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Maastricht University

Faculteit Geneeskunde en Levenswetenschappen
School voor Levenswetenschappen
master in de biomedische wetenschappen

Masterthesis

The evaluation of pre-conceptional physical activity on the cardiovascular profile of women at risk for gestational hypertensive disorders

Pauline Volders

Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen, afstudeerrichting klinische biomedische wetenschappen

PROMOTOR :

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BEGELEIDER :

Mevrouw Pauline DREESEN

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Evaluation of the effect of physical activity on the cardiovascular profile of pre-conceptional women at risk for GHD in a subsequent pregnancy*

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*Running title: P*re-conceptional physical activity*

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Keywords: Gestational hypertensive disorders, physical activity, cardiovascular profile, cardiac output, total peripheral resistance

ABSTRACT

BACKGROUND - Gestational hypertensive disorders (GHDs) pose significant maternal and fetal health risks during pregnancy. While previous studies have investigated the association between physical activity before conception and the incidence of GHD, their evaluation of the impact on the maternal cardiovascular system remains limited. Therefore, this retrospective study aims to investigate the effect of physical activity on the complete cardiovascular system of pre-conceptional women at risk for GHD in subsequent pregnancies.

METHODS - The cardiovascular system of 40 pre-conceptional women at risk for GHD was assessed at baseline. Six months after receiving the advice to perform physical activity, the cardiovascular system was reassessed. Baseline cardiac output (CO) and total peripheral resistance (TPR) values were used to categorize patients.

RESULTS - Women with a low baseline CO profile exhibited a significant increase in CO of 0.5 L/min after the advice to perform pre-conceptional physical activity, whereas those with a high baseline CO profile experienced a significant decrease of 0.4 L/min. Similarly, women with a low baseline TPR profile displayed a tendency towards an increased TPR, whereas those with a high baseline TPR profile experienced a significant reduction in TPR of 191 dyn·s·cm^{-5} subsequent to the advised physical activity regimen.

CONCLUSION - This study reveals the presence of distinct pre-conceptional cardiovascular profiles and elucidates the differential impact of physical activity on these profiles. These findings lay the foundation for personalized obstetric care for pre-conceptional women at risk of GHD in subsequent pregnancies.

List of abbreviations

ACI	Acceleration index
BMI	Body mass index
CO	Cardiac output
CV	Cardiovascular
ECG	Electrocardiogram
ECW	Extracellular water volume
ECW/ICW	Ratio of ECW to ICW
EH	Essential hypertension
EPE	Early-onset preeclampsia
GH	Gestational hypertension
GHD	Gestational hypertensive disorders
HELLP	Hemolysis, elevated liver enzymes, and low platelet count
HR	Heart rate
HVI	Hepatic vein impedance index
HVPT	Hepatic vein pulse transit
ICW	Intracellular water volume
IQR	Interquartile range
ISSHP	International Society for the Study of Hypertension in Pregnancy
IUGR	Intrauterine growth restriction
L Aut PI	Left uterine artery Doppler pulsatility index
L Aut RI	Left uterine artery Doppler resistivity index
L RIVI	Left renal interlobar vein impedance index
L RVPT	Left renal interlobar vein pulse transit
LPE	Late-onset preeclampsia
MAP	Mean arterial pressure
PC	Pre-conceptional
PCPS	Pre-conceptional post-sport
PE	Preeclampsia
PI	Pulsatility index
R RIVI	Right renal interlobar vein impedance index
R RVPT	Right renal interlobar vein pulse transit
R Aut PI	Right uterine artery Doppler pulsatility index
R Aut RI	Right uterine artery Doppler resistivity index
RIVI	Renal interlobar vein impedance index
RVPT	Renal interlobar vein pulse transit
SD	Standard deviation
SV	Stroke volume
TBW	Total body water volume
TPR	Total peripheral resistance
VI	Velocity index

INTRODUCTION

Gestational hypertensive disorders (GHDs) encompass a heterogeneous group of syndromes and represent a significant pregnancy-related concern. Globally, GHD affects a considerable number of pregnancies, with an estimated prevalence of 5-10%. In Flanders, this translates to approximately 3,000 cases out of the 64,000 pregnancies annually [1]. Moreover, the incidence of GHD is rising due to the increasing prevalence of cardiometabolic diseases among younger women [2].

Classification

GHD is characterized by a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg during pregnancy. The International Society for the Study of Hypertension in Pregnancy (ISSHP) identifies three categories of GHD: chronic or essential hypertension (EH), gestational hypertension (GH), and preeclampsia (PE) (**Table 1**) [1, 3]. The latter can be further classified as early-onset PE (EPE) if diagnosed before 34 weeks of gestation or late-onset PE (LPE) if diagnosed after this point [1]. Additionally, preeclamptic patients may progress to the HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, a severe and life-threatening pregnancy pathology [4].

Risk factors

Numerous risk factors have been reported that contribute to the development of GHD. These factors include a high pre-pregnancy body mass index (BMI>30 kg/m²), advanced maternal age (≥40 years), multiple gestations, and a history of previous pregnancy complications. Maternal comorbidities, including chronic hypertension, pregestational diabetes mellitus, auto-immune diseases, and chronic kidney diseases further contribute to the likelihood of developing GHD [5-10]. Low maternal birth weight has also been identified as an additional risk factor for developing GHD [11-14]. Finally, the presence of a family history of PE increases a woman's risk for GHD by 24% up to even 163%. It is worth noting that a familial history of PE in the paternal lineage does not influence a woman's risk for EPE and only demonstrates a weak association with her risk for LPE [15].

Complications

GHD is associated with a wide range of complications, varying in severity from mild hypertension without any other symptoms to multisystem conditions with potentially life-threatening consequences for both mother and fetus [16]. Maternal complications of GHD include an increased risk of stroke, which may persist for more than a decade [17]. Additionally, preeclamptic women have a higher incidence of placental abruption compared to those with normotensive pregnancies [18]. Other maternal complications include organ failure (e.g., renal insufficiency, liver disorders, and neurological disorders [1]), as well as disseminated intravascular coagulation [16]. Fetal complications associated with GHD include intrauterine growth restriction (IUGR),

Table 1 – Classification of gestational hypertensive disorders according to the International Society for the Study of Hypertension in Pregnancy.

Chronic/essential hypertension (EH)	High blood pressure (≥ 140/90 mmHg), predating the pregnancy or recognized at <20 weeks' gestation.
Gestational hypertension (GH)	High blood pressure (≥ 140/90 mmHg) arising de novo after 20 weeks' gestation in the absence of proteinuria and without biochemical or hematological abnormalities.
Preeclampsia (PE)	High blood pressure (≥ 140/90 mmHg) arising de novo after 20 weeks' gestation accompanied by proteinuria and/ or evidence of maternal acute kidney injury (AKI), liver dysfunction, neurological features, hemolysis or thrombocytopenia, or fetal growth restriction.

prematurity, and low birth weight [16, 19]. Furthermore, a nationwide population-based cohort study showed an increased risk of intrauterine death among preeclamptic pregnancies [20].

Pathophysiology

In uncomplicated pregnancy, the maternal cardiovascular (CV) system adapts quickly after embryo implantation. These maternal adaptations are essential for a normal course of pregnancy and are most likely triggered by a uniform vasodilatation, resulting in the activation of volume-restoring mechanisms. This causes an increase in cardiac output (CO) and a decrease in total peripheral resistance (TPR), resulting in a high-volume, low-resistance circulation. These hemodynamic changes ensure adequate blood supply to the fetus without compromising the mother's health [21].

Recent studies have emphasized the importance of these maternal CV adaptations during pregnancy. As such, it was demonstrated that a large subset of women suffering from GHD exhibit disturbed CV adaptations during pregnancy [22]. Building upon these findings, our research group identified distinct abnormal CV profiles during various stages of pregnancy, which can be specifically associated with different GHD outcomes **(Fig. 1)** [22, 23]. In essence, we observed that women who develop GH begin pregnancy with a lower TPR (Type 1 GH) or higher CO (Type 2 GH) compared to uncomplicated pregnancies. In contrast, women experiencing EPE initiate pregnancy with a higher TPR and low/normal CO, whereas those experiencing LPE demonstrate a higher CO and lower TPR relative to uncomplicated pregnancies. The most significant difference between GH and PE is the lack of abnormal venous Doppler flow measurements in GH [23]. This explains why GH is not associated with symptoms of organ dysfunction, as is the case in PE.

Current management

The definitive treatment for GHD is the delivery of the fetus. However, considering the potential complications associated with premature birth, delivery is preferable delayed for as long as medically feasible. Therefore gynecologists try to manage GHD through preventive measures such as remote blood pressure monitoring and low-dose aspirin intake initiated during or before pregnancy [1, 7].

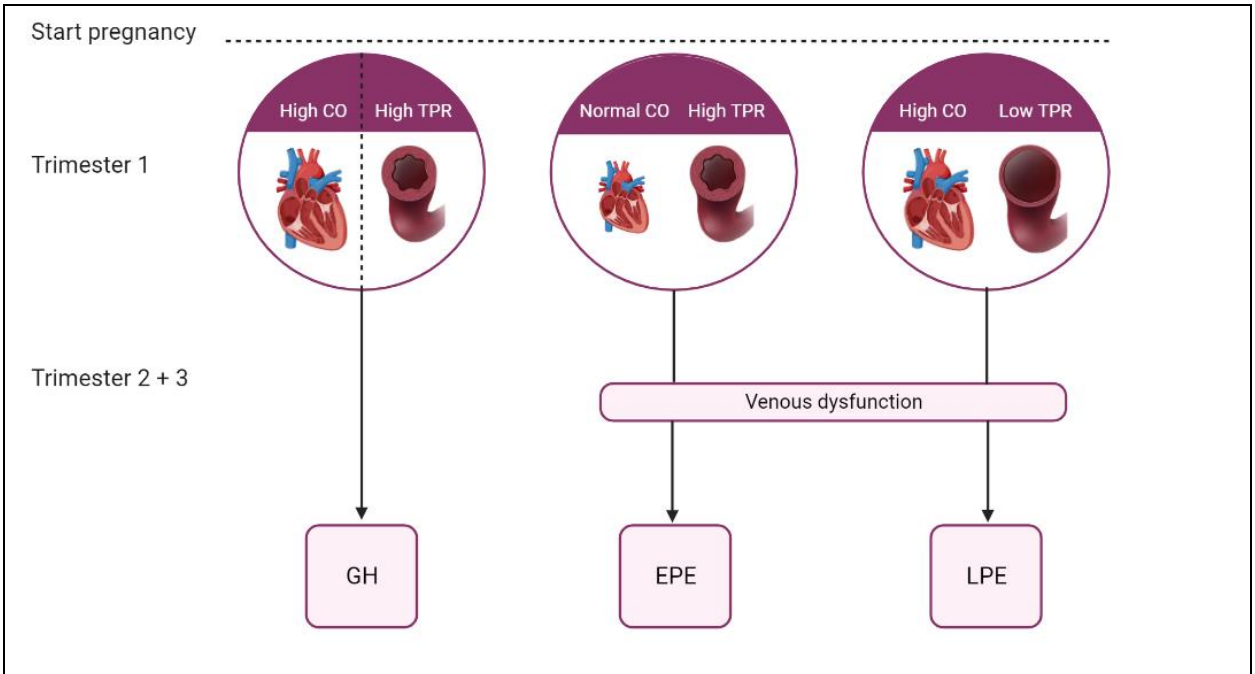

Fig. 1 – **Cardiovascular profiles during pregnancy.** Our research team has successfully demonstrated the presence of distinct abnormal cardiovascular profiles at the onset of pregnancy, which are closely associated with specific GHD outcomes. Of note, the specific cardiovascular changes that occur in cardiac output and total peripheral resistance during trimesters 2 and 3 are not presented in this figure. CO: cardiac output; TPR: total peripheral resistance; GH: gestational hypertension; EPE: early-onset preeclampsia; LPE: late-onset preeclampsia.

Furthermore, recent studies have highlighted the role of physical activity in the prevention of GHD. Traditionally, women were advised to refrain from exercise during pregnancy due to the adverse outcomes it might cause. However, recent evidence indicates that regular exercise at a moderate intensity during pregnancy does not pose a risk of complications [24-26]. In fact, regular physical activity during pregnancy offers numerous benefits. For example, recent studies have demonstrated that aerobic exercise during pregnancy is associated with a significantly reduced risk of GHD, primarily attributable to its beneficial effects on the maternal CV system [19, 27]. Consequently, the standard of care in Belgium recommends that women at risk of GHD engage in physical activity at least three times a week for a minimum of 30 minutes during pregnancy, which aligns with the ISSHP guidelines [7].

Nevertheless, it is essential to consider that engaging in physical activity during pregnancy with the intention of reducing the risk of GHD might be initiated too late, as gestational adaptations have already been established. Therefore, engaging in physical activity even before pregnancy would be more beneficial. This proactive approach allows women to improve their CV system prior to actual conception, enabling them to start subsequent pregnancies with a more favorable CV profile. Remarkably, the greatest reduction in risk of GHD is observed in women who exercise *prior* to conception [28-32]. However, the reported studies primarily focus on the association between physical activity and the incidence of GHD or its effects on specific aspects of the CV system rather than comprehensively examining its impact on the overall CV system. As such, important aspects of the preventive potential of physical activity in this context remain unexplored.

Study aim

The primary objective of this study is to compare the overall CV system of pre-conceptional (PC) women with an increased risk for GHD in subsequent pregnancies before and after receiving the advice to engage in physical activity. The central research question is whether different CV profiles exist before conception and whether physical activity exerts a profile-specific effect on the CV system. Therefore, we hypothesize that distinct CV profiles are present pre-conceptionally and that physical activity prior to conception induces adaptations in the CV system in a profile-specific manner.

EXPERIMENTAL PROCEDURES

This research represents a retrospective study conducted at Ziekenhuis Oost-Limburg (ZOL, Genk, Belgium). Ethical approval for this study was obtained from the institutional review board of the local ethical committee of Ziekenhuis Oost-Limburg (reference: Z-2021055).

Study population and procedure

Inclusion criteria included PC women at an increased risk for GHD in subsequent pregnancies. An increased risk for GHD was defined by the presence of one or more of the following risk factors: essential hypertension, prior pregnancy complications, familial GHD, low own birth weight, high pre-pregnancy BMI (>30 kg/m²), advanced maternal age (>40 years old) or other relevant conditions such as thrombophilia, kidney diseases, diabetes mellitus, or auto-immune disorders. Only PC women at risk for GHD who received a CV measurement both before (PC) and after (PCPS) receiving the advice to engage in physical activity were included for analysis. The CV measurements were performed as part of routine clinical care (i.e., LimPrOn) from May 2016 to February 2023. The prescribed physical activity regimen entailed a frequency of 30-50 minutes, three times a week, with a minimum duration of six months.

Cardiovascular profile

Cardiovascular measurements were performed by combining three non-invasive techniques to gather information about the arteries, heart, veins, and body fluid status (**Fig. 2**) [23]. The interpretation of the collected CV parameters is presented in **Table. 2**. All parameters were recorded in a resting phase. The first technique employed was electrocardiogram (ECG)-assisted Doppler ultrasonography. This method allowed for the examination of Doppler signals at the hepatic and renal veins (**Fig. S1**), as well as the uterine arteries [22]. The Doppler samples obtained from the liver and kidneys were used to measure the maximum and minimum flow velocities. To assess the venous tone of the hepatic and renal veins, impedance

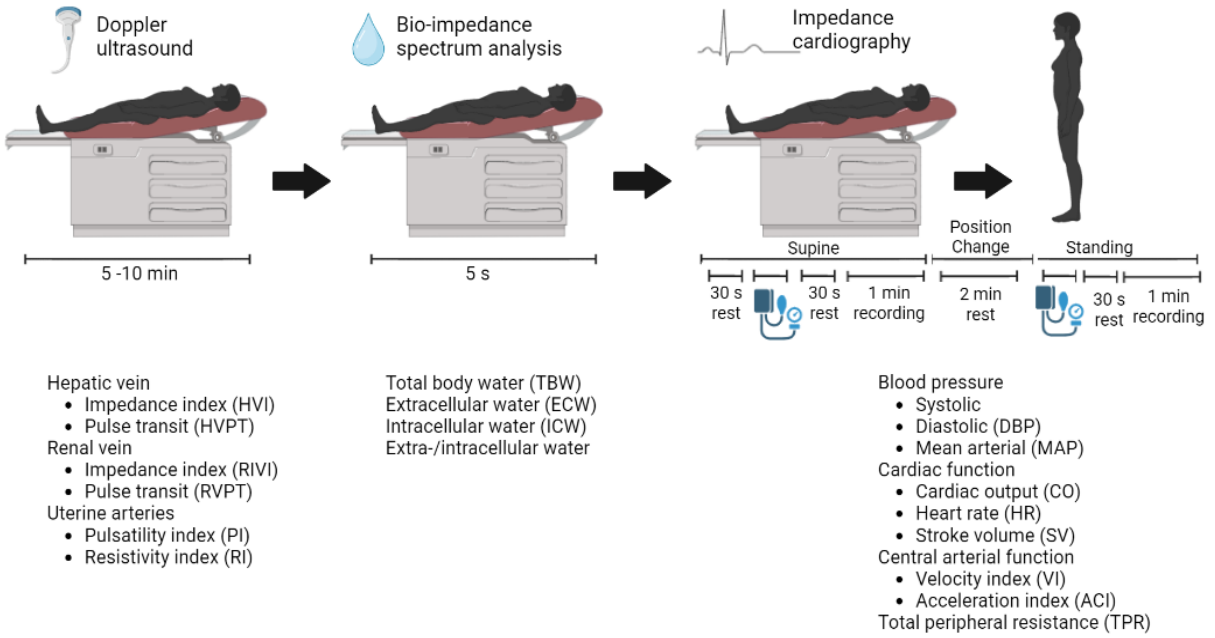

Fig. 2 – **Techniques used to assess the overall CV system.** In consecutive order (from left to right): Doppler ultrasound and bio-impedance spectrum analysis in supine position followed by impedance cardiography in supine and standing position. Parameters collected by each technique are presented with each technique respectively [23].

indices were calculated using the formula [(maximum velocity - minimum velocity)/ maximum velocity], resulting in the hepatic vein impedance index (HVI) and renal interlobar vein impedance index (RIVI). Additionally, the hepatic vein pulse transit (HVPT) and renal interlobar vein pulse transit (RVPT) were determined by measuring the time interval between the ECG P wave and the corresponding venous Doppler A wave. To account for variations in heart rate, all pulse transits were normalized relative to the ECG wave duration measured between consecutive R signals in milliseconds. Furthermore, the resistivity index (RI) [(peak systolic velocity - minimal diastolic velocity) / peak systolic velocity] and pulsatility index (PI) [(peak systolic velocity - minimal diastolic velocity) / mean velocity] in the arcuate uterine arteries were assessed using the automated algorithm of the Doppler ultrasound scanner.

The second measurement technique employed was bioimpedance spectrum analysis, which provides an estimation of total body water volume (TBW), including extracellular and intracellular water volumes (ECW and ICW) using a multiple-frequency bioelectrical impedance analyzer (Maltron BioScan 920-II, Maltron International, Essex, UK). Patients were measured in a supine position, with four electrodes placed on the right hand and right foot. The electrodes receiving the electrical signal were positioned on the dorsal side of the wrist and ankle, while the electrodes sending the electrical signal were attached to the distal end of the metacarpal and metatarsal bones (**Fig. S2A**) [22].

The third and final measurement technique used to assess the CV system was impedance cardiography, employing the non-invasive continuous cardiac output monitor (NICCOMO, Medis Medizinische Messtechnik, Ilmenau, Germany). Four electrodes were placed: two on the axillary line under the thorax and two on the neck. Parameters were measured twice: once in the supine position and once in the standing position, allowing for the evaluation of the cardiovascular orthostatic response (**Fig. S2B**). The measurements in the upright position were recorded after a two-minute adaptation period following the postural change, as is reported to be representative of the long-lasting effects after posture change [33]. The measured

parameters were classified into three groups. 1) The cardiac function parameters included stroke volume (SV) in mL, heart rate (HR) in beats per minute, and cardiac output (CO) in L/min, calculated using the formula of Bernstein (CO= HR X SV). 2) Central arterial function parameters such as the aorta flow velocity index (VI) in 1/1000/s and acceleration index (ACI) in 1/100/s^2 were assessed. 3) Total peripheral resistance (TPR) was calculated as mean arterial pressure (MAP) multiplied by 80 and divided by CO, expressed in dyn·s·cm^{-5}. Blood pressure was recorded using automated sphygmomanometry [22, 23]. Given that CO and TPR are key parameters in predicting pregnancy outcomes during pregnancy, we aimed to evaluate the effect of PC physical activity on the CV system in a profile-specific way by specifically categorizing the study population according to baseline CO and TPR values. This resulted in the following profiles: low CO (<5.0 L/min), normal

Table 2: Summary of collected parameters during the cardiovascular measurement and their interpretation.

Parameter	Technology	PC reference range	Interpretation
Impedance index (HVI and RIVI)	Doppler ultrasound	HVI: 1.11 -1.57 L RIVI: 0.33-0.42 R RIVI: 0.32-0.44	Reflect the intracycle variability of blood flow velocities in the veins and is directly related to venous tone, i.e., venous wall stiffness.
Pulse transit (HVPT and RVPT)	Doppler ultrasound	HVPT: 0.14-0.23 ms L RVPT: 0.23-0.36 ms R RVPT: 0.22-0.36 ms	Inversely related to venous tone, i.e., venous wall stiffness.
Pulsatility index (PI) Resistivity index (RI)	Doppler ultrasound	L Aut PI: 0.92-1.35 R Aut PI: 1.03-1.29 L Aut RI: 0.63-0.82 R Aut RI: 0.68-0.78	Reflects the vascular resistance of the blood flow caused by the microvascular bed distal to the measurement point.
Body water volumes (TBW, ECW, ICW, ECW/ICW)	Bio-impedance spectrum analysis	TBW: 31.11-36.56 L ECW: 13.15-15.92 L ICW: 17.66-20.46 L ECW/ICW: 0.73-0.79	Provides estimation of the water volumes in the body. Increased values are associated with GHD.
Blood pressure (DBP and MAP)	Impedance cardiography	DBP: 77-93 mmHg MAP: 87-105 mmHg	GHD is characterized by a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg during pregnancy.
Cardiac output (CO)	Impedance cardiography	CO: 5.0-6.5 L/min	Defines the volume of blood (L) pumped by the heart each minute. Represents one of the key predictors of GHD during pregnancy.
Stroke volume (SV)	Impedance cardiography	SV: 50-100 mL	Defines the volume of blood (mL) pumped out of the left ventricle per beat.
Central arterial function (VI and ACI)	Impedance cardiography	VI: 55-81 1/1000/s ACI: 124-191 1/100/s^2	Reflects arterial function. Reduced VI and/or ACI reflect abnormal central arterial function.
Total peripheral resistance (TPR)	Impedance cardiography	TPR : 1149-1537 dyn·s·cm^{-5}	TPR represents the overall arterial resistance in the systemic circulation. Represents one of the key predictors of GHD during pregnancy. Calculated using the formula: [MAP × 80/CO]

HVI: hepatic vein impedance index; RIVI: renal interlobar vein impedance index; L RIVI: left renal interlobar vein impedance index; R RIVI: right renal interlobar vein impedance index; HVPT: hepatic vein pulse transit; RVPT: renal interlobar vein pulse transit; L RVPT: left renal interlobar vein pulse transit; R RVPT: right renal interlobar vein pulse transit; PI: pulsatility index; RI: resistivity index; R aut PI: right uterine artery Doppler pulsatility index; R aut RI: right uterine artery Doppler resistivity index; L aut PI: left uterine artery Doppler pulsatility index; L aut RI: left uterine artery Doppler resistivity index; TBW: total body water volume; ECW: extracellular water volume; ICW: intracellular water volume; ECW/ICW: ratio of ECW to ICW; DBP: diastolic blood pressure; MAP: mean arterial pressure; CO: cardiac output; SV: stroke volume; VI: velocity index; ACI: aorta flow acceleration index; TPR: total peripheral resistance [23].

CO (5.0-6.5 L/min), high CO (>6.5 L /min), low TPR (< 1149 dyn·s·cm^{-5}), normal TPR (1149-1537 dyn·s·cm^{-5}), and high TPR (>1537 dyn·s·cm^{-5}).

Data collection

All study parameters were recorded using a computerized system, ensuring the integrity of the study (Castor EDC). Variables collected at baseline included age, BMI, parity, indication for CV measurement, comorbidities, familial history of cardiovascular disease, and medication usage. Cardiovascular measurements were performed at baseline and at least six months after receiving the advice to perform physical activity.

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) for normally distributed and skewed distributions, respectively. Categorical data were reported as absolute values and proportions. Demographic data were compared among three groups (low, normal, high) using one-way ANOVA for mean comparisons, Kruskal Wallis test for median comparisons, and Chi-square test for proportion comparisons. Pre- and post-activity parameters were compared using a two-sided paired Student's t-test for means and the non-parametric Wilcoxon signed-rank test for medians. A significance level of 5% ($P<0.05$) was considered statistically significant. For categorical data, a more stringent significance level of 1.7% ($P<0.017$) was applied due to multiple testing. Statistical analyses were performed using SPSS 28.0.1.1 (IBM, Chicago, IL).

RESULTS

Study population

Out of the total cohort of women (n=1675) who received a CV measurement at Ziekenhuis Oost-Limburg as part of routine clinical care between May 2016 and February 2023, a subset of 177 (10.57%) were measured prior to conception (PC). However, 137 women (8.18%) were excluded because no CV measurement was performed after the advice to perform physical activity (PCPS). Consequently, 40 women (2.39%) with both a PC and PCPS CV measurement were included for statistical analysis (**Fig. 3**). Detailed demographic characteristics are presented in **Table 3**. The study population consisted of both nulliparous women (18.92%) and multiparous women (81.08%). Among the multiparous women, 24 (80.00%) had a documented history of GHD in a previous pregnancy. Additionally, five multiparous women (16.67%) suffered from complications other than GHD in previous pregnancies. Notably, only one woman (3.33%) experienced a complication-free pregnancy in the past.

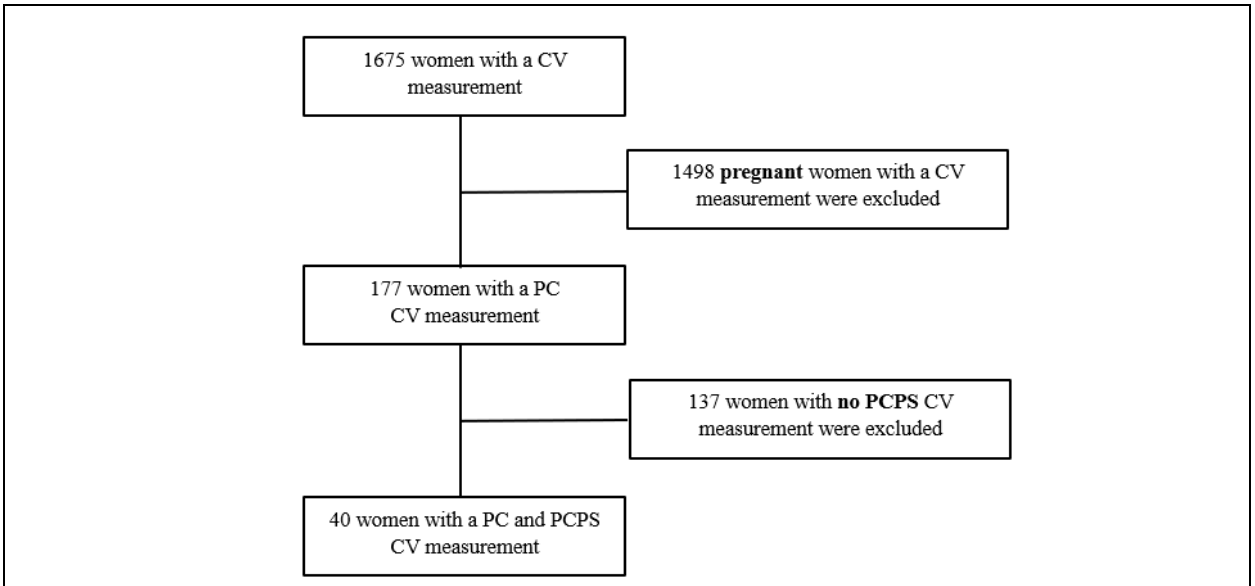

Fig. 3 – **Study population**. CV: cardiovascular; PC: pre-conceptional; PCPS: pre-conceptional post-sport.

Table 3: Demographic factors and characteristics of the total pre-conceptional study population.

	Total study population (N = 40)
Age (years)	31.3 (±3.7)
BMI (kg/m²)	22.6 (19.8-29.7)
Parity	
Nulliparous	7 (18.92%)
Multiparous	30 (81.08%)
Outcome last pregnancy	
Normal	1 (3.33%)
GHD	24 (80.00%)
Other	5 (16.67%)
Indication CV measurement	
EH	6 (15.0%)
Previous pregnancy complications	31 (77.5%)
GH	1 (3.23%)
EPE	10 (32.26%)
LPE	5 (16.13%)
HELLP	11 (35.48%)
IUGR	11 (35.48%)
Other	3 (9.68%)
Familial GH	1 (2.5%)
Familial EH	1 (2.5%)
Low own birth weight	5 (12.5%)
Other	11 (27.5%)
Comorbidity	
Hypertension	9 (22.5%)
Diabetes	0 (0.0%)
Thyroid problems	2 (5.0%)
Thrombophilia	0 (0.0%)
Kidney problems	1 (2.5%
Other	6 (15.0%)
Family history of CVD	16 (40.0%)
Medication use	
Ace inhibitor	2 (5.0%)
Beta blocker	5 (12.5%)
Calcium antagonist	2 (5.0%)
Other	4 (10.0%)

Continuous data is presented as median (IQR) or mean (± SD). Categorical variables are displayed as n (%). CV: cardiovascular; EH: essential hypertension; GH: gestational hypertension; EPE: early-onset preeclampsia; LPE: late-onset preeclampsia; HELLP: hemolysis, elevated liver enzymes, low platelet count; IUGR: intrauterine growth restriction; CVD: cardiovascular disease.

General effect of physical activity

To assess the impact of physical activity on the overall CV system, we first examined its effect within the overall study population. The post-sport CV system measurements were performed, on average, 30 weeks after the initial recommendation to engage in physical activity. A statistically significant decrease in TPR was observed when comparing the PC visit to the PCPS visit (1543 vs. 1410 dyn·s·cm^{-5}, p=0.016) (**Table 4**). However, no significant change was detected in CO (p=0.064). Consequently, DBP and MAP exhibited significant reductions (92 vs. 88 mmHg, p=0.009 and 103 vs. 99 mmHg, p=0.030, respectively). Remarkably, L RIVI and R Aut RI, which were already elevated at baseline, exhibited a notable tendency to further increase following the advice to perform physical activity, although not statistically significant (p=0.055).

Profile-specific effect of physical activity

Demographic characteristics of the subgroups categorized by CO and TPR are presented in **Table S1 and S2**, respectively.

High CO or low TPR profile

Among the study population, nine women (22.50%) displayed a high baseline CO profile, while eight women (20.00%) exhibited a low baseline TPR profile. Evaluating the impact of physical activity on the CV system, it was observed that women with a high baseline CO profile experienced a significant reduction in CO (7.5 vs. 7.1 L/min, p=0.041) (**Fig. 4A and table 5**). In fact, 33.33% of women with a high baseline CO profile transitioned to a normal CO profile following the physical activity advice (**Fig. S3**). Conversely, women with a low baseline TPR profile tended to show an increase in TPR after the recommended physical activity, although not significant (1039 vs. 1044 dyn·s·cm^{-5}, p=0.093) (**Fig. 4B and table 6**). Specifically, 25.00% of women with a low baseline TPR profile achieved a normal TPR after the exercise advice (**Fig. S4**). Since CO and TPR play a pivotal role in the establishment and manipulation of MAP, it was examined whether these physical activity-related shifts in CO and TPR also affected MAP. However, no significant change in MAP was observed post-sport, with values remaining within the reference range (**Tables 5 and 6**).

Further analysis of the post-sport CV system parameters revealed that women with a high baseline CO profile exhibited a significant increase in **HVI** (0.091 vs. 1.30, p=0.038), as well as a significant increase in **L Aut PI** (1.39 vs. 1.55, p=0.038) (**Table 5**). Similarly, women with a low baseline TPR profile demonstrated a significant increase in L Aut PI (1.37 vs. 1.55, p=0.029) (**Table 6**). To determine whether the shift in CO was related to the shift in HVI and L Aut PI, a correlation analysis was performed, which revealed no significant correlation between the shift in CO and the shift in HVI or L Aut PI (**Fig. S5**).

Normal CO or normal TPR profile

Within the total study population, 19 women (47.50%) exhibited a normal baseline CO profile, while 11 women (27.50%) displayed a normal baseline TPR profile. The recommended physical activity did not induce a significant change in CO or TPR in these women (**Fig. 4 and tables 5 and 6**). Consequently, MAP remained within the normal range. However, upon individual analysis, a subset of patients exhibited profile transitions, with 31.58% of women with a normal baseline CO profile transitioning to either a high or low CO profile (**Fig. S3**) and 27.27% of women with a normal baseline TPR profile transitioning to a low TPR profile following the physical activity advice (**Fig. S4**). Moreover, results show that women with a normal baseline CO profile experienced a significant increase in **L RIVI** following the advice to perform physical activity in the pre-conception period (0.43 vs. 0.50, p=0.017) (**Table 5**). Similarly, women with a normal baseline TPR profile tended to show an increased L RIVI post-activity advice, although not significant (0.43 vs. 0.49, p=0.091) (**Table 6**).

Low CO or high TPR profile

Twelve women (30.00%) exhibited a low baseline CO profile, while 21 women (52.50%) demonstrated a high baseline TPR profile. Among women with a low baseline CO profile, a significant increase in CO was observed following the activity advice (4.4 vs. 4.9 L/min, p=0.009) (**Fig. 4A and table 5**). Specifically, 50.00% of women with a low baseline CO profile transitioned to a normal CO

Table 4: Effect of physical activity on the CV system.

	PC (N = 40)	PCPS (N= 40)	P-value	Reference
HVPT (ms)	0.16 (0.13-0.20)	0.15 (0.11-0.21)	0.682	0.14-0.23
HVI	1.35 (0.86-1.58)	1.37 (1.23-1.57)	0.224	1.11-1.57
R RVPT (ms)	0.22 (0.17-0.32)	0.26 (0.16-0.33)	0.568	0.22-0.36
R RIVI	0.51 (±0.13)	0.51 (±0.11)	0.821	0.32-0.44
L RVPT (ms)	0.30 (±0.09)	0.29 (±0.09)	0.329	0.23-0.36
L RIVI	0.45 (±0.10)	0.49 (±0.13)	0.055	0.33-0.42
R Aut PI	1.34 (1.22-1.56)	1.43 (1.28-1.59)	0.194	1.03-1.29
R Aut RI	0.80 (0.71-0.88)	0.84 (0.78-0.89)	0.055	0.68-0.78
L Aut PI	1.37 (±0.22)	1.42 (±0.19)	0.202	0.92-1.35
L Aut RI	0.81 (0.76-0.87)	0.85 (0.78-0.89)	0.364	0.63-0.82
TBW (L)	32.73 (30.20-37.43)	31.99 (29.37-37.47)	0.619	31.11-36.56
ECW (L)	14.04 (12.65-16.85)	13.77 (12.17-16.24)	0.962	13.15-15.92
ICW (L)	18.47 (17.23-20.73)	18.14 (16.90-20.61)	0.330	17.66-20.46
ECW/ICW	0.74 (0.72-0.78)	0.75 (0.72-0.78)	0.925	0.73-0.79
DBP (mmHg)	92 (±12)	88 (±9)	**0.009**	77-93
MAP(mmHg)	103 (±12)	99 (±9)	**0.030**	87-105
VI (1/1.000/s)	61 (±19)	63 (±15)	0.156	55-81
ACI (1/100/s^2)	139 (104-166)	149 (113-175)	0.108	124-191
LVET (ms)	239 (221-252)	240 (226-265)	0.224	218-250
CO (L/min)	5.6 (±1.3)	5.9 (±1.2)	0.064	5.0-6.5
TPR (dyn·s·cm^{-5})	1543 (1247-1780)	1410 (1165-1614)	**0.016**	1149-1537

Data is represented as median (IQR) or mean (± SD). HVPT: hepatic vein pulse transit; HVI: hepatic vein impedance index; R RVPT: right renal interlobar vein pulse transit; R RIVI: right renal interlobar vein impedance index; L RVPT: left renal interlobar vein pulse transit; L RIVI: left renal interlobar vein impedance index; R aut PI: right uterine artery Doppler pulsatility index; R aut RI: right uterine artery Doppler resistivity index; L aut PI: left uterine artery Doppler pulsatility index; L aut RI: left uterine artery Doppler resistivity index; TBW: total body water volume; ECW: extracellular water volume; ICW: intracellular water volume; ECW/ICW: ratio of ECW to ICW; DBP: diastolic blood pressure; MAP: mean arterial pressure; VI: velocity index; ACI: aorta flow acceleration index; LVET: left ventricular ejection time; CO: cardiac output; TPR: total peripheral resistance. A p-value < 0.05 is considered statistically significant.

profile after the physical activity recommendation (**Fig. S3**). Conversely, women with a high baseline TPR profile displayed a significant reduction in TPR following the advice (1760 vs. 1569, p=0.001) (**Fig. 4B and table 6**). Notably, 42.86% of women with a high baseline TPR profile achieved a normal TPR profile following the exercise recommendation (**Fig. S4**). Again, MAP did not exhibit a significant change, although women with a high baseline TPR profile tended to have a reduced MAP, although not significant (107 vs. 102 mmHg, p=0.066). In contrast to women with a high baseline CO or low TPR profile, the venous system parameters remained unaffected after the recommendation to engage in physical activity in women with a low baseline CO or high TPR profile (**Tables 5 and 6**). Instead, women with a low baseline CO profile experienced a significant increase in **ACI and VI** (121 vs. 163 1/100/s^2, p=0.015 and 58 vs. 69 1/1.000/s, p=0.042, respectively). Similarly, women with a high baseline TPR profile demonstrated a significant increase in ACI (131 vs. 162 1/1.000/s, p=0.030) and a tendency towards an increased VI (60 vs. 66 1/100/s^2, p=0.096). Additionally, DBP significantly decreased in women with a high baseline TPR profile (96 vs. 92 mmHg, p=0.047).

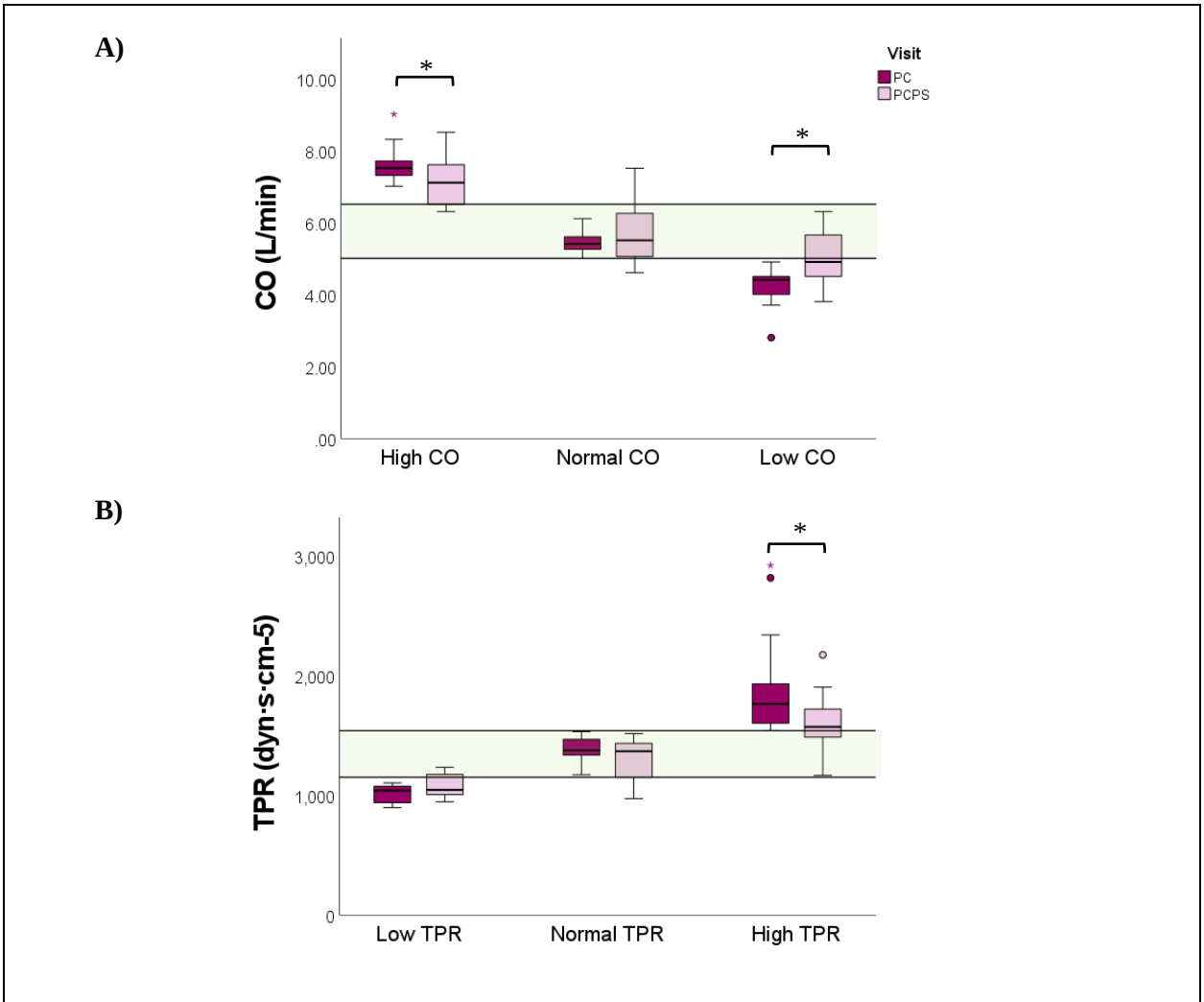

Fig. 4 – **CO and TPR evaluated before and after physical activity in PC women.** A) The total study population (n=40) was categorized into low (n=12), normal (n=19), and high (n=9) CO profiles. CO was compared before and after the advice to perform physical activity for at least six months for each CO profile. B) The study population was categorized into high (n=21), normal (n=11), and low (n=8) TPR profiles. TPR was evaluated before and after the advice to exercise for each TPR profile. Data is presented as boxplots with median and IQR. CO: cardiac output; TPR: total peripheral resistance; PC: pre-conceptional; PCPS: pre-conceptional post-sport.*p<0.05. °Outlier. *extreme outlier

Table 5: Effect of physical activity on the CV system of PC women subdivided based on CO.

	Low CO			Normal CO			High CO			
	PC (N = 12)	**PCPS (N = 12)**	**P-value**	**PC (N = 19)**	**PCPS (N = 19)**	**P-value**	**PC (N = 9)**	**PCPS (N = 9)**	**P-value**	**Reference**
HVPT (ms)	0.14 (0.11-0.20)	0.14 (0.10-0.20)	0.875	0.15 (0.13-0.17)	0.15 (0.13-0.21)	0.286	0.22 (0.17-0.31)	0.16 (0.11-0.31)	0.110	0.14-0.23
HVI	1.37 (0.92-1.74)	1.33 (1.22-1.55)	0.937	1.42 (0.86-1.59)	1.41 (1.29-1.60)	0.398	0.91 (0.28-1.40)	1.30 (0.85-1.57)	**0.038**	1.11-1.57
R RVPT (ms)	0.21 (±0.08)	0.25 (±0.10)	0.250	0.25 (±0.09)	0.25 (±0.08)	0.782	0.31 (±0.13)	0.30 (±0.13)	0.840	0.22-0.36
R RIVI	0.52 (±0.11)	0.49 (±0.14)	0.270	0.50 (±0.10)	0.53 (±0.08)	0.254	0.49 (±0.18)	0.50 (±0.12)	0.802	0.32-0.44
L RVPT (ms)	0.25 (±0.07)	0.26 (±0.09)	0.598	0.31 (±0.09)	0.30 (±0.08)	0.470	0.36 (±0.10)	0.31 (±0.11)	0.167	0.23-0.36
L RIVI	0.48 (±0.11)	0.46 (±0.15)	0.601	0.43 (±0.08)	0.50 (±0.12)	**0.017**	0.44 (±0.10)	0.49 (±0.11)	0.151	0.33-0.42
R Aut PI	1.37 (±0.21)	1.31 (±0.26)	0.536	1.28 (±0.23)	1.39 (±0.23)	0.102	1.48 (±0.29)	1.59 (±0.08)	0.286	1.03-1.29
R Aut RI	0.80 (0.72-0.87)	0.79 (0.73-0.87)	0.844	0.79 (0.70-0.82)	0.83 (0.78-0.86)	0.093	0.88 (0.69-0.93)	0.89 (0.87-0.90)	0.213	0.68-0.78
L Aut PI	1.46 (±0.21)	1.36 (±0.21)	0.216	1.31 (±0.23)	1.40 (±0.18)	0.133	1.39 (±0.18)	1.55 (±0.11)	**0.038**	0.92-1.35
L Aut RI	0.87 (0.78-0.90)	0.83 (0.74-0.87)	0.476	0.79 (0.75-0.85)	0.81 (0.78-0.86)	0.136	0.85 (0.78-0.87)	0.87 (0.86-0.90)	0.213	0.63-0.82
TBW (L)	31.02 (29.77-31.39)	30.54 (28.70-31.15)	0.480	32.90 (29.08-38.06)	32.04 (28.44-38.70)	0.968	35.45 (34.48-43.32)	36.62 (33.10-38.80)	0.515	31.11-36.56
ECW (L)	13.12 (12.54-13.71)	12.87 (11.94-13.49)	0.666	14.12 (12.20-17.21)	14.16 (11.64-17.27)	0.494	16.03 (14.85-22.01)	15.87 (14.03-16.82)	0.594	13.15-15.92
ICW (L)	17.68 (17.11-18.11)	17.43 (16.67-18.06)	0.432	18.78 (16.98-21.59)	17.52 (16.48-21.47)	0.365	20.22 (19.33-23.36)	20.75 (19.07-22.12)	0.859	17.66-20.46
ECW/ICW	0.74 (0.71-0.77)	0.73 (0.72-0.77)	0.722	0.73 (0.72-0.78)	0.76 (0.71-0.82)	0.679	0.75 (0.73-0.86)	0.75 (0.73-0.76)	0.594	0.73-0.79
DBP (mmHg)	91 (84-99)	88 (84-90)	0.077	91 (82-99)	90 (82-100)	0.158	86 (84-95)	86 (82-92)	0.286	77-93

Table 5: Effect of physical activity on the CV system of PC women subdivided based on CO (continued).

MAP(mmHg)	104 (95-110)	101 (94-102)	0.130	102 (93-110)	100 (91-110)	0.132	99 (92-106)	99 (95-105)	0.953	87-105
VI (1/1.000/s)	58 (±16)	69 (±14)	**0.042**	63 (±22)	63 (±16)	0.964	58 (±16)	57 (±10)	0.768	55-81
ACI (1/100/s^2)	121 (112-160)	163 (142-185)	**0.015**	144 (102-188)	149 (98-175)	0.872	132 (82-152)	116 (98-155)	0.953	124-191
LVET (ms)	237 (221-252)	236 (214-265)	0.784	239 (231-250)	244 (228-267)	0.387	247 (201-269)	228 (219-264)	0.343	218-250
CO (L/min)	4.4 (4.0-4.5)	4.9 (4.5-5.7)	**0.009**	5.4 (5.2-5.6)	5.5 (5.0-6.5)	0.499	7.5 (7.3-8.0)	7.1 (6.5-8.0)	**0.041**	5-6.5
TPR (dyn·s·cm^{-5})	1897 (1673-2254)	1596 (1409-1809)	**0.003**	1529 (1353-1613)	1488 (1207-1569)	0.243	1056 (937-1093)	1053 (1005-1225)	0.086	1149-1537

Continuous data is represented as median (IQR) or mean (± SD). PC: pre-conceptional; PCPS: pre-conceptional post-sport; HVPT: hepatic vein pulse transit; HVI: hepatic vein impedance index; R RVPT: right renal interlobar vein pulse transit; R RIVI: right renal interlobar vein impedance index; L RVPT: left renal interlobar vein pulse transit; L RIVI: left renal interlobar vein impedance index; R aut PI: right uterine artery Doppler pulsatility index; R aut RI: right uterine artery Doppler resistivity index; L aut PI: left uterine artery Doppler pulsatility index; L aut RI: left uterine artery Doppler resistivity index; TBW: total body water volume; ECW: extracellular water volume; ICW: intracellular water volume; ECW/ICW: ratio of ECW to ICW; DBP: diastolic blood pressure; MAP: mean arterial pressure; VI: velocity index; ACI: aorta flow acceleration index; LVET: left ventricular ejection time; CO: cardiac output; TPR: total peripheral resistance. A p-value < 0.05 is considered statistically significant.

Table 6: Effect of physical activity on the CV system of PC women subdivided based on TPR.

	Low TPR			Normal TPR			High TPR			
	PC (N = 8)	**PCPS (N = 8)**	**P-value**	**PC (N = 11)**	**PCPS (N = 11)**	**P-value**	**PC (N = 21)**	**PCPS (N = 21)**	**P-value**	**Reference**
HVPT (ms)	0.21 (0.17-0.32)	0.19 (0.10-0.32)	0.161	0.15 (0.13-0.16)	0.16 (0.13-0.23)	0.424	0.16 (0.12-0.20)	0.15 (0.11-0.20)	0.986	0.14-0.23
HVI	0.92 (±0.59)	1.14 (±0.46)	0.128	1.27 (±0.36)	1.39 (±0.29)	0.404	1.31 (±0.49)	1.37 (±0.39)	0.589	1.11-1.57
R RVPT (ms)	0.30 (±0.13)	0.30 (±0.18)	0.972	0.23 (±0.09)	0.26 (±0.07)	0.327	0.24 (±0.09)	0.25 (±0.09)	0.729	0.22-0.36
R RIVI	0.50 (0.29-0.69)	0.54 (0.42-0.59)	0.889	0.52 (0.48-0.60)	0.51 (0.47-0.53)	0.139	0.52 (0.39-0.56)	0.55 (0.40-0.60)	0.651	0.32-0.44
L RVPT (ms)	0.36 (±0.11)	0.32 (±0.12)	0.278	0.32 (±0.09)	0.29 (±0.08)	0.205	0.27 (±0.08)	0.28 (±0.09)	0.661	0.23-0.36
L RIVI	0.45 (±0.10)	0.50 (±0.12)	0.246	0.43 (±0.09)	0.49 (±0.09)	0.091	0.45 (±0.10)	0.48 (±0.15)	0.404	0.33-0.42
R Aut PI	1.48 (±0.31)	1.59 (±0.08)	0.340	1.37 (±0.22)	1.38 (±0.28)	0.936	1.29 (±0.22)	1.36 (±0.23)	0.347	1.03-1.29
R Aut RI	0.89 (0.78-0.93)	0.89 (0.86-0.90)	0.400	0.80 (0.70-0.85)	0.83 (0.72-0.88)	0.683	0.79 (0.70-0.84)	0.81 (0.75-0.87)	0.082	0.68-0.78
L Aut PI	1.37 (±0.18)	1.55 (±0.12)	**0.029**	1.41 (±0.22)	1.42 (±0.17)	0.940	1.35 (±0.24)	1.38 (±0.20)	0.644	0.92-1.35
L Aut RI	0.83 (0.77-0.87)	0.88 (0.85-0.90)	0.208	0.83 (0.76-0.88)	0.83 (0.78-0.86)	0.790	0.80 (0.75-0.88)	0.82 (0.74-0.88)	0.322	0.63-0.82
TBW (L)	36.33 (34.46-46.18)	35.62 (33.02-39.42)	0.263	34.03 (29.08-40.00)	32.87 (28.44-38.40)	0.722	31.14 (29.91-35.42)	30.68 (28.72-32.65)	0.768	31.11-36.56
ECW (L)	16.05 (14.80-22.95)	15.15 (13.90-17.00)	0.401	14.36 (12.20-17.37)	14.38 (11.64-16.93)	0.790	13.20 (12.57-14.92)	13.05 (11.97-14.20)	0.651	13.15-15.92
ICW (L)	20.82 (19.15-24.25)	20.48 (19.03-22.42)	0.575	19.67 (16.98-22.63)	17.52 (16.48-20.92)	0.110	17.75 (17.22-19.70)	17.49 (16.75-18.64)	0.821	17.66-20.46
ECW/ICW	0.75 (0.72-0.90)	0.75 (0.72-0.76)	0.674	0.73 (0.71-0.78)	0.76 (0.71-0.90)	0.965	0.74 (0.72-0.78)	0.74 (0.72-0.78)	0.952	0.73-0.79
DBP (mmHg)	87 (±6)	85 (±6)	0.425	88 (±13)	84 (±8)	0.169	96 (±11)	92 (±9)	**0.047**	77-93

Table 6: Effect of physical activity on the CV system of PC women subdivided based on TPR (continued).

MAP (mmHg)	97 (±8)	98 (±6)	0.616	98 (±13)	94 (±8)	0.109	107 (±12)	102 (±10)	0.066	87-105
VI (1/1.000/s)	60 (±15)	57 (±11)	0.356	61 (±24)	63 (±18)	0.575	60 (±18)	66 (±14)	0.096	55-81
ACI ($1/100/s^2$)	136 (92-157)	117 (109-159)	1.000	143 (82-188)	149 (87-173)	0.859	131 (107-166)	162 (136-190)	**0.030**	124-191
LVET (ms)	248 (199-275)	234 (226-270)	0.401	237 (231-250)	249 (235-273)	**0.045**	238 (222-251)	232 (216-256)	0.728	218-250
CO (L/min)	7.6 (7.2-8.2)	7.3 (6.6-8.1)	0.073	5.5 (5.3-5.9)	5.8 (5.1-6.8)	0.646	4.5 (4.4-5.3)	5.1 (4.6-5.9)	**0.025**	5-6.5
TPR ($dyn \cdot s \cdot cm^{-5}$)	1039 (926-1079)	1044 (998-1196)	0.093	1374 (1329-1511)	1366 (1117-1456)	0.534	1760 (1600-1941)	1569 (1448-1756)	**0.001**	1149-1537

Continuous data is represented as median (IQR) or mean (± SD). PC: pre-conceptional; PCPS: pre-conceptional post-sport; HVPT: hepatic vein pulse transit; HVI: hepatic vein impedance index; R RVPT: right renal interlobar vein pulse transit; R RIVI: right renal interlobar vein impedance index; L RVPT: left renal interlobar vein pulse transit; L RIVI: left renal interlobar vein impedance index; R aut PI: right uterine artery Doppler pulsatility index; R aut RI: right uterine artery Doppler resistivity index; L aut PI: left uterine artery Doppler pulsatility index; L aut RI: left uterine artery Doppler resistivity index; TBW: total body water volume; ECW: extracellular water volume; ICW: intracellular water volume; ECW/ICW: ratio of ECW to ICW; DBP: diastolic blood pressure; MAP: mean arterial pressure; VI: velocity index; ACI: aorta flow acceleration index; LVET: left ventricular ejection time; CO: cardiac output; TPR: total peripheral resistance. A p-value < 0.05 is considered statistically significant.

A correlation analysis was performed to establish whether the shift in CO was related to the shift in ACI and VI. No significant correlation was found between the shift in CO and the shift in ACI or VI (**Fig. S6**).

Relationship between the physical activity interval and the shift CV in parameters

In order to establish whether a more extended period between the PC and PCPS measurement was related to a more pronounced shift in CO and TPR, a correlation analysis was performed (**Fig. S7 and S8**). However, no significant correlation was observed between the change in CO or TPR and the time interval between the PC and PCPS measurements.

Pregnancy outcome before and after physical activity

After evaluating the profile-specific effect of physical activity, we sought to confirm whether the advice to engage in PC physical activity resulted in a reduced incidence of GHD in a subsequent pregnancy within the study population. In total, ten women (25.00%) experienced a pregnancy prior to the advice to exercise pre-conceptionally, as well as a pregnancy following the advice. Remarkably, all ten women experienced complicated pregnancies prior to the physical activity recommendation, ranging in severity from different types of GHD to even miscarriages (**Fig. S9**). Intriguingly, five of these individuals (50.00%) experienced an uncomplicated pregnancy after the advice to engage in physical activity. Only two women (20.00%) continued to experience GHD in the pregnancy following the advice to exercise in the pre-conception period. Furthermore, two women (20.00%) developed gestational diabetes in the subsequent pregnancy, while one (10.00%) had to endure a miscarriage.

Most interestingly, all five women characterized by a high baseline CO and low TPR profile experienced a post-sport pregnancy free from GHD. In contrast, both women exhibiting a low baseline CO and high TPR profile still suffered from GHD in the post-sport pregnancy. These observations sparked interest in the individual CV systems of the two women who still experienced GHD in the post-sport pregnancy. Results revealed minimal changes in CO following the physical activity advice (**Fig. S10**). Additionally, although their TPR decreased, it remained elevated. In summary, despite observing an increased VI and ACI, these two women persisted within the same PC CV profile, characterized by a low CO and high TPR. Nonetheless, the onset of GHD in their post-sport pregnancy was delayed compared to the pre-sport pregnancy (pre: 27w+5d vs. post: 30w+2d and pre: 28w+0d vs. 31w+3d, respectively).

DISCUSSION

Numerous studies have explored the preventive potential of physical activity in the context of GHD. However, the focus of these studies has been primarily limited to the effects during pregnancy. For example, a randomized controlled trial conducted by Barakat et al., involving 765 women, demonstrated that a physical activity program during pregnancy served as an effective preventive measure against GHD, as it significantly reduced the incidence of GHD [34]. These findings are consistent with other studies, highlighting the significance of physical activity during pregnancy for reducing the risk of GHD [19, 35-37]. Delving deeper into this topic, Witvrouwen et al. investigated the mechanisms through which physical activity mitigates the risk of GHD during pregnancy [27]. Their study revealed notable improvements in various aspects of the CV system, such as enhanced endothelial function, reduced arterial stiffness, and increased angiogenesis. These findings further support the importance of physical activity for promoting the CV system during pregnancy in order to reduce the risk of GHD.

However, recent studies have shown that the greatest reduction in the risk of GHD is observed in women who exercise *prior* to conception [38, 39]. For example, Aune et al. demonstrated a 40% reduction in the risk of developing PE when women participated in 5-6 hours of physical activity a week prior to conception [39]. However, these studies have primarily focused on investigating the relationship between PC physical activity and the incidence of GHD in subsequent pregnancies.

In our research, we aimed to delve deeper into the underlying mechanisms through which physical

activity prior to conception contributes to this substantial risk reduction. The key findings of our study are that 1) just like in pregnancy, distinct CV profiles exist prior to conception according to CO and TPR values; 2) the impact of physical activity depends on the type of PC CV profile.

Physical activity does not achieve the expected results on the CV system when analyzed for the total study population

Upon analyzing the effects of PC physical activity on the CV system of the total study population, we found no significant changes in CO following the recommendation to engage in physical activity. This observation is consistent with previous studies that have specifically examined the effects of physical activity on resting CO. These studies have consistently shown that regular exercise leads to increased resting SV and decreased resting HR, resulting in no significant change in resting CO [40, 41].

However, our analysis also revealed a paradoxical pattern with both improvements in TPR, MAP, and DBP as well as deteriorations in L RIVI and R Aut RI following the advice to engage in physical activity. This intriguing observation raises questions about the beneficial effects of PC physical activity in optimizing the CV system before engaging in subsequent pregnancies. To better understand these complex relationships, we conducted a more comprehensive investigation by categorizing patients according to their baseline CO and TPR values, which allowed us to identify distinct PC CV profiles similar to those observed during pregnancy. Interestingly, the impact of physical activity on these profiles varied significantly.

Physical activity normalizes a high CO or low TPR profile, possibly by increasing HVI

Among women with a high baseline CO profile, we observed a significant decrease in CO following the physical activity advice. Conversely, women with a low baseline TPR profile exhibited a tendency for an increase in TPR, although not significant. These changes indicate that physical activity has the potential to normalize high CO or low TPR profiles, thereby promoting the CV system prior to pregnancy. The decrease in CO among women with a high CO profile could be attributed to the observed significant increase in venous wall stiffness, reflected by the elevated HVI. This increased stiffness reduces venous compliance, restricting the amount of blood returned to the heart, leading to a decrease in preload and subsequently reducing SV and CO, according to Starlings' law [42]. However, no significant correlation was found between the shift in CO and HVI in our study population. Nonetheless, a negative trend was observed, suggesting a potential relationship between both parameters. Further analysis with a larger sample size is necessary to explore this relationship more comprehensively.

The observed tendency for an increased post-sport TPR in women with a low baseline TPR profile could be attributed to the compensatory response of the body. Women characterized by a low baseline TPR also exhibited a high baseline CO. Upon analyzing their post-sport CV system, a tendency towards a decreased CO was observed. In response to a reduced CO, the body initiates compensatory mechanisms, such as increasing TPR, to maintain MAP within the normal range and ensure adequate blood flow to vital organs. Hence, the observed tendency towards an increased TPR following the advice to exercise could be attributed to this compensatory response [42].

Nonetheless, the observed significant increase in L Aut PI among women with a high baseline CO or low TPR profile presents an intriguing aspect that requires further investigation. Although the precise explanation remains elusive, our findings suggest plausible local effects and interactions of physical activity within the uterine vascular bed. However, it is essential to note that during pregnancy, the normal physiological response is a decrease in L Aut PI [23]. Hence, the importance of the observed increase lies in assessing whether the CV adaptations induced by pregnancy can restore normal values of this pulsatility index. Further research is needed to elucidate the underlying mechanisms and explore the clinical implications of this finding.

The majority of women exhibit unchanged normal CO and TPR profiles in response to physical activity

When analyzing the CV system at least six months after receiving the advice to engage in physical

activity, we did not observe significant changes in CO or TPR for women with normal baseline CO or normal TPR profiles, respectively. The lack of change in these parameters is favorable, as the normal CO and TPR values were maintained without any undesirable increase or decrease. However, it is important to note that among women with a normal baseline CO profile, 31.58% experienced a transition to either a high or low CO profile following the physical activity advice. Similarly, among women with a normal baseline TPR profile, 27.27% exhibited a transition to a low TPR profile. These transitions suggest a dynamic nature of the CV system and highlight individual variations in response to physical activity. It is worth noting that the observed transitions may not be favorable, as they indicate a shift towards a less optimal CV profile, which increases the risk of GHD during pregnancy [22]. Therefore, while the lack of significant changes in CO and TPR for women with normal baseline profiles is generally positive, the observed transitions in a subset of patients raise concerns about the potential negative impact of physical activity on their initial favorable CV profiles.

Additionally, women with a normal baseline CO profile showed a significant increase in L RIVI, while those with a normal baseline TPR profile demonstrated a non-significant tendency towards increased L RIVI following the physical activity advice. This intriguing finding suggests reduced blood flow and impaired venous drainage from the left kidney. The consequences of such alterations include an increased renal workload and impaired renal oxygenation, ultimately impacting the kidney's overall functionality and long-term efficiency [42-44]. However, it is essential to acknowledge that PC women typically have lower venous filling compared to pregnant women, rendering them more susceptible to external factors such as abdominal muscle contractions or breathing movements during measurement [22]. Consequently, while Doppler ultrasound remains the most advanced technique currently available for assessing the venous compartment in non-pregnant women, its limitations within this context must be considered.

Physical activity normalizes a low CO or high TPR profile, possibly by increasing ACI

Physical activity played a significant role in normalizing both low baseline CO and high TPR profiles. The observed changes in CO and TPR can be attributed to several underlying mechanisms. For example, regular exercise enhances cardiac contractility, leading to an increased CO [40, 45]. Additionally, shear stress during physical activity may stimulate nitric oxide synthesis, resulting in a reduced TPR [46]. These physiological adaptations induced by physical activity could explain the observed normalization of low CO or high TPR profiles.

During our study, we also observed a significant increase in ACI following physical activity in women with low baseline CO or high TPR profiles. This finding suggests that physical activity exerts a favorable effect on the CV system by enhancing cardiac blood outflow. This enhanced blood outflow leads to reduced afterload, contributing to the restoration of CO to normal levels [42]. Our results showed no significant correlation between the shift in CO and ACI. However, several outliers were present, which could have influenced the analysis. Further analysis with a larger sample size is necessary to explore this relationship more comprehensively.

It is crucial to emphasize that while a low baseline CO and high TPR exhibited significant increases and decreases, respectively, not all women with initially low CO or high TPR values achieved normalization. This discrepancy could potentially be attributed to inadequate levels of physical activity among these individuals. However, we lack information regarding adherence to the physical activity advice, which hinders our ability to draw definitive conclusions in this regard.

The response to physical activity may vary among individuals

Previous studies have already demonstrated a reduced incidence of GHD among women who exercise prior to conception. However, these studies did not discriminate between high resistance (i.e., TPR) versus high volume (i.e., CO) circulations. Hence, we conducted a descriptive analysis on ten women who had documented maternal and neonatal outcomes for both the pre-

and post-physical activity advice pregnancies. Comparing the outcomes, we observed a notable reduction in GHD incidence among women with a high baseline CO and low TPR profile, suggesting a beneficial effect of PC physical activity on this CV profile. However, the persistence of GHD in women with a low baseline CO and high TPR profile despite the advice to perform physical activity prior to conception raises questions about the underlying mechanisms. Our findings indicate that minimal changes were observed in their individual CO level when we compared the CV measurement before and after receiving the advice to exercise prior to conception. Additionally, although their TPR decreased to some extent, it remained elevated. As previously mentioned, individual responses to physical activity can vary, and there may be other factors contributing to the persistence of GHD in these particular women. It is possible that underlying physiological or genetic factors, beyond the influence of physical activity, play a role in their CV adaptation potential [40]. However, it is essential to consider that limited physical activity could also have been a contributing factor, as we lack documentation on their activity levels. Furthermore, there is a possibility that some women may revert to their original 'unfavorable' CV profile once the adaptations induced by pregnancy take place. However, it is noteworthy that the onset of GHD in the post-sport pregnancy of these women was delayed compared to the pre-sport pregnancy. This delay in GHD onset is favorable as it reduces the risk of prematurity. Further research is needed to elucidate these possibilities.

Research novelty

Our research introduces several novel aspects that significantly contribute to extending the knowledge on the impact of physical activity on the CV system of PC women at risk for GHD in a subsequent pregnancy. Firstly, we specifically focused on investigating the effect of physical activity on the CV system of PC women, diverging from previous studies that predominantly focused on pregnant women. Secondly, our research distinguishes itself from others as our research group is the only one measuring the extended aspects of the CV system, including the heart, arterial and venous compartment, and body fluid status. This comprehensive evaluation provides a more holistic understanding of the effects of physical activity on the CV system in PC women. Furthermore, our investigation uniquely considered the existence of distinct PC CV profiles and evaluated the effect of physical activity on these specific profiles, thereby enhancing the precision and depth of our findings.

Our research represents a pioneering contribution by elucidating the underlying physiological mechanisms through which physical activity prior to conception mitigates the risk of GHD in subsequent pregnancies, offering novel insights into the field. In essence, our findings serve as a foundation for future studies aiming to develop personalized exercise programs that are tailored to the distinctive PC CV profile of each woman. This represents a significant shift in maternal healthcare, emphasizing proactive interventions before conception rather than reactive measures during pregnancy. Such a proactive and personalized approach has the potential to improve pregnancy outcomes and alleviate the burden of GHD on both mother and fetus.

Limitations of this study

Our study has several limitations that should be considered when interpreting the results. Firstly, the small sample size within each CV profile group limits the generalizability of our findings. This small sample size also forced us to analyze the effect of physical activity on CO and TPR separately rather than considering the effect when CO and TPR are combined in one profile. However, since women can exhibit different combinations of CO and TPR, future investigations with larger sample sizes should explore the effect of physical activity on these combined profiles. Nonetheless, we expect future results to align with our findings since CO and TPR are directly linked to one another by MAP.

Secondly, although we conducted a comprehensive analysis, we did not observe a significant correlation between the change in CO or TPR and the time interval between the PC and PCPS measurements. This suggests that the physical activity intervention duration may not have substantially influenced the observed changes in CO and TPR. However, a significant limitation of our study is the lack of specific information regarding the type, intensity, and adherence to the

prescribed physical activity regimen by the patients. This limitation hinders our ability to ascertain the direct impact of physical activity on the observed changes in CO and TPR. Therefore, future studies should address this limitation by collecting detailed information on the nature and adherence to the physical activity regimen, enabling a more comprehensive understanding of the relationship between physical activity and CV parameters in the pre-conception period.

Future perspectives

In light of our findings, several future perspectives emerge that can further improve our understanding of the relationship between physical activity and the PC CV system. Firstly, it is crucial to conduct larger-scale studies that explore the effect of physical activity on CV profiles combining CO and TPR in PC women at risk for GHD. Secondly, the extent to which physiological adaptations induced by pregnancy may counteract or enhance the efforts to bring the PC CV parameters into a favorable starting position remains unknown. Therefore, future studies should also consider the effect of pregnancy on the PC CV profiles to better understand the interplay between pregnancy-induced adaptations and the effectiveness of PC interventions for optimizing the CV system before pregnancy. Thirdly, it is essential that future studies document detailed information on the type, intensity, and adherence of patients to physical activity interventions. This will help establish evidence-based guidelines in obstetric care. In the long term, these guidelines will provide a recommendation on the type of exercise, duration, intensity, and other factors best suited for each PC CV profile, aiming to maximize the effectiveness of physical activity as a preventive measure against GHD.

Our research team has already initiated a new prospective study on this topic, which is ongoing at the time of publication. This ongoing study aims to elucidate further the effect of physical activity on the CV system of PC women at risk for GHD in a subsequent pregnancy and refine our understanding of its implications for GHD (**Fig. S11**).

In addition to these future perspectives, there is an upcoming need for the development of improved techniques for assessing the venous compartment in PC women. While our study represents a pioneering effort to include the venous compartment in the evaluation of physical activity on different PC CV profiles, it is evident that current imaging modalities have limitations in accurately measuring the venous hemodynamic function. Improvements in imaging technologies, such as novel ultrasound techniques or other non-invasive methods, are essential to better understand the effect of physical activity on the venous compartment in PC women at risk for GHD in a subsequent pregnancy.

CONCLUSION

In conclusion, the present study demonstrates that distinct CV profiles are also present prior to conception and that physical activity in the pre-conceptional period induces adaptations in the CV system in a profile-specific manner. However, limitations such as the small sample size and lack of specific information on the activity regimen should be acknowledged. Further research with larger samples and comprehensive data collection is needed to deepen our understanding of the relationship between physical activity and PC CV profiles. Additionally, the effects of pregnancy on these exercise-induced changes require further investigation. Overall, this study offers insights into the preventive effect of physical activity prior to conception and highlights the importance of lifestyle interventions in improving pregnancy outcomes.

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Author contributions – PD conceived and designed the research presented in this thesis. WG performed the cardiovascular measurements. PD, PV, BV, and SN imported data in the electronic case report file. PV performed data analysis. WG and PD provided assistance. PV wrote the thesis, and PD and WG provided feedback.

SUPPORTING INFORMATION

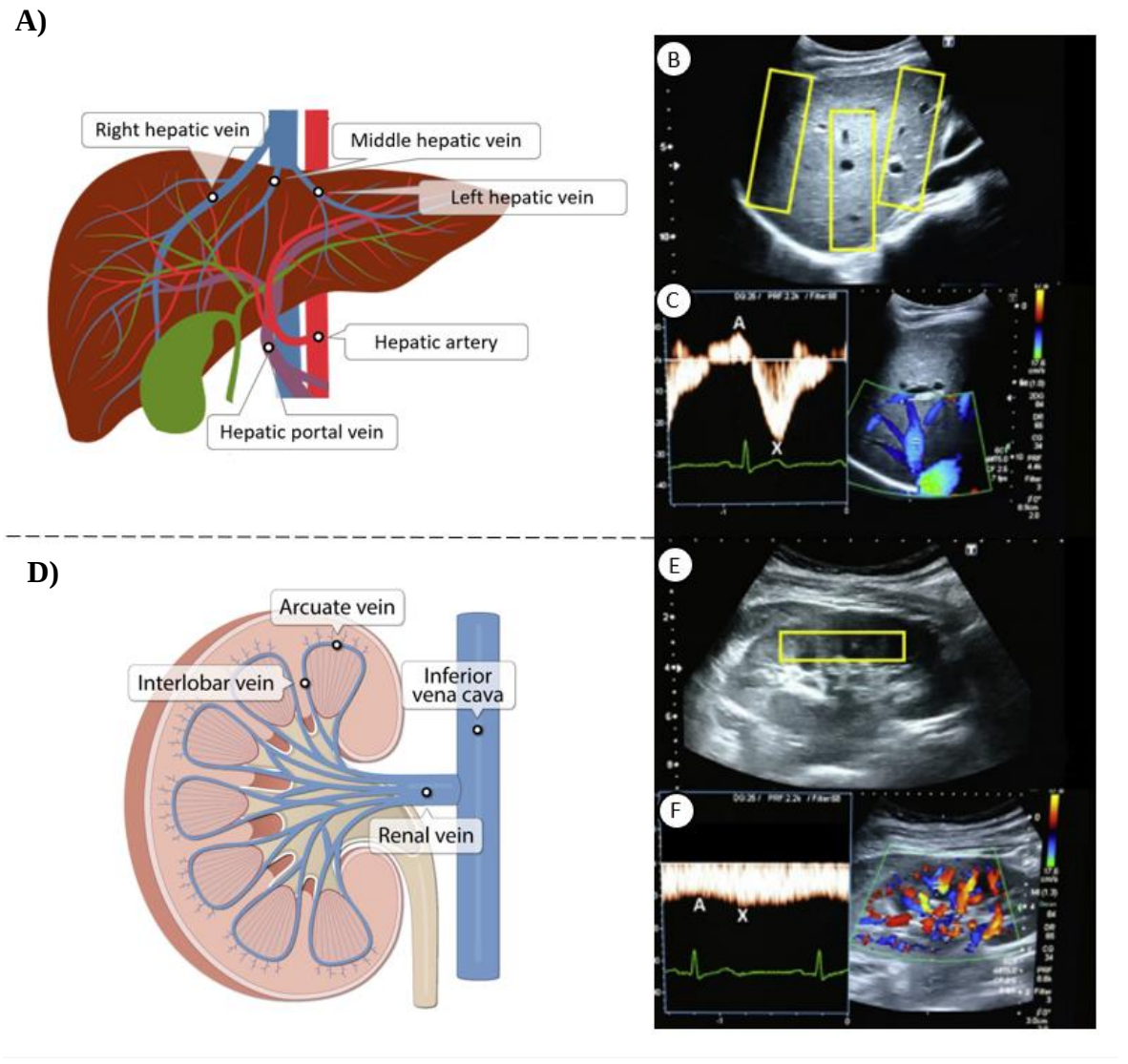


Fig. S1 – **Ultrasound imaging of liver and kidney. A)** Schematic representation of the hepatic circulation indicating the veins of interest, i.e., right, middle, and left hepatic vein. **B)** These three branches should be searched in the regions of interest marked by the yellow frames. **C)** The hepatic vein and its branches are identified by color Doppler flow mapping. This allows discrimination between the hepatic vein (blue) and portal vein (red), as shown in the right panel. Doppler signals are sampled at three different locations, generating an output as shown in the left panel. The venous maximum velocity X and minimum velocity A are measured and averaged, after which the impedance index can be calculated with the formula [(maximum velocity – minimum velocity)/ maximum velocity]. The venous pulse transit is measured by the time interval between the ECG P wave and the corresponding venous Doppler A wave. **D)** Schematic representation of the renal circulation indicating the veins of interest, i.e., interlobar vein. **E)** The region of interest in the kidneys is located between the intrarenal pyelon and renal cortex. **F)** The renal vein is identified by color Doppler flow mapping. This allows discrimination between the interlobar vein (blue) and interlobar artery (red), as shown in the right panel. Doppler signals are sampled at three different locations, generating an output shown in the left panel. Renal impedance index and pulse transit are measured in the same way as for the liver [20].

A)

B)

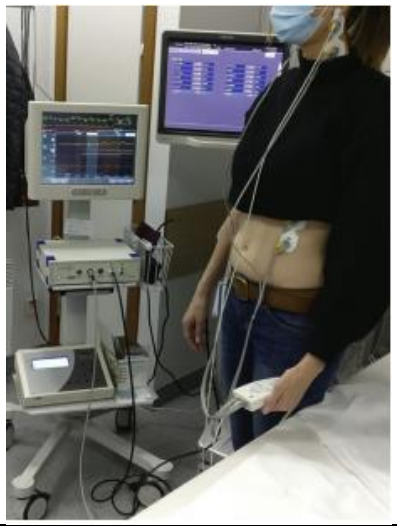


Fig. S2 – **Illustration of the bioimpedance spectrum analysis and impedance cardiography.** A) Bioimpedance spectrum analysis is used to measure body water volume homeostasis. This analysis is performed in the supine position by placing four electrodes: two on the right hand and two on the right foot. B) During impedance cardiography the function of the heart, the central, and peripheral arteries are measured. This is measured in both supine as well as standing position in order to evaluate the cardiovascular orthostatic response. For this measurement two electrodes are placed in the neck and two laterally at the lower thorax [20].

Table S1: Demographic factors and characteristics of PC women subdivided based on CO level.

	Low CO N = 12	Normal CO N = 19	High CO N = 9	P^{N-L}	P^{N-H}	P^{L-H}
Age (years)	31.3 (±3.8)	31.4 (±4.1)	31.1 (±2.7)	0.996	0.984	0.996
BMI (kg/m2)	19.8 (18.5-22.3)	22.3 (20.0-26.8)	31.6 (27.6-33.5)	0.249	**0.035**	**<0.001**
Indication CV measurement						
EH	1 (8.3%)	4 (21.1%)	1 (11.1%)	0.348	0.521	0.830
Previous pregnancy complications	9 (75.0%)	13 (84.2%)	6 (66.7%)	0.527	0.291	0.676
Familial GH	0 (0.0%)	1 (5.3%)	0 (0.0%)	0.419	0.483	1.000
Familial EH	0 (0.0%)	1 (5.3%)	0 (0.0%)	0.419	0.483	1.000
Low own birth weight	2 (16.7%)	3 (15.8%)	0 (0.0%)	0.948	0.207	0.198
Other	4 (33.3%)	3 (15.8%)	4 (44.4%)	0.255	0.102	0.604
Previous pregnancy outcome						
Normal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	1.000	1.000
GH	0 (0.0%)	1 (5.3%)	0 (0.0%)	0.419	0.483	1.000
EPE	3 (25.0%)	6 (31.6%)	1 (11.1%)	0.694	0.243	0.422
LPE	3 (25.0%)	0 (0.0%)	2 (22.2%)	0.022	0.033	0.822
HELLP	4 (33.3%)	6 (31.6%)	1 (11.1%)	0.919	0.243	0.237
IUGR	3 (25.0%)	7 (36.8%)	1 (11.1%)	0.492	0.159	0.422
Other	0 (0.0%)	2 (10.5%)	1 (11.1%)	0.245	0.963	0.237
Comorbidity						
Hypertension	4 (33.3%)	5 (26.3%)	0 (0.0%)	0.675	0.090	0.054
Diabetes	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	1.000	1.000
Thyroid problems	0 (0.0%)	2 (10.5%)	0 (0.0%)	0.245	0.312	1.000
Thrombophilia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	1.000	1.000
Kidney problems	0 (0.0%)	1 (5.3%)	0 (0.0%)	0.419	0.483	1.000
Other	4 (33.3%)	1 (5.3%)	1 (11.1%)	0.038	0.575	0.237
Family history of CV	4 (33.3%)	9 (47.4%)	3 (33.3%)	0.166	0.774	0.211
Medication use						
Ace inhibitor	1 (8.3%)	3 (15.8%)	0 (0.0%)	0.546	0.207	0.375
Beta blocker	3 (25.0%)	3 (15.8%)	0 (0.0%)	0.527	0.207	0.105
Calcium antagonist	1 (8.3%)	3 (15.8%)	0 (0.0%)	0.546	0.207	0.375
Other	1 (8.3%)	3 (15.8%)	2 (22.2%)	0.546	0.678	0.368

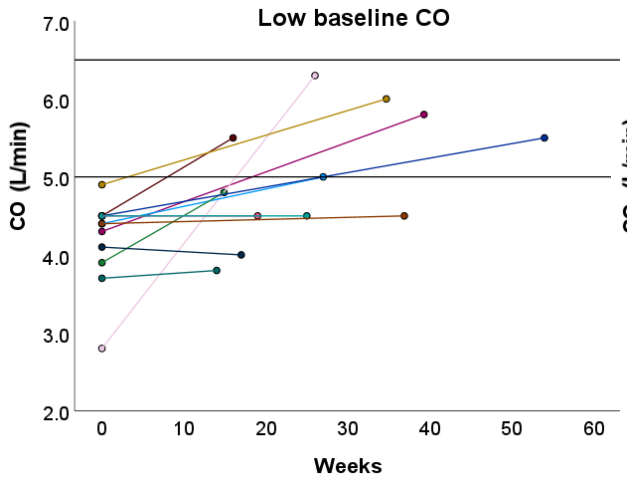
Continuous data is represented as median (IQR) or mean (± SD). Categorical variables are displayed as n (%). CV: cardiovascular; EH: essential hypertension; GH: gestational hypertension; EPE: early-onset preeclampsia; LPE: late-onset preeclampsia; HELLP: hemolysis, elevated liver enzymes, low platelet count; IUGR: intrauterine growth restriction. The level of significance for differences between groups is indicated by P^{N-L}: normal versus low, P^{N-H}: normal versus high, P^{L-H}: low versus high. For continuous data, a p-value < 0.050 is considered statistically significant. Because the chi-square test does not take into account multiple testing, the significance level for categorical data was made more stringent i.e. a p-value <0.017 is considered statistically significant.

Table S2: Demographic factors and characteristics of PC women subdivided based on TPR level.

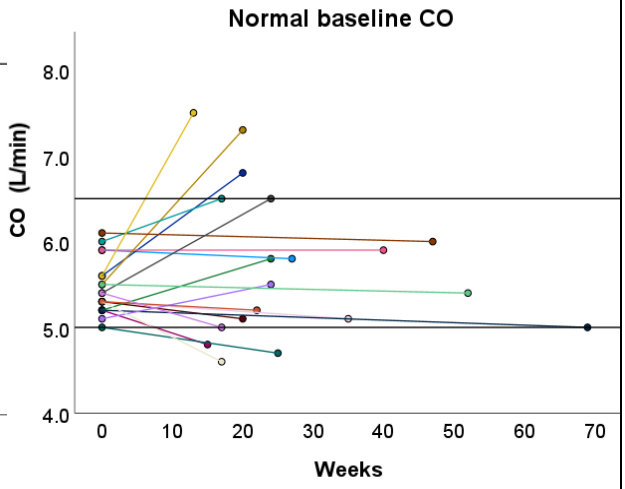
	Low TPR N = 8	Normal TPR N = 11	High TPR N = 21	P^{N-L}	P^{N-H}	P^{L-H}
Age (years)	31.4 (±2.7)	31.1 (±4.0)	31.3 (±3.9)	0.985	0.983	1.000
BMI (kg/m2)	31.0 (26.4-32.6)	22.7 (20.2-35.1)	20.1 (18.7-24.0)	0.412	0.060	**<0.001**
Indication CV measurement						
EH	1 (12.5%)	1 (9.1%)	4 (19.0%)	0.811	0.461	0.677
Previous pregnancy complications	5 (62.5%)	10 (90.9%)	16 (76.2%)	0.134	0.311	0.461
Familial GH	0 (0.0%)	0 (0.0%)	1 (4.8%)	1.000	0.462	0.530
Familial EH	0 (0.0%)	1 (9.1%)	0 (0.0%)	0.381	0.160	1.000
Low own birth weight	0 (0.0%)	1 (9.1%)	4 (19.0%)	0.381	0.461	0.184
Other	4 (50.0%)	2 (18.2%)	5 (23.8%)	0.141	0.715	0.173
Previous pregnancy outcome						
Normal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	1.000	1.000
GH	0 (0.0%)	0 (0.0%)	1 (4.8%)	1.000	0.462	0.530
EPE	1 (12.5%)	3 (27.3%)	6 (28.6%)	0.435	0.938	0.366
LPE	2 (25.0%)	0 (0.0%)	3 (14.3%)	0.080	0.188	0.495
HELLP	0 (0.0%)	4 (36.4%)	7 (33.3%)	0.055	0.864	0.061
IUGR	1 (12.5%)	4 (36.4%)	6 (28.6%)	0.243	0.652	0.366
Other	1 (12.5%)	1 (9.1%)	1 (4.8%)	0.811	0.631	0.462
Comorbidity						
Hypertension	0 (0.0%)	2 (18.2%)	7 (33.3%)	0.202	0.365	0.061
Diabetes	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	1.000	1.000
Thyroid problems	0 (0.0%)	1 (9.1%)	1 (4.8%)	0.381	0.631	0.530
Thrombophilia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	1.000	1.000
Kidney problems	0 (0.0%)	1 (9.1%)	0 (0.0%)	0.381	0.160	1.000
Other	1 (12.5%)	0 (0.0%)	5 (23.8%)	0.228	0.078	0.502
Family history of CV	2 (25.0%)	4 (36.4%)	10 (47.6%)	0.817	0.042	0.050
Medication use						
Ace inhibitor	0 (0.0%)	1 (9.1%)	3 (14.3%)	0.381	0.673	0.259
Beta blocker	0 (0.0%)	1 (9.1%)	5 (23.8%)	0.381	0.311	0.129
Calcium antagonist	0 (0.0%)	2 (18.2%)	2 (9.5%)	0.202	0.482	0.366
Other	2 (25.0%)	1 (9.1%)	3 (14.3%)	0.348	0.673	0.495

Continuous data is represented as median (IQR) or mean (± SD). Categorical variables are displayed as n (%). CV: cardiovascular; EH: essential hypertension; GH: gestational hypertension; EPE: early-onset preeclampsia; LPE: late-onset preeclampsia; HELLP: hemolysis, elevated liver enzymes, low platelet count; IUGR: intrauterine growth restriction. The level of significance for differences between groups is indicated by P^{N-L}: normal versus low, P^{N-H}: normal versus high, P^{L-H}: low versus high. For continuous data, a p-value < 0.050 is considered statistically significant. Because the chi-square test does not take into account multiple testing, the significance level for categorical data was made more stringent i.e. a p-value <0.017 is considered statistically significant.

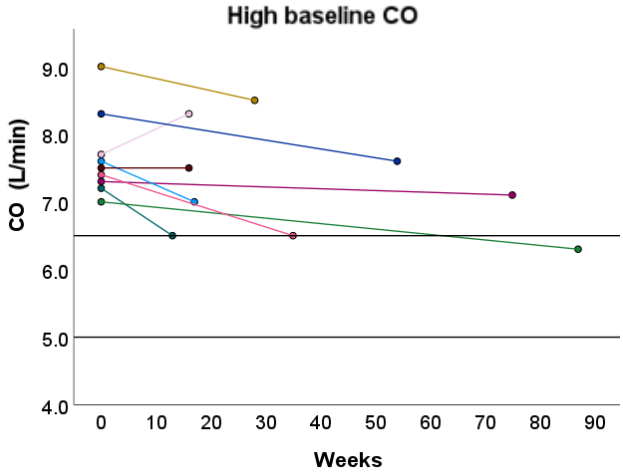
A)



B)



C)

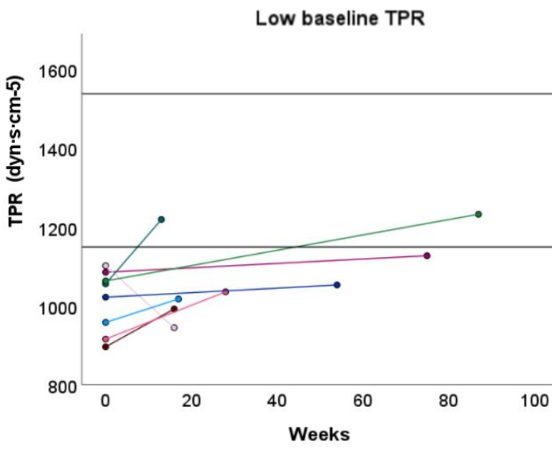


D)

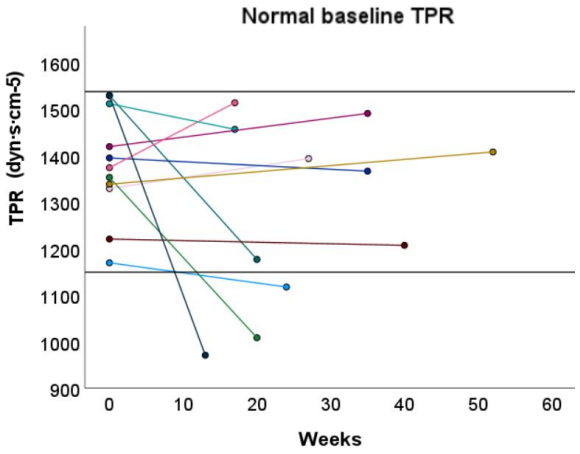
		PCPS			
		Low CO	**Normal CO**	**High CO**	**Total**
PC	**Low CO**	6	6	0	12
	Normal CO	3	13	3	19
	High CO	0	3	6	9
	Total	9	22	9	40

Fig. S3 – C**hange in CO for each individual patient**. The individual change in CO between the pre-sport and post-sport measurement is presented in function of the weeks between the measurements for the women with a low (A), normal (B), and high (C) baseline CO profile. Panel D represents a cross-tabulation of the group division based on CO at baseline and after the advice to perform physical activity. CO: cardiac output; PC: pre-conceptional; PCPS: pre-conceptional post-sport.

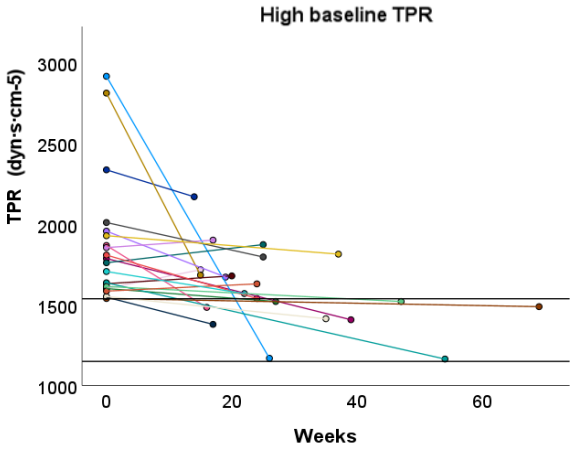
A)



B)



C)



D)

		PCPS			
		Low TPR	**Normal TPR**	**High TPR**	**Total**
PC	**Low TPR**	6	2	0	8
	Normal TPR	3	8	0	11
	High TPR	0	9	12	21
	Total	9	19	12	40

Fig. S4 – C**hange in TPR for each individual patient**. The individual change in TPR between the pre-sport and post-sport measurement is presented in function of the weeks between the measurements for the women with a low (A), normal (B), and high (C) baseline TPR profile. Panel D represents a cross-tabulation of the group division based on TPR at baseline and after the advice to perform physical activity. TPR: total peripheral resistance; PC: pre-conceptional; PCPS: pre-conceptional post-sport.

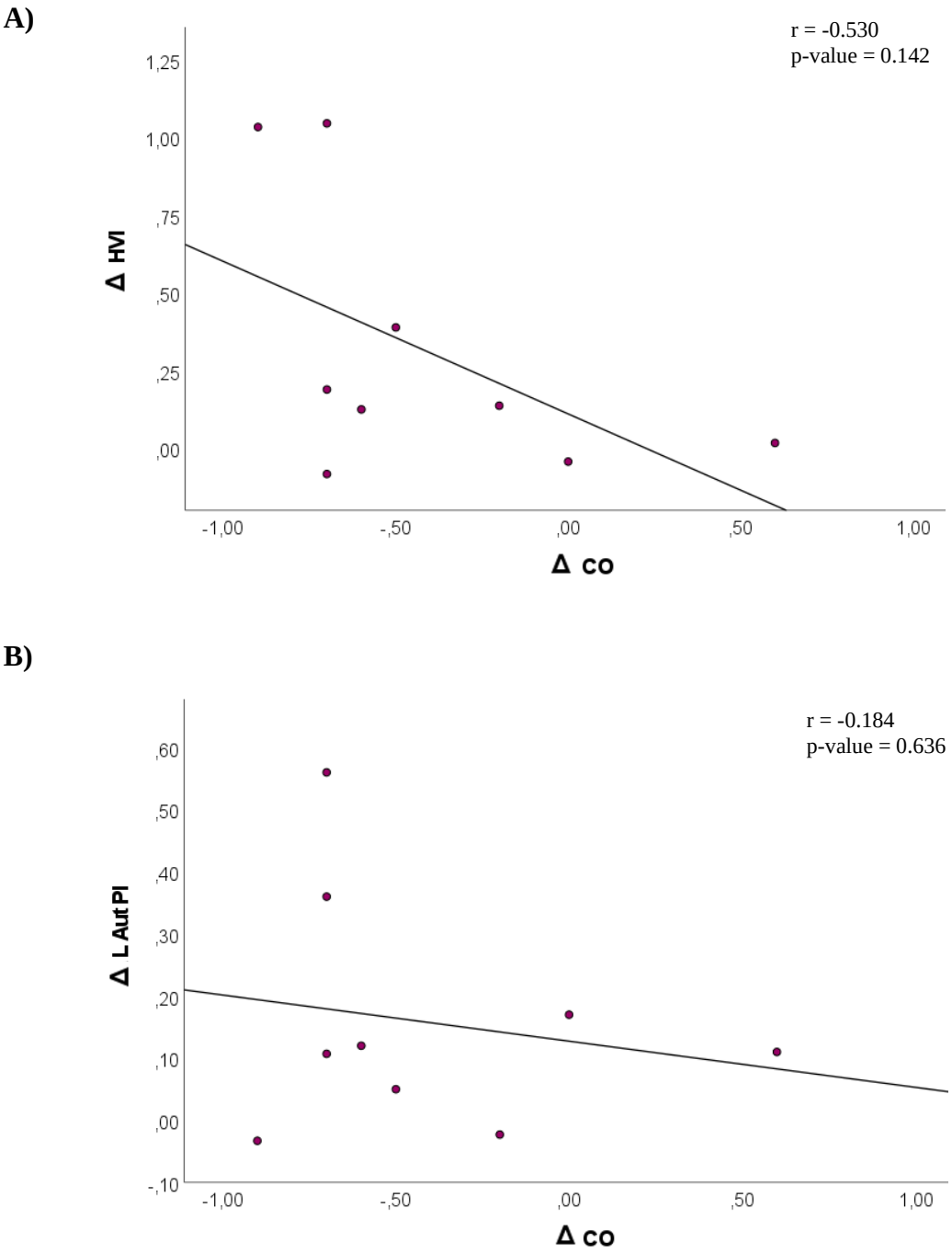


Fig. S5 – **Correlation between the change in CO and the change in HVI (A) and L Aut PI (B) for women with a high baseline CO profile.** CO: cardiac output; HVI: hepatic vein impedance index; L Aut PI: left uterine artery Doppler pulsatility index. A p-value <0.05 is considered statistically significant.

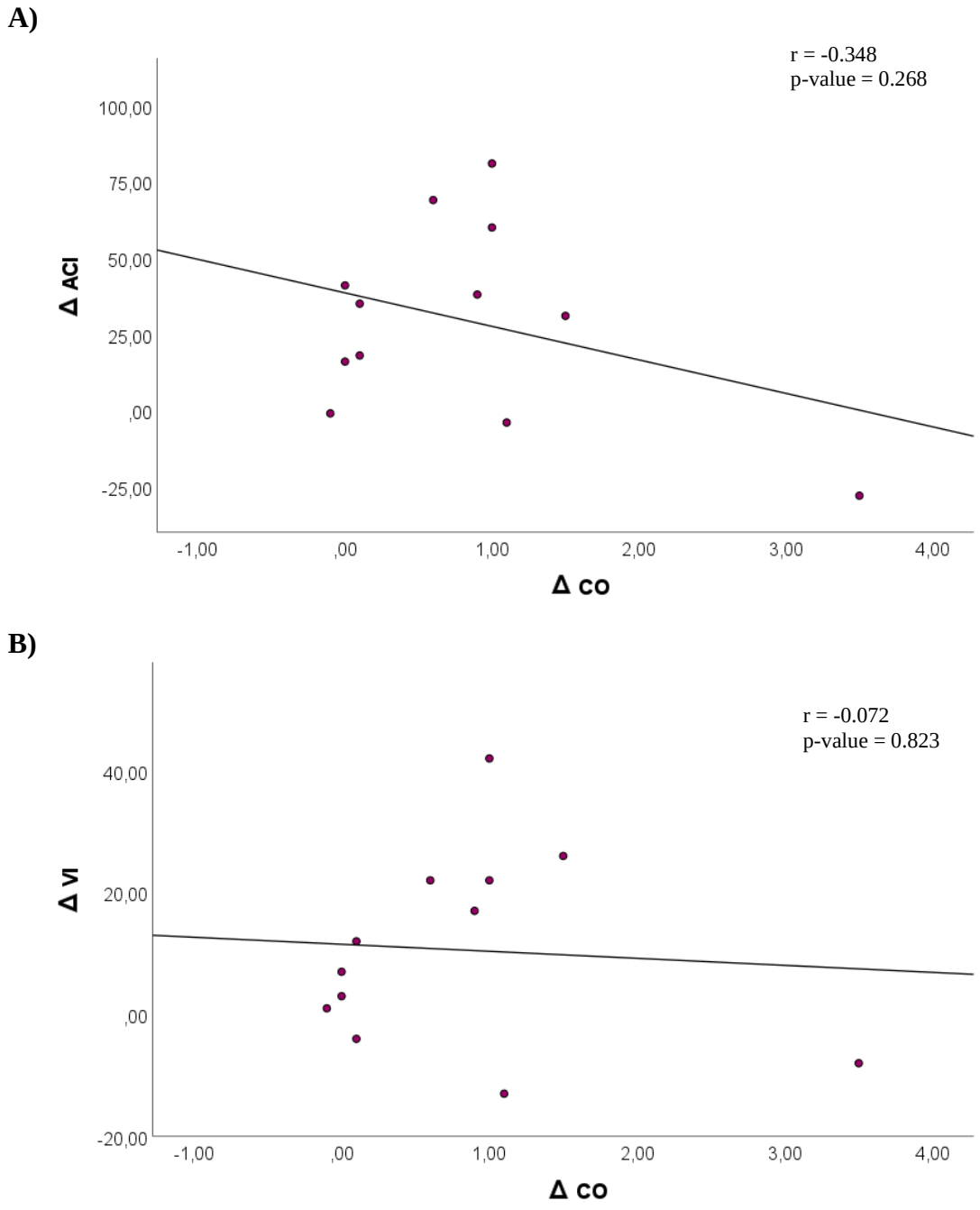


Fig. S6 – Correlation between the change in CO and the change in ACI (A) and VI (B) for women with a low baseline CO profile. CO: cardiac output; ACI: aorta flow acceleration index; VI: velocity index. A p-value <0.05 is considered statistically significant.

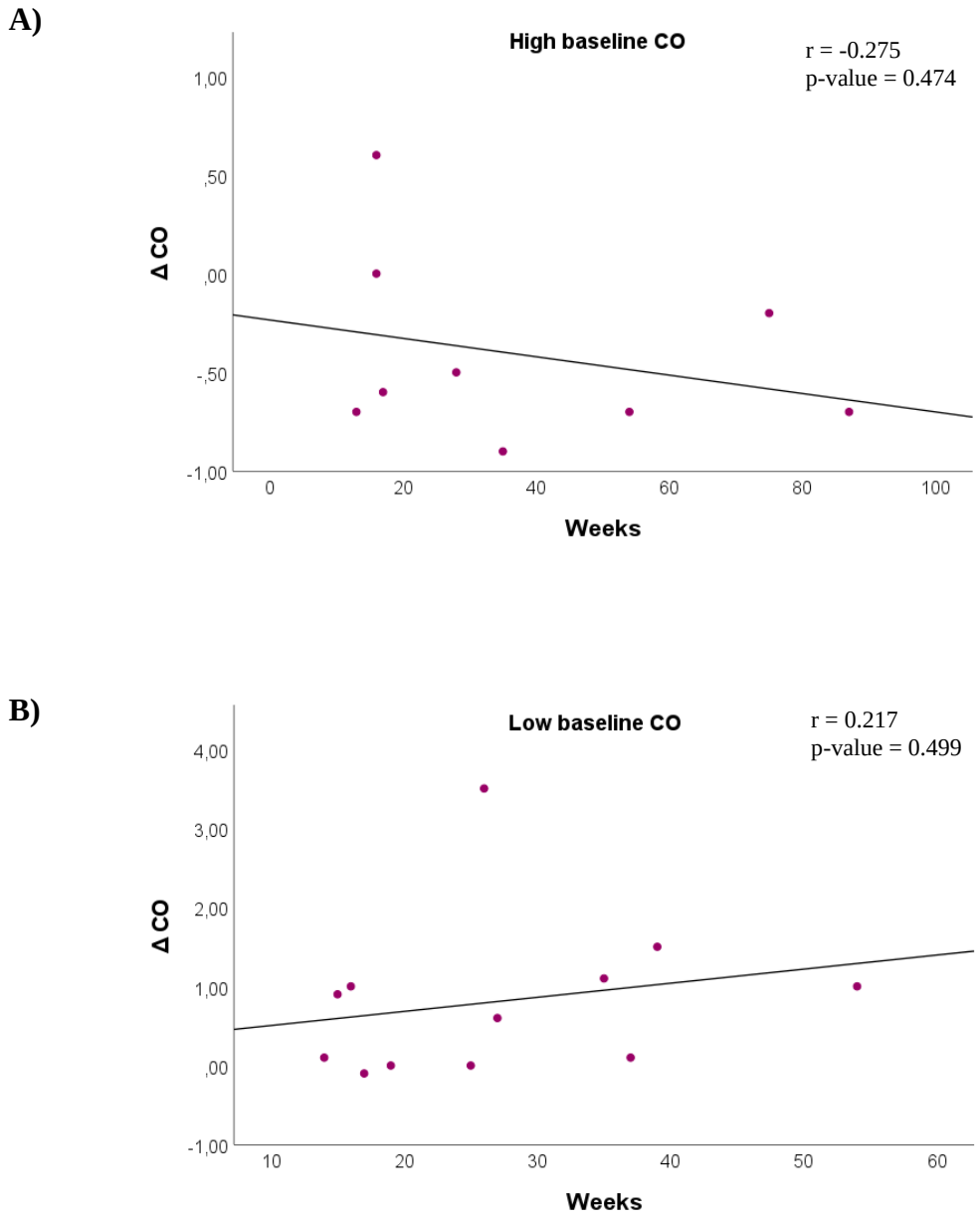


Fig. S7 – Correlation between the change in CO and the weeks between the pre-sport and post-sport measurement for women with a high baseline CO profile (A) and a low baseline CO profile (B). CO: cardiac output. A p-value <0.05 is considered statistically significant.

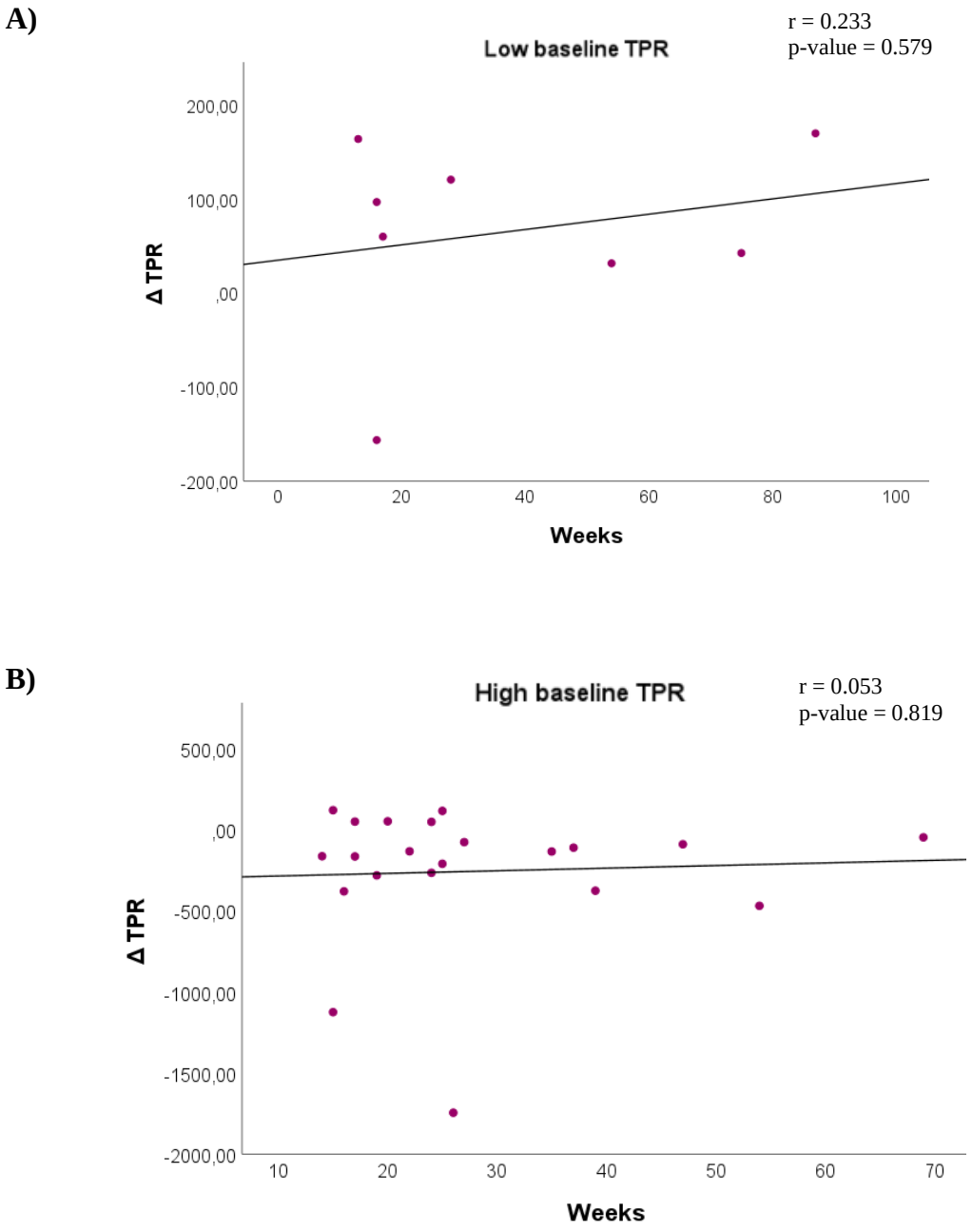


Fig. S8 – **Correlation between the change in TPR and the weeks between the pre-sport and post-sport measurement for women with a low baseline TPR profile (A) and a high baseline TPR profile (B).** TPR: total peripheral resistance. A p-value <0.05 is considered statistically significant.

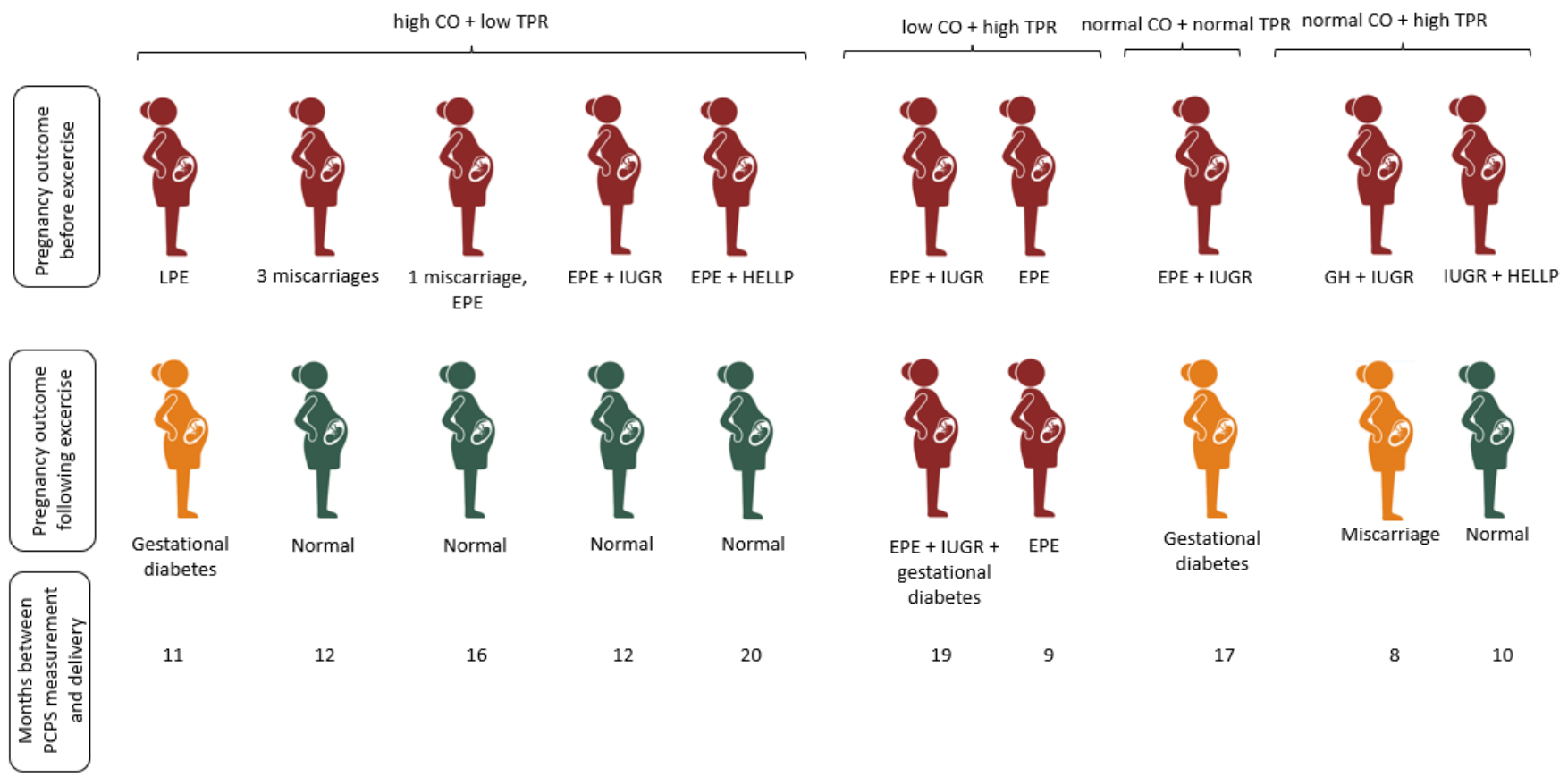
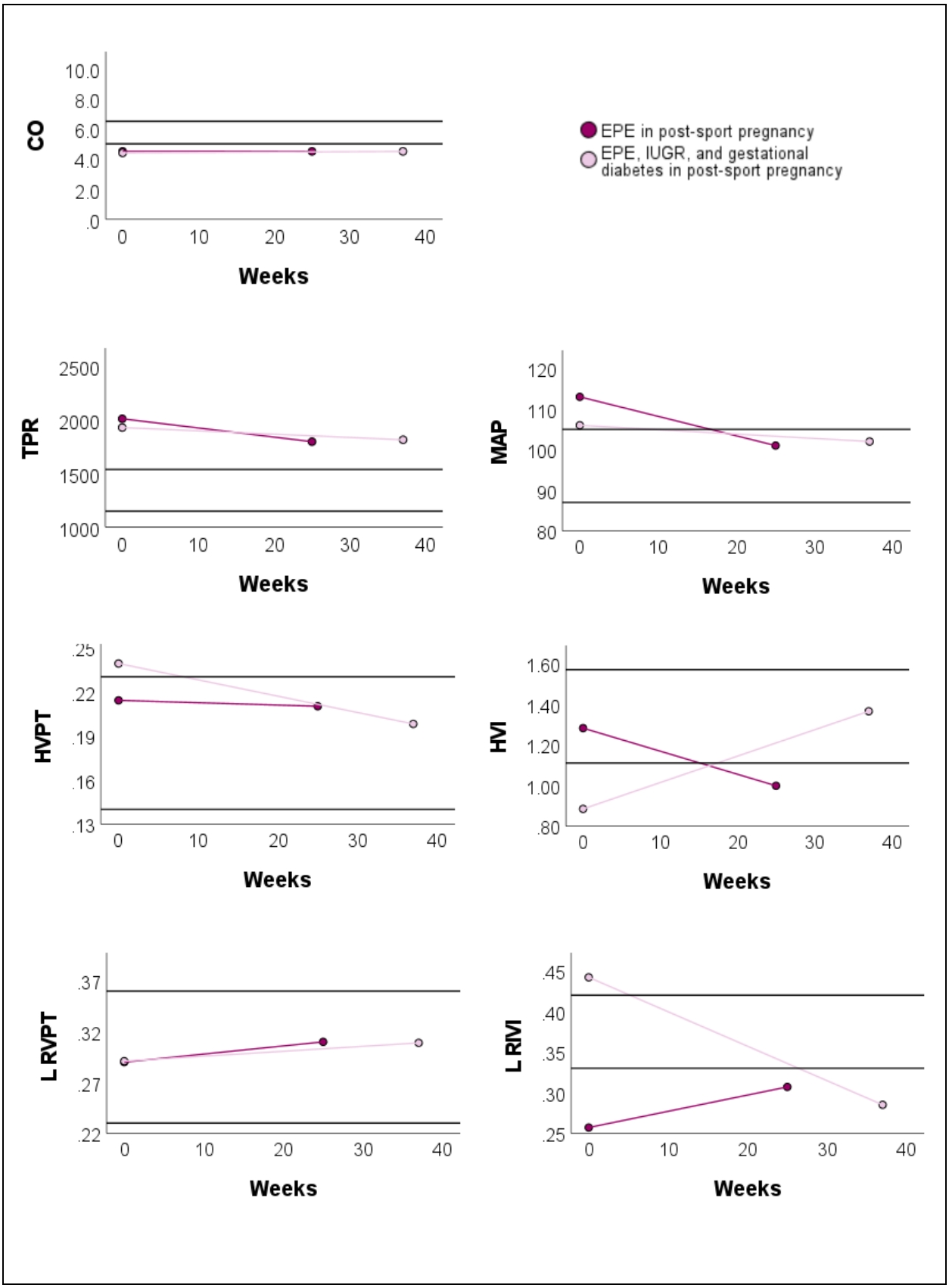


Fig. S9 – **Pregnancy outcome comparison between the pregnancy prior to physical activity and the one following the physical activity advice**. A comparison was made between the pregnancy outcomes prior to and following the physical activity advice in ten women who delivered newborns during both periods. Green: uncomplicated pregnancy; yellow: pregnancy complicated by other conditions; red: GHD-complicated pregnancy; LPE: late-onset preeclampsia; EPE: early-onset preeclampsia; IUGR: intrauterine growth restriction; HELLP: hemolysis, elevated liver enzymes, low platelet count; CO: cardiac output; TPR: total peripheral resistance; PCPS: pre-conceptional post-sport.


CO
10.0
8.0
6.0
4.0
2.0
.0
0
10
20
30
40
Weeks
EPE in post-sport pregnancy
EPE, IUGR, and gestational diabetes in post-sport pregnancy
TPR
2500
2000
1500
1000
Weeks
MAP
120
110
100
90
80
Weeks
HVPT
.25
.22
.19
.16
.13
Weeks
HVI
1.60
1.40
1.20
1.00
.80
Weeks
L RVPT
.37
.32
.27
.22
Weeks
L RVI
.45
.40
.35
.30
.25
Weeks

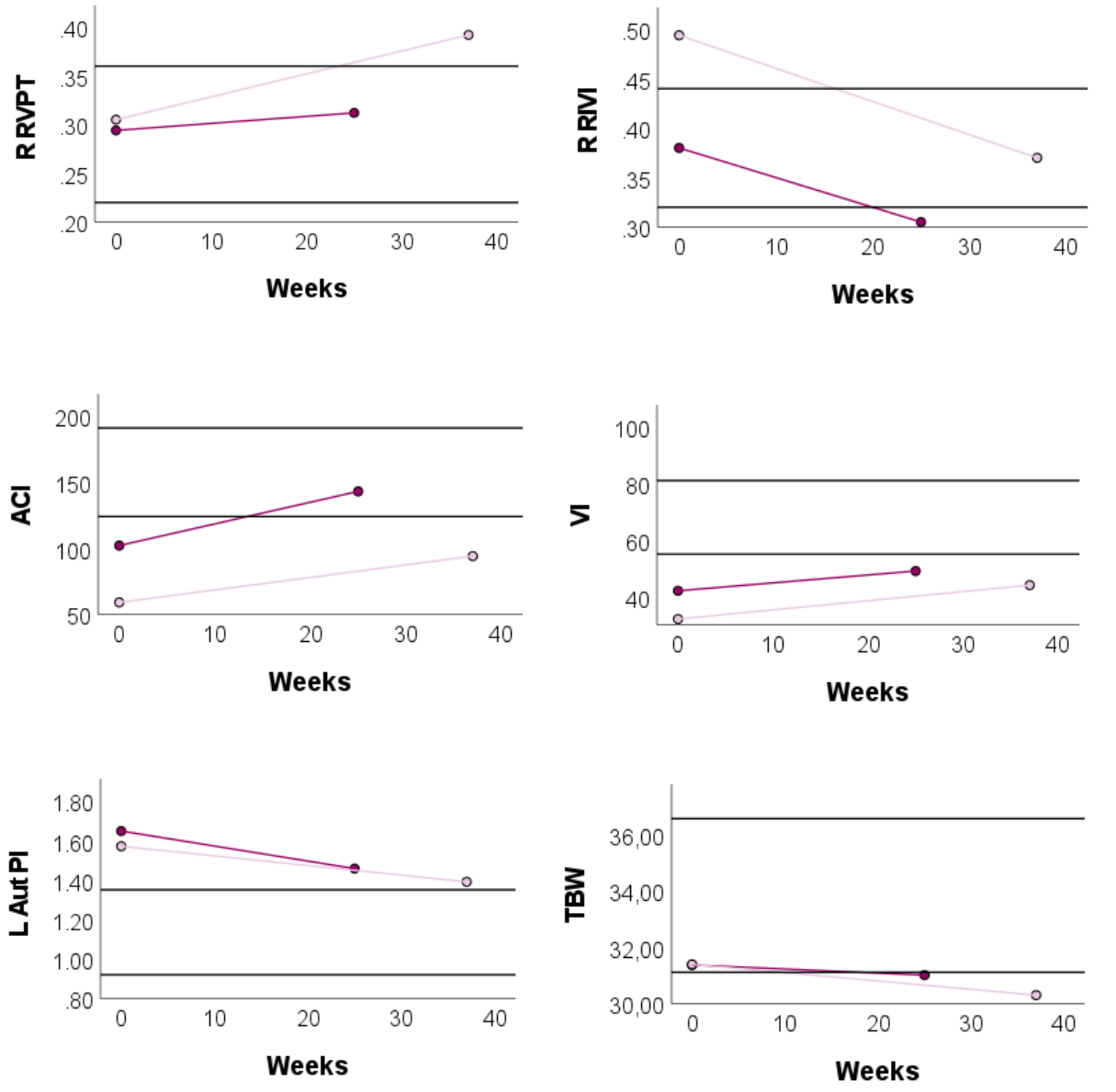


Fig. S10 – **Comparison of the pre-sport and post-sport pre-conceptional cardiovascular parameters.** Pre-sport and post-sport pre-conceptional cardiovascular parameters were compared to assess the impact of physical activity. This comparison was conducted on two women who still experienced GHD during the post-sport pregnancy. EPE: early-onset preeclampsia; IUGR: intrauterine growth restriction; CO: cardiac output; TPR: total peripheral resistance; MAP: mean arterial pressure; HVPT: hepatic vein pulse transit; HVI: hepatic vein impedance index; L RVPT: left renal interlobar vein pulse transit; L RIVI: left renal interlobar vein impedance index; R RVPT: right renal interlobar vein pulse transit; R RIVI: right renal interlobar vein impedance index; ACI: aorta flow acceleration index; VI: velocity index; L aut PI: left uterine artery Doppler pulsatility index; TBW: total body water volume.

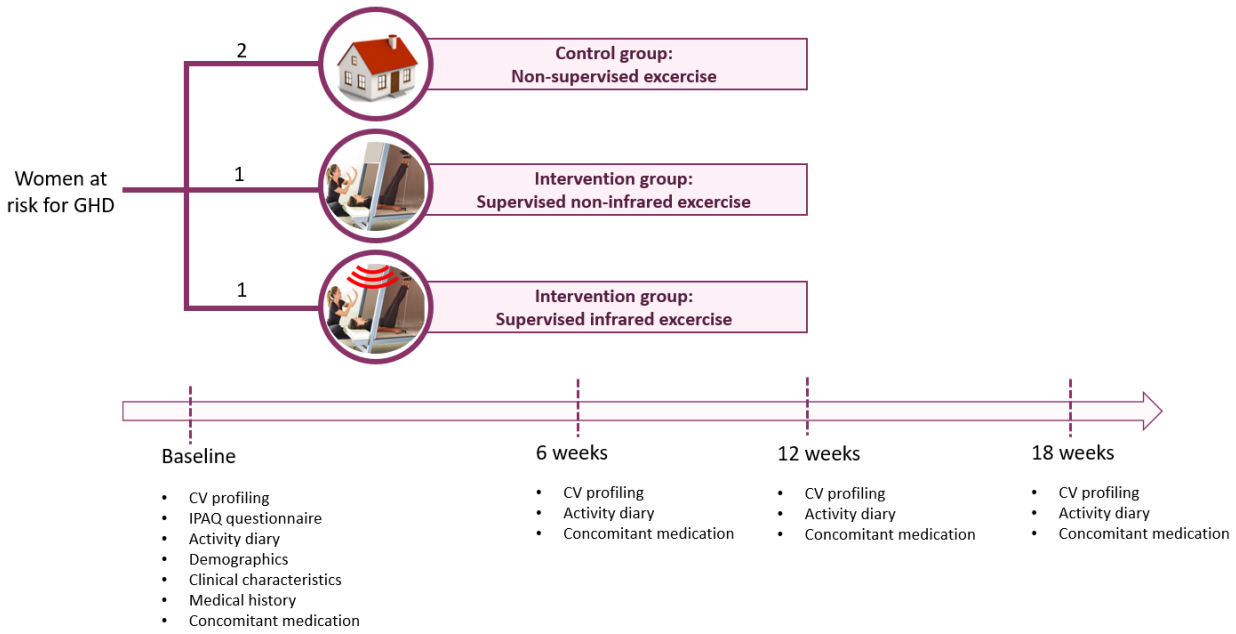


Fig. S11 – Study design of the SPORTY study. Pre-conceptional women at risk for GHD are included according to specific in- and exclusion criteria (similar to the ones presented in this thesis). All study participants who provided written informed consent and are eligible to participate in the study will undergo a baseline cardiovascular profiling assessment. Next, all participants are 2:1:1 randomly assigned to a non-supervised exercise group (control), a supervised non-infrared exercise group (intervention), or a supervised infrared exercise group (intervention), stratified by baseline cardiac output as part of the cardiovascular profiling. All participants are asked to complete the International Physical Activity Questionnaire (IPAQ) to report their baseline physical activity status. Demographics, clinical characteristics, and medical history are obtained and collected at baseline. For ethical reasons, all study groups are advised to exercise throughout the entire study period, but only the two supervised exercise groups will receive a personalized and guided exercise plan. In addition, all participants will receive an activity diary and are asked to fill in their weekly exercise throughout the entire study period. Six and 12 weeks after the start of the physical activity period, participants will undergo a follow-up cardiovascular profile measurement in order to evaluate the effect of the physical activity. Six weeks after the intervention period is stopped (week 18), a third follow-up cardiovascular profiling assessment is performed to evaluate how long the adaptations in the cardiovascular profile induced by supervised training last in case the supervision is halted. Changes in concomitant medication are reported throughout the entire study period. GHD: gestational hypertensive disorder; CV: cardiovascular; IPAQ: International Physical Activity Questionnaire.