analyze any relationship between all relevant CPET variables (independent variables) and  $\text{VO}_{2\text{peak}}$  (dependent variable). Linearity was assessed by partial regression plots. Normality was assessed by Q–Q Plots. To investigate the strength of association with  $\text{VO}_{2\text{peak}}$ , the relevant variables with significant associations in univariate analyses and cardiopulmonary and clinical variables known to affect  $\text{VO}_{2\text{peak}}$  were selected for multiple regression analysis. Binary logistic regression analysis for assessing the odds ratios for achieving poor CRF ( $\text{VO}_{2\text{peak}} < 85\%$  of expected as dependent variable) was performed, adjusting for preeclampsia and BMI in the first model. In the second regression model, the covariates PA level (steps per day) and hypertension were added and adjusted for in the analysis. The Wald test was used to determine the statistical significance of each independent variable. A *p*-value  $\leq 0.05$  was considered statistically significant for all analyses.



**Figure 1.** Flowchart of the study participants.

**Table 1.** Clinical characteristics of the study population.

	Previous preeclampsia <i>n</i> = 62	Controls <i>n</i> = 35	<i>p</i> value
Age, year	40 ± 4	39 ± 3	0.10
Age at index pregnancy, year	33 ± 4	32 ± 3	0.10
Time since delivery, years	7 ± 2	7 ± 1	0.25
Clinical registrations			
Weight, kg	74 ± 11	64 ± 9	<0.01
BMI, kg/m <sup>2</sup>	26.4 ± 3.7	22.5 ± 2.7	<0.01
Overweight, <i>n</i> (%)	23 (35)	5 (14)	0.02
Obesity, <i>n</i> (%)	10 (17)	0 (0)	0.01
SBP, mmHg	135 ± 18	114 ± 10	<0.01
DBP, mmHg	84 ± 12	68 ± 11	<0.01
HR <sub>rest</sub>	82 ± 10	75 ± 8	0.02
[Hb], g × dL <sup>-1</sup>	13.7 ± 2.0	14.4 ± 0.8	0.05
SpO <sub>2rest</sub> , %	98 ± 1	98 ± 2	0.13
Pulmonary function			
FEV <sub>1</sub> , % of predicted	106 ± 11	110 ± 12	0.17
FEV <sub>1</sub> /FVC, %	81 ± 6	76 ± 19	0.22
DL <sub>CO</sub> , % of predicted	103 ± 13	104 ± 12	0.51
MMV, % of predicted	109 ± 19	113 ± 14	0.18
Cardiac function			
LV EDV, ml	74 ± 7†	83 ± 11	<0.01
LV mass, gr	116 ± 21†	94 ± 25	<0.01
LV EF, %	53 ± 8†	61 ± 5	<0.01
CI, L/min/m <sup>2</sup>	3.0 ± .4†	3.4 ± 0.6	0.02
LV GLS, %	-17.2 ± 2.4†	-21.3 ± 1.3	0.01
e <sup>-</sup> mean, cm/sek	11.0 ± 2.4†	15.3 ± 1.4	<0.01
E/e <sup>'</sup>	7.0 ± .5 †	5.2 ± 1.3	<0.01
Smokers			
Never, <i>n</i> (%)	48 (80)	33 (94)	0.34
Former, <i>n</i> (%)	7 (12)	2 (6)	0.48
Current smoker, <i>n</i> (%)	5 (8)	0 (0)	0.08
Family history of CVD, <i>n</i> (%)	50 (83)	9 (26)	<0.01
Educational level			
Primary school, <i>n</i> (%)	4 (7)	9 (26)	<0.01
Graduated high school, <i>n</i> (%)	15 (25)	4 (12)	0.11
Higher education, <i>n</i> (%)	41 (68)	31 (88)	0.03

Variables are presented as mean ± SD. *Abbreviations*; BMI, body mass index; CVD, cardiovascular disease; CI, cardiac index; DBP, diastolic blood pressure; DL<sub>CO</sub>, diffusing capacity for carbon monoxide; EDV, end diastolic volume; FEV<sub>1</sub>, forced expiratory volume in 1 sec; FVC, forced vital capacity; [Hb], hemoglobin concentration; LV, left ventricle; LV GLS, left ventricular global longitudinal strain; MVV, maximum voluntary ventilation. SBP, systolic blood pressure.

## Results

A total of 96 patients and 65 controls were identified and invited by an open invitation letter. Subsequently, 62 patients

with previous severe preeclampsia and 35 healthy controls were included (Figure 1). Twenty-eight (45%) patients had early-onset preeclampsia, and 34 (54%) had late onset.

The clinical characteristics of the study groups are presented in Table 1. Mean age ( $40 \pm 3$  years) and median time since delivery ( $7 \pm 2$  years) were similar across the study groups.

Nine (13%) women in the early group and six (9%) women in the late group had suffered more than one preeclamptic pregnancy at follow-up. Six (9%) patients in the early group and four (6%) patients in the late group had one preeclamptic pregnancy before the index pregnancy with preeclampsia, which was subject to our retrospective clinical registrations. Two (3%) patients in the early group and one (1%) in the late group suffered preeclampsia in later pregnancies until follow-up. Time since delivery in the index pregnancy to follow-up was  $7 \pm 1$  years in the study population and was comparable across the study groups ( $p = 0.25$ ).

Two patients (3%) suffered from previous myocardial infarction after preeclampsia. The BMI was 15% higher in the preeclamptic groups ( $p < 0.01$ ). Twenty-three patients (38%) were overweight, and 10 (17%) were obese. All controls were within the normal weight range. Hypertension was present in 18 patients (30%) before inclusion, and five (8%) patients were diagnosed with hypertension at inclusion. Hypertensive patients at follow-up were treated with beta-blocker ( $n = 9$ ), AT-II or ACE-inhibitors ( $n = 9$ ),

calcium-inhibitors ( $n = 4$ ) and diuretics ( $n = 1$ ). In the hypertensive patients, seven (11%) patients had moderate hypertension and one patient had severe hypertension on repeated BP measurements at follow-up. LV systolic function was reduced, demonstrated by 14% lower EF ( $p < 0.01$ ) and 19% lower GLS ( $p = 0.01$ ) in the preeclamptic group compared with controls. Seven patients (11%) had an EF of 45% to 50%. Total cholesterol was normal in the preeclamptic groups ( $4.8 \pm 0.8$  mmol·L<sup>-1</sup>; local laboratory reference value [3.9–7.8 mmol·L<sup>-1</sup>]).

### Cardiopulmonary exercise testing

All achieved the end criteria of RER  $\geq 1.10$ , had high blood lactate levels (mean  $10.8 \pm 2.1$  mmol·L<sup>-1</sup> for all participants), and reported a subjective maximal exertion rating of 17 on the 20-point Borg scale.

The difference in CRF measured during CPET between patients and controls is presented in Table 2. Both absolute (mL·min<sup>-1</sup>) and relative (mL·kg<sup>-1</sup>·min<sup>-1</sup>) VO<sub>2peak</sub> were 11 and 20% lower in the patients compared with the controls ( $p < 0.01$ ), respectively. Correspondingly, CO<sub>peak</sub> values were 16% lower ( $p < 0.01$ ). Relative VO<sub>2peak</sub> was poor in 23 (38%) patients, compared with two (6%) controls ( $p < 0.01$ ). Of these patients, 12 had cardiac limitation during

**Table 2.** Cardiopulmonary response during CPET.

	Previous preeclampsia <i>n</i> = 62	Controls <i>n</i> = 35	<i>p</i> value
<b>Aerobic capacity</b>			
VO <sub>2peak</sub> mL·min <sup>-1</sup>	2277 ± 385	2518 ± 303	<0.01
VO <sub>2peak</sub> mL·kg <sup>-1</sup> ·min <sup>-1</sup>	31.4 ± 7.2	39.1 ± 5.4	<0.01
VO <sub>2peak</sub> % predicted	91 ± 20	108 ± 15	<0.01
VO <sub>2</sub> at VT, mL·min <sup>-1</sup>	1788 ± 317	1998 ± 302	<0.03
VT in % of VO <sub>2peak</sub>	83 ± 22	80 ± 7	0.76
<b>Cardiovascular response</b>			
SBP <sub>peak</sub> mmHg	196 ± 22	185 ± 13	0.05
DBP <sub>peak</sub> mmHg	88 ± 15	73 ± 11	0.01
HR <sub>peak</sub> beats·min <sup>-1</sup>	177 ± 10	188 ± 10	0.03
Target HR <sub>peak</sub> % predicted	99 ± 15	104 ± 4	0.07
Oxygen pulse <sub>peak</sub> mL·HR <sub>peak</sub> <sup>-1</sup>	11.2 ± 2.3	13.7 ± 1.9	0.02
SV <sub>peak</sub> mL	54 ± 6	62 ± 7	0.01
CO <sub>peak</sub> L·min <sup>-1</sup>	9.6 ± 1.4	11.5 ± 1.2	<0.01
<b>Pulmonary response</b>			
VE <sub>peak</sub> L·min <sup>-1</sup>	85 ± 8	91 ± 12	0.09
Respiratory frequency, breath·min <sup>-1</sup>	46 ± 9	42 ± 5	0.05
Breathing reserve, %	29.9 ± 7.3	31.7 ± 10.5	0.15
SpO <sub>2peak</sub> %	92 ± 3	94 ± 3	0.16
<b>Gas exchange variables</b>			
VE/VCO <sub>2</sub> slope	27.6 ± 7.7	24.9 ± 3.3	0.08
VE/VCO <sub>2</sub> ratio nadir	3.2 ± 4.5	26.1 ± 3.0	0.14
<b>End-criteria variables for maximal effort</b>			
RER	1.23 ± .08	1.29 ± 0.07	0.25
Target HR <sub>peak</sub> % predicted	97 ± 5	104 ± 4	<0.01
RPE, BORG scale <sub>peak 6–20</sub>	17.9 ± .7	17.8 ± 0.8	0.46
Blood lactate, mmol·L <sup>-1</sup>	1.1 ± 2.5	11.5 ± 2.1	0.63
<b>Recovery 2 min after exercise</b>			
SBP, mmHg	159 ± 21	130 ± 27	<0.01
DBP, mmHg	84 ± 11	66 ± 8	<0.01
HR, beats·min <sup>-1</sup>	117 ± 16	105 ± 10	0.01
SpO <sub>2</sub> , %	97 ± 1	98 ± 1	0.13

Variables are presented as mean ± SD. **Abbreviations:** CO<sub>peak</sub>, cardiac output at peak effort; CPET cardiopulmonary exercise test; DBP; diastolic blood pressure; HR<sub>peak</sub>, peak heart rate; MVV, maximal voluntary ventilation, RER, respiratory exchange ratio; RPE, ratings of perceived exertion; SBP; systolic blood pressure; Sp, spectrophotometry; SV<sub>peak</sub>, peak stroke volume; VE<sub>peak</sub>, peak minute ventilation; VO<sub>2peak</sub>, peak oxygen uptake; VT, ventilatory threshold.

**Table 3.** Physical activity in women at follow-up 7 years after severe preeclampsia.

	Previous preeclampsia n = 46	Controls n = 23	p value
Total registration time, days	6.24 ± 1.2	6.35 ± 0.9	0.457
Steps per day, n	6383 ± 1829	8825 ± 2452	<0.01
Counts per minute	306 ± 94	407 ± 104	<0.01
Total wear time, min	775 ± 91	812 ± 60	0.08
Sedentary time, min	72 ± 6	62 ± 7	<0.01
MVPA time, min	36 ± 14	58 ± 15	<0.01
Fulfilled WHO's recommendation, n (%)	25 (54%)	19 (83%)	0.02

Variables are presented as mean ± SD. *Abbreviations:* MVPA, moderate to vigorous physical activity; WHO, World Health Organization.

CPET, and 11 (18%) were classified as deconditioned or unfit without cardiopulmonary limiting factors. When compared with predictive reference values (20), the difference in  $VO_{2peak}$  for our patient group was 9% lower.

No patients had signs of ischemia, exercise-induced hypoxemia, or abnormal pulmonary perfusion, demonstrated by normal saturation during maximal effort and a normal  $VE/VCO_2$  slope. In addition, there was no difference in  $VO_{2peak}$  between the early and late preeclampsia groups.

The PA values are presented in Table 3. The patients spent 38% less time in MVPA levels and 14% more time being sedentary ( $p < 0.01$ ) compared to controls. Twenty-one (45%) patients did not meet the WHO PA recommendations and were classified as physically inactive compared with four (17%) women in the control group ( $p = 0.02$ ). The patients who fulfilled the WHO level of PA had a 16% higher  $VO_{2peak}$  ( $p = 0.04$ ) compared with those who did not.

In the 33 patients (54%) who were classed as overweight ( $n = 23$ ) or obese ( $n = 10$ ), hypertension and diabetes were present in 75% and 88% of them, respectively. In addition, their  $VO_{2peak}$  was lower than in the lean patients ( $p = 0.04$ ), and they spent less time in moderate to vigorous PA ( $p = 0.03$ ).

The BP values at peak exercise were higher in the obese compared with lean patients ( $p = 0.04$ ), and the prevalence of hypertensive response to PA was higher among adipose patients (60%) compared with lean (40%) patients.

### Associations with cardiorespiratory fitness

Multivariable analyses for associations with  $VO_{2peak}$  are presented in Table 4. Univariate analysis showed that BMI,

$SBP_{rest}$ ,  $DBP_{rest}$ ,  $SBP_{peak}$ ,  $DBP_{peak}$ ,  $HR_{peak}$ ,  $CO_{peak}$ , PA (counts per minute), and the time spent being sedentary were significantly associated with  $VO_{2peak}$ . The final multivariable regression model showed that BMI, followed by PA (counts per minute),  $CO_{peak}$  and  $DBP_{rest}$  together accounted for 76% of the variability in the  $VO_{2peak}$ .

A binomial logistic regression was conducted to investigate the effects of PE adjusted for BMI on the predictor variable  $VO_{2peak}$ . This logistic regression model was statistically significant, with  $\chi^2 = 24.95$ ,  $p < 0.001$ . The model explained 35.0% (*Nagelkerke R2*) of the variance in the patients with low CRF, correctly classifying 79% of cases. The PE groups were 20.3 times more likely to have poor CRF than the healthy controls. BMI was not a significant covariable to this model ( $p = 0.125$ ).

Adding PA level added strength to the second regression model by including the continuous covariate steps per day, explained 58% of the variance in patients with low CRF, and correctly classified 81% of cases. This regression model showed that PE and lower PA levels increased the likelihood of having poor CRF.

### Discussion

This cross-sectional study characterized CRF and PA levels in women 7 years after severe preeclampsia and showed significantly lower CRF and PA compared with healthy controls. About half of the patients with poor CRF were characterized as unfit with no evidence of cardiopulmonary limitations. In contrast, the other half with poor CRF had significant and clinical cardiac limitations shown by lower LV systolic and diastolic function at rest, lower  $CO_{max}$ , and lower oxygen pulse

**Table 4.** Multiple regression analysis using  $VO_{2peak}$  as a dependent variable in women after severe preeclampsia.

$VO_{2peak}$		Unstandardized Coefficients		Standardized Coefficients Beta	95% Confidence Interval for Beta		p value	$\Delta R^2$
		Beta	Std. Error		Lower Bound	Upper Bound		
Model	PE group	-1201.03	1233.51		-2688.63	286.57		0.764
	CPM	2.84	0.96	0.32	0.27	4.77	0.004	
	BMI	-63.21	24.30	0.29	-114.22	-12.21	0.001	
	$CO_{peak}$	-103.48	67.47	-0.31	-339.55	-67.42	0.013	
	$DBP_{rest}$	18.28	8.51	0.22	1.12	35.44	0.037	

*Note.* Model = "Enter" method was applied in SPSS statistics; The Beta value represents the slope of the linear regression or the number of units the outcome variable (peak VO<sub>2</sub>) change with a 1-unit change in the predictor variable. *Abbreviations:* BMI, body mass index;  $CO_{peak}$ , cardiac output at peak exercise; CPM, counts per minute;  $DBP_{rest}$ , diastolic blood pressure at rest;  $\Delta R^2$ , adjusted coefficient of determination.

at maximal effort. In addition, one-third of the patients showed a hypertensive response to exercise. No patients had clinical signs of heart failure. The strongest predictor for the reduction in  $VO_{2\text{peak}}$  was BMI, followed by PA (counts per minute),  $CO_{\text{peak}}$  and  $DBP_{\text{rest}}$ . Preeclampsia and lower PA level increased the likelihood of having poor CRF.

CRF is stated to be one of the most important correlates for overall health status, where  $VO_{2\text{peak}}$  provides the “gold standard” measurement of CRF (11). The  $VO_{2\text{peak}}$  reflects an individual’s CRF and is inversely associated with death from CVD or all-cause mortality in healthy as well as in unhealthy individuals (10). Compared with healthy controls, the  $VO_{2\text{peak}}$  was 20% lower ( $7.7 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) in a preeclamptic population, representing almost three decades of physiological aging (20). In addition, the ventilatory threshold was correspondingly lower (23%) in the preeclamptic population, indicating an earlier anaerobic metabolism caused by lower oxygen availability and a lower CRF during sub-maximal exercise. From a physiological point of view, this lower  $VO_{2\text{peak}}$  is unfortunate for these individuals because there is evidence that a decline in  $VO_{2\text{peak}}$  of 1 metabolic equivalent of task (MET;  $3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) is associated with a high risk of developing lifestyle diseases (36). Therefore, an effort to reduce the loss of CRF by increasing the PA level after pregnancy will be of significant importance.

To our knowledge, only one study has characterized CRF at long-term follow-up after preeclampsia. A nationwide Danish study measured  $VO_{2\text{peak}}$  in 28 women with previous preeclampsia and 27 controls 8 years after giving birth (12). Surprisingly, the  $VO_{2\text{peak}}$  averages in the Danish preeclamptic population and their controls were as much as 38% and 16% higher, compared with the present patients and controls, respectively. This is despite the Danish patients performing CPET on an exercise bicycle, with a significantly lower  $HR_{\text{peak}}$  in both groups compared with  $HR_{\text{peak}}$  measured in the present study (167 and 176 vs 177 and 188 beats/min, respectively), indicating lower stress to the cardiopulmonary system. The significant negative gap in  $VO_{2\text{peak}}$  in our study population compared with those in the Danish study is striking because it is well-known that steep treadmill walking generates more muscle mass activation, giving 10% to 20% higher  $VO_{2\text{peak}}$  values compared with cycling (37,38). Nevertheless, one explanation for the difference in  $VO_{2\text{peak}}$  might be the significantly higher BMI, higher occurrence of persistent hypertension after preeclampsia, and poorer LV systolic and diastolic function in our patient population. In addition, the patients included in our study had suffered from severe preeclampsia, whereas there were no data on the severity of preeclampsia in the Danish population. Also, milder preeclamptic disease is associated with a lesser risk of future CVD. These factors may have disadvantageous effect

on CRF, which might explain some of the differences between the two studies.

One-third (28%) of the present patients were deconditioned or unfit, compared with 3% of the controls. This was demonstrated by normal echocardiographic indices at rest, normal ECG, normal gas exchange response during CPET, and no signs of ventilatory limitation or hypoxemia. Correspondingly, for the patients with cardiopulmonary limitations, the deconditioned patients also had a significantly higher prevalence of HRE, lower PA levels, and higher BMI values compared with the patients with a normal CRF. BMI, which was the most significant contributor to poor CRF in the preeclamptic group (Table 4), is a well-known contributor to lower  $VO_{2\text{peak}}$ , lower PA level, and worse health (35). Hence, the overweight and obese patients (60%) spent less time in moderate to vigorous PA and were significantly less physically active than the other patients. In addition, the obese patients had significantly higher diastolic BP at rest, and the prevalence of hypertensive response to PA was higher among adipose patients compared with the lean ones. Obesity can lead to hemodynamic alterations, neuro-hormonal and metabolic abnormalities, and LV remodeling and dysfunction (39). Therefore, significant efforts to reduce weight gain after pregnancy in those with preeclampsia will also be of considerable importance.

Another key factor that might have contributed to poorer health was the SBP during CPET. One-third of the patients demonstrated HRE, defined as an SBP >196 mmHg during maximal effort (33). With CRF in the lower ten percentile range (below 75% of predicted values), the incidence of HRE response to exercise was even higher. This is an important finding during CPET because HRE is an early warning signal with a prognostic value for developing hypertension later in life (40). Data from the Framingham Offspring Cohort Study have shown that HRE has associations with traditional CVD risk factors (41). They found a higher prevalence of increased LVM in individuals with HRE, probably from increased arterial stiffness and impaired endothelial function (42). Here, the individuals with HRE demonstrated a significantly higher LVM than those with a normal exercise response. This aligns with the findings of a 10% greater LVM in individuals with HRE in the Framingham study cited above.

To our knowledge, this is the first study to measure PA objectively after a long-term follow-up in women after severe preeclampsia. The accelerometer data showed a significantly lower PA level and more time spent sedentary in the patients compared with controls. Consequently, a higher  $VO_{2\text{peak}}$  was associated with higher PA levels, and the patients meeting the WHO recommendations (34) had



a significantly higher  $VO_{2peak}$  than those who did not. Notably, the patients with cardiac limitation at rest also showed lower PA levels.

An earlier study has demonstrated low PA levels one year after preeclampsia after

PA modifies cardiac remodeling over time with increased LV compliance and improved ventriculo-arterial coupling (43). Also, higher levels of PA before and during early pregnancy have demonstrated a lower risk of preeclampsia and vice versa (44). Taken together, our findings emphasize the importance of maintaining PA to maintain good cardiovascular function in women with a history of preeclampsia.

### Strength and limitations

The strengths of this study are the relatively long follow-up interval since severe preeclamptic pregnancies and the comprehensive cardiopulmonary evaluations with methods that allowed us to identify organ-specific impairments, including a high-technology cardiopulmonary exercise test and measure of  $CO_{peak}$ .

The major limitation of this study was the cross-sectional observational design, which did not permit us to define causal relationships. We did not screen the control before inclusion in the study regarding weight and BMI; therefore, the controls were not matched to the patients in this regard.

Anthropometric composition, especially with abdominal obesity, is known to influence CRF (45). The patients included here had a significantly higher BMI than controls, which may confound the results. Preeclampsia and CVD share risk factors such as obesity and metabolic syndrome. Data suggest that obese pregnant women with metabolic abnormalities have a high incidence of preeclampsia. Metabolic disturbances can lead to insufficient placentation with vascular dysfunction and ischemia, causing systemic endothelial dysfunction in preeclampsia (46). Unfortunately, we did not record anthropometric data apart from the BMI. Total body fat and lean body mass through a DEXA scan could have distinguished the body composition of the populations and explored the relationship to CRF to a more considerable degree.

In addition, the lack of preconception and peripartum data prevented any analysis of longitudinal data—however, our comprehensive physiological assessment allowed for a thorough analysis of factors associated with  $VO_{2peak}$  and PA.

An a priori sample size calculation was not performed before the study was conducted; The prevalence of severe preeclampsia is relatively rare and is reported in up to about 12 on 1000 deliveries (47). This limits the availability of study participants, even across 6 years. We invited every woman diagnosed with severe preeclampsia ( $n = 96$ ) between 2005 and 2010 to participate. We managed to include 62 patients. We could not provide data on the

excluded patients, including the non-responders, as we did not have approval from the Regional Committee for Medical and Health Research Ethics or the local institutional board at Oslo University Hospital to register data on patients not providing written informed consent. We cannot rule out that non-response bias has affected our results' external validity and generalizability.

### Conclusions

Our study showed poor CRF in a majority of patients during long-term follow-up after severe preeclampsia. Adiposity, lower PA level, and hypertensive response to exercise were associated with lower  $VO_{2peak}$  among the deconditioned or unfit patients. CPET can identify individuals with cardiovascular limitations and reveal cardiovascular risk factors where PA might be especially beneficial to reduce the risk of future CVD. Therefore, our findings highlight the need for targeted clinical follow-up and PA interventions after severe preeclampsia. The causes of exercise intolerance after this pregnancy disorder are incompletely understood, and exercise-interventional studies and more longitudinal data on affected women are needed.

### Article highlights

- The study provides a detailed insight into cardiorespiratory fitness and physical activity from long-term follow-up on women after preeclamptic pregnancies.
- The strength of this study is the comprehensive cardiopulmonary evaluations with methods that allowed us to identify organ-specific impairments, including a high-technology cardiopulmonary exercise test and measure of cardiac output.
- The findings highlight the need for targeted clinical follow-up and physical activity interventions after severe pre-eclampsia.

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### Contributorship statement

LG, EE, MEE, and EL designed the study. LG acquired the data. LG and EE analyzed the data. LG, MEE, and EE interpreted the data. LG and EE drafted the manuscript. All authors have critically reviewed the manuscript and approved the final version.

## Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

## Disclosure statement

The authors declare no conflicts of interest.

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## Data availability statement

No additional data is available.

## Ethics approval

The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK Southeast, No. 2013-585b) and the local institutional board at Oslo University Hospital. Written informed consent was obtained from all study participants following the Declaration of Helsinki (13).

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