The target matters – general vs. individualized exercise prescription for fertile-aged women with metabolic risk: a randomized controlled trial

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Research

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Abstract

Background

Little is known about the associations of different depths of individualization of the exercise intervention on cardiorespiratory fitness (CRF), metabolic outcomes and cardiac autonomic regulation in at-risk subjects. This randomized trial compared the effect of general physical activity (PA) guideline -targeted and highly individualized exercise intervention on maximal oxygen uptake, heart rate variability, body composition, and glucose and lipid profiles in fertile-aged women with increased risk for gestational diabetes.

Methods

Forty-five women with previous gestational diabetes or BMI>30kg/m 2 were randomized into general advice without intervention (Group 1), individualized intervention planned according to PA questionnaires and general guidelines for exercise training (Group 2) and highly individualized intervention based on results from the pre-intervention cardiopulmonary exercise test (CPET) groups (Group 3). All subjects performed pre-intervention CPET on a cycle ergometer with step incremental protocol until volitional fatigue, followed by a 3-month intervention period and post-intervention CPET. Examinations included HRV assessment during CPET and body composition (bioimpedance), blood glucose and lipid profiles.

Results

Total dropout was 53.8% at various points of the study leaving 8 subjects in Group 1, 12 subjects in Group 2 and 10 subjects in Group 3. CRF improved only in Group 3 (+1.9 ml/kg/min, 95% CI 0.3 to 3.5). This was associated with an increase in high-density lipoprotein (0.18 mmol/L, 95% CI 0.04 to 0.32) and increased HRV. In Group 2, we found a decrease in body mass index (-0.7 kg/m 2, 95% CI -1.3 to -0.1), fasting insulin (-4.14 mU/L, 95% CI -6.58 to -1.70), insulin resistance (-1.21, 95% CI -1.88 to -0.54), and low-density lipoprotein (-0.44 mmol/L, 95% CI -0.79 to -0.09). The dropouts in Group 1 had significantly less weight, smaller waist circumference, less visceral fat, and higher maximal oxygen uptake compared to the continuers in Group 1.

Conclusions

To improve CRF and cardiac autonomic function the exercise intervention should be highly individualized. PA intervention focused to achieve general exercise guidelines is not enough to improve CRF over 3-month period but combined with weight loss has beneficial effects on the metabolic profile. In randomized controlled trials, dropout may be biased.

Trial Registration clinicaltrials.gov (NCT01675271)

Introduction

Gestational diabetes mellitus (GDM) is a risk factor of future diabetes (1–3) and related to future cardiovascular diseases (CVD) (4,5). Therefore, women diagnosed with GDM constitute a distinct group with marked disease risk identifiable in a relatively early age. Higher levels of physical activity (PA) before and during early pregnancy have shown to be associated with lower risk of developing GDM (6–8).

Cardiorespiratory fitness (CRF), defined as individual's capacity of maximal oxygen uptake (VO_{2max}), is a powerful predictor of cardiovascular risk factors, morbidity and premature cardiovascular mortality (9–11). As a modifiable factor, PA holds great opportunities for individuals and societies in prevention of metabolic diseases. A considerable body of evidence has demonstrated that moderate PA reduces the risk of e.g. diabetes and CVD (12). However, the association with health outcomes is stronger for CRF than PA alone (13,14). While PA has broad health benefits (15,16) and is recommendable for everyone, in health care it becomes a serious treatment of choice for individuals with genetic predisposition or early signs of non-communicable diseases.

Heart rate variability (HRV) defined as the variability of inter-beat intervals, reflects the overall capability of the cardiovascular system to respond to physiological internal demands as well as to external environmental stimuli. High HRV during rest is a marker of healthy and compliant cardiovascular system, whereas during acute stress, heart rate is increased and HRV is decreased (17). A variety of metabolic diseases are accompanied with persistent alarm state of the body, and decreased HRV has been reported with all major risk factors for CVD, both modifiable and non-modifiable (18). Early phases of diabetes, such as elevated fasting glucose and impaired glucose tolerance, are found to be associated with cardiac autonomic dysfunction (19,20). In addition, changes in cardiac autonomic balance in GDM have been observed (21,22). Exercise and training, especially when associated with increase in VO_{2max}, have been shown to increase resting HRV reflecting increased parasympathetic cardiac regulation (23,24). These data suggest the essential role of cardiac autonomic control in mediating the effects of exercise therapy.

For exercise to be a serious treatment choice, its dose, type and form of delivery should be verified. Exercise prescriptions, although based on consensus statements in e.g. type 2 diabetes, are lacking optimized and personalized clinical tools (25,26). In the literature, not much is known about the associations of different depths of individualization of the exercise intervention on CRF, metabolic outcomes and cardiac autonomic regulation. Few studies have showed the effectiveness of individual ventilatory threshold –guided exercise prescription in improving VO_{2max} (27,28) and one very recent study compared the effect of high intensity interval training and moderate intensity continuous training on CRF (29). To our knowledge, no publications are available concerning different exercise interventions, metabolic markers and HRV in young women with increased metabolic risk.

Our study aimed to answer the question whether individualized exercise intervention targeting general guidelines of PA or highly individualized exercise intervention targeting increased CRF effects more favorably on metabolism, cardiac autonomic function and fitness of fertile-aged risk women.

Method

The study was performed in Helsinki metropolitan area between 2012 and 2015. It complies with the Declaration of Helsinki and was approved by Ethical Board of HUCH (14 September 2006, Dnro 300/E9/06). The protocol was registered at Clinicaltrials.gov (NCT01675271).

Study Design

This study was a prospective three-arm randomized controlled trial comparing the effect of different depths of individualization of exercise intervention on CRF, HRV and metabolic outcomes in fertile-aged women with increased risk for GDM.

Participants

Inclusion criteria were BMI ≥ 30 kg/m^2 or a history of GDM and desire to become pregnant within 6 months. Women with previous GDM were recruited by letters using hospital registers (523 letters sent). In addition, leaflets were used to reach obese and primiparous women. Exclusion criteria included age < 18y, smoking, medication affecting the autonomic nervous system (e.g. β-blockers, selective serotonin reuptake inhibitors) or glucose metabolism (e.g. oral corticosteroids and metformin), pre-existing diabetes (tested with 75 g 2-h oral glucose tolerance test before entrance to the study), physical disability disallowing exercising, current substance abuse, severe psychiatric disorders, significant difficulties to co-operate (e.g. inadequate Finnish language skills), and pregnancy.

Procedure

The first visit was in the maternity hospital outpatient clinic where randomization took place and participants signed a written informed consent. The study nurses randomized the subjects into Group 1, 2 or 3 using randomly permuted blocks. Pregnancy test was performed, and a positive test resulted in discontinuation. The following procedure included pre-intervention examinations, 3-month exercise intervention period and post-intervention examinations. The examinations were same for all participants and included cardiopulmonary exercise test (CPET), HRV analysis, measurement of body composition, and blood samples for evaluation of glucose homeostasis and lipid profile. For women with a BMI ≥ 25 kg/m^2, we recommended 5–10% weight loss.

Pre- and post-intervention examinations

CPET

The participants arrived in the laboratory approximately 2 hours post meal consumption with no alcohol ingestion within past 24 hours and no physical exercise within 12 hours. They filled and signed the Physical Activity Readiness Questionnaire. We performed a 12-lead electrocardiogram (ECG) in a supine

position. Each subject performed a CPET on a cycle ergometer (Monark Ergomedic 839 E, Monark Exercise AB, Vansbro, Sweden). The incremental exercise protocol was preceded by a 5 min rest while the subjects sat relaxed on the cycle ergometer followed by a 5 min baseline unloaded cycling. The step incremental protocol (30 W load increase at 3 min intervals) was then initiated, and the subjects continued exercising until volitional fatigue. We monitored heart rate and electrical activity of the heart continuously by ECG (PowerLab, ADInstruments, Oxford, UK) with a sampling frequency of 1 kHz. We measured breath-by-breath ventilation (V_E) by a low-resistance turbine (Triple V, Jaeger Mijnhardt, Bunnik, The Netherlands) to determine inspiratory and expiratory volumes and flow. Inspired and expired gases were sampled continuously and analyzed for concentrations of O_2, CO_2, N_2, and Ar by mass spectrometry (AMIS 2000, Innovision A/S, Odense, Denmark) after calibration with precision analyzed gas mixtures. We collected breath-by-breath respiratory data in raw data mode and transferred the raw data to a computer where gas delays were determined for each breath to align concentrations with volume data, and to build a profile of each breath. We then calculated breath-by-breath alveolar gas exchange with the AMIS algorithms and interpolated the data to obtain values second by second. We determined maximal oxygen uptake (VO_{2max}) as the highest value of a 60 s moving average “window”.

Heart rate variability analyses

We assessed autonomic regulation of beat-to-beat variation in heart rate in 3-minute samples under four conditions: 1) relaxed sitting, 2) unloaded cycling, 3) 30 W cycling and 4) 60 W cycling. We chose these conditions as they mimic normal daily activity and are below severe exercise intensity for all subjects. We exported ECG data from Powerlab to Kubios HRV Premium, version 3.0.2.2 (Kubios Oy, Kuopio, Finland) that was used for R-wave detection and artifact correction as well as for HRV analyses, according to the guidelines of Task Force of the European Society of Cardiology (1996).

We used the following HRV parameters to interpret cardiac autonomic regulation: 1) mean heart rate (mean HR), 2) root mean square of successive differences (RMSSD), 3) standard deviation of beat-to-beat intervals (SDNN), and 4) Poincaré plot parameter SD2/SD1. Mean HR specifies the overall level of cardiovascular system’s activity under different conditions. RMSSD reflects short-term variations reflecting predominantly parasympathetic (vagal) nervous activity, while SDNN reflects both short- and long-term HRV. Finally, SD2/SD1 is a ratio of overall variability and short-term variability, thus giving information about sympatho-vagal balance.

Anthropometrics and body composition

We measured height and weight in light indoor clothing and without shoes on and waist circumference 2 cm above the umbilical level. We calculated BMI as a weight in kilograms divided by height in meters squared (kg/m^2) and determined the body composition by the bioimpedance method (InBody 720, Biospace Co., Ltd., Seoul, South Korea).

Glucose homeostasis and lipid profile

Blood samples were analyzed in the Helsinki University Hospital laboratory and the analyses included a 75 g 2-hour oral glucose tolerance test, measurements of fasting plasma glucose and insulin and glycated hemoglobin (HbA1c) as well as serum lipids including total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides. Homeostatic model assessment (HOMA) for assessing insulin resistance (IR) was calculated using formula HOMA-IR = (fasting plasma glucose * fasting plasma insulin)/22.5 according to the original model from Matthews et al. (30).

Exercise intervention protocols

We planned the exercise programs to be more individualized and more supported from Group 1 (no individualization, minor support) to Group 3 (highly individualized, highly supported).

Group 1

The subjects received general information of health benefits of exercising and healthy diet without individualized advice. No support was offered to this group during the study.

Group 2

Exercise intervention was planned according to PA questionnaires of each subject and based on general guidelines for exercise training at the time of study (31). The aim of the intervention was to achieve a minimum of 30 minutes of moderate intensity exercise five times a week or 50 minutes three times a week, include strength training in weekly routines and to adopt an overall active lifestyle (e.g. using stairs, walking instead of a car or bus whenever possible).

Group 3

We used the results from the CPET of each subject to individualize their exercise training with the aim of not only increasing PA but also improving VO_{2max} and overall fitness. To guide endurance training we used the subject´s ventilatory thresholds (32) and corresponding heart rate zones and the subjects used heart rate monitors (Suunto t6c, Suunto Oy, Vantaa, Finland; Polar RS800CX, Polar Electro Oy, Kempele, Finland) to target these zones. The exercise physiologist gave the subjects (1–3 subjects at a time) a 30-min face-to-face meeting on general effects and principles of endurance and resistance training. Guidance for strength training was provided by Unisport, University of Helsinki. The subjects used internet-based exercise diary (Firstbeat.net) enabling us to follow-up the exercise program during the intervention period.

Statistical analysis

VO_{2max} measurements was the major determinant of sample size as it indicates the effect of training on aerobic capacity. The calculation of statistical power for the main variables was based on < 5% risk for Type 1 error and with 80% statistical power. With an accuracy of 2% in VO_{2max} value and an assumed 20% attrition rate on subjects during this project, 12 subjects were needed into each subject category.

Results of this study are reported as mean or estimate with 95% confidence interval. We used one-way analysis of variance to compare if the groups were dissimilar at pre-intervention. Furthermore, comparison of subjects who completed the study to those who discontinued study prior final examination was conducted with Wilcoxon rank-sum test. We evaluated the effect of interventions on metabolic markers, CRF and HRV with linear mixed models to account for potential differences among subjects and a correlation between pre- and post-intervention examinations.

We used a random intercept model in evaluation of metabolic markers and CRF with intervention, group and their interaction as fixed effects. To evaluate changes in HRV within groups, we used a random intercept and slope model with intervention, group, load and their interactions as fixed effects, as well as subject-specific random intercept and intervention slope. We used fitted model estimated means to evaluate within-group differences by evaluating paired confidence intervals. We used restricted maximum likelihood estimation to fit models, and verified that models met multivariate assumptions. We adjusted all variables for age, weight and height, excluding VO_{2max}, weight and BMI, which we only adjusted for age. Lastly, we calculated Spearman correlation between the difference in pre- and post-intervention CRF and other parameters within groups. We chose a significance level of 0.05 across all evaluations, as we consider our study explorative, and used MATLAB R2016b (The MathWorks, inc., Natick, MA, USA) to calculate all statistical analyses.

Results

Of 45 women attending the baseline CPET 37 had a history of GDM (6 with BMI ≥ 30 kg/m^2) and 8 were recruited by BMI criterion only. Six women (75%) in Group 1, 9 (75%) in Group 2 and three (30%) in Group 3 had BMI ≥ 25 kg/m^2 and were encouraged to reduce weight by 5–10%. Fifteen subjects who attended pre-intervention examinations did not attend post-intervention measurements leaving 30 subjects with both pre- and post-intervention CPET data. These subjects constituted the final study population (consort participant flow diagram in Fig. 1). The dropout rate between recruitment and pre-intervention CPET was 30.8% and between pre- and post-intervention CPET was 33.3% resulting to the total dropout of 53.8%.

Pre-intervention Anthropometric, CRF And Metabolic Measurements

Pre-intervention anthropometric, CRF and metabolic data of the study groups are shown in Table 1. There appeared to be a difference in weight, visceral fat, fasting insulin and HOMA-IR between the groups ($P < 0.05$). Because of a high dropout rate, we compared the subjects also by dividing them as continuers and dropouts. This data showed that dropouts compared with the continuers in the Group 1 were shorter (161 vs. 171 cm), had minor weight (64.9 vs. 93.0 kg), smaller waist circumference (79.1 vs. 99.4 cm), less visceral fat (76.6 vs. 150.5 cm^2) and had higher VO_{2max} (31.2 vs. 22.2 ml/min/kg), all $P < 0.05$. In Group 3, there was a tendency towards the opposite. The dropouts were heavier (83.8 vs. 67.6 kg), waist

circumference greater (91.2 vs. 82.8 cm) and visceral fat more abundant (122.8 vs. 84.3 cm^2). These differences, however, did not quite reach statistical significance. This different dropout pattern between the groups lead to apparent bias in the study design. This was considered in the statistical analyses, as described earlier.

Table 1
Pre-intervention anthropometric, metabolic and cardiorespiratory fitness data presented as mean (95% CI).

	Group 1 N = 8	Group 2 N = 12	Group 3 N = 10	P-value
Age (year)	33.4 (30.2, 36.5)	33.5 (31.2, 35.9)	31.9 (29.3, 34.6)	n.s
Weight (kg)	93.0 (76.0, 110.0)	77.5 (67.2, 87.8)	67.6 (52.7, 82.5)	< 0.05
Height (cm)	171 (166, 177)	166 (162, 170)	162 (156, 169)	n.s
BMI (kg/m^2)	31.9 (25.7, 38.1)	28.0 (25.1, 31.0)	25.3 (21.6, 29.0)	n.s
Waist circumference (cm)	99.4 (83.3, 115.5)	89.6 (80.8, 98.4)	82.8 (75.0, 90.6)	n.s
Fat (%)	40.8 (33.5, 48.1)	35.8 (31.2, 40.3)	32.0 (26.5, 37.4)	n.s
Visceral fat (cm^2)	150.5 (101.2, 199.7)	112.6 (86.9, 138.3)	84.3 (53.1, 115.5)	< 0.05
Fasting glucose (mmol/L)	5.5 (5.1, 5.9)	5.6 (5.2, 6.0)	5.6 (4.9, 6.3)	n.s
Fasting insulin (mU/l)	15.5 (10.2, 20.8)	13.1 (7.9, 18.3)	7.2 (3.7, 10.7)	< 0.05
HbA1c (mmol/L)	33.6 (31.0, 36.2)	36.7 (34.5, 38.8)	34.7 (32.7, 36.7)	n.s
HOMA-IR	3.8 (2.4, 5.1)	3.4 (1.9, 4.8)	1.8 (0.8, 2.8)	< 0.05
Cholesterol (mmol/L)	4.6 (4.1, 5.2)	4.67 (4.1, 5.2)*	4, 9 (4.3, 5.5)	n.s
HDL (mmol/L)	1.4 (1.1, 1.7)	1.6 (1.3, 1.9)*	1.8 (1.4, 2.1)	n.s
LDL (mmol/L)	2.8 (2.3, 3.4)	2.9 (2.4, 3.3)*	3.0 (2.5, 3.6)	n.s
Triglycerides (mmol/L)	1.4 (0.8, 2.1)	0.9 (0.7, 1.1)*	0.8 (0.5, 1.1)	n.s
VO_{2max} (ml/kg/min)	22.2 (17.4, 27.0)	27.0 (24.4, 29.7)	28.2 (24.4, 32.0)	n.s
*N = 11, n.s = statistically non-significant				

Intervention Effects

The effects of interventions are shown in Table 2. During the 3-month intervention period VO_{2max} increased (+ 1.9 ml/kg/min) only in the individualized intervention Group 3. It was accompanied by an increase in maximal workload (+ 11 W) and HDL cholesterol (+ 0.18 mmol/L). In the Group 2, we found a decrease in BMI (-0.7 kg/m^2), fasting insulin (-4.14 mU/L), HOMA-IR (-1.21), and LDL cholesterol (-0.44 mmol/L). In Group 1, fasting insulin decreased (-3.3 mU/L). The reducing effect of exercise intervention in Group 2 on fasting insulin was − 4.65 mU/L, which was significantly greater than the effect of highly individualized exercise intervention in Group 3. Accordingly, intervention effect on HOMA-IR in Group 2 was − 1.30 compared with Group 3.

Table 2

, title: The effect of interventions on CRF, metabolic markers and HRV.

	Estimate	P	P < 0.05 between groups
VO_{2max} (ml/min/kg)			
Group 1	0.8 (-0.9, 2.6)		
Group 2	0.8 (-0.7, 2.3)		
Group 3	1.9 (0.3, 3.5)	< 0.05	
Weight (kg)			
Group 1	-1.4 (-3.4, 0.6)		
Group 2	-2.1 (-3.7, -0.4)	< 0.05	
Group 3	-0.4 (-2.2, 1.4)		
Maximal work (W)			
Group 1	0 (-9, 8)		1 vs. 3
Group 2	5 (-2, 12)		
Group 3	11 (4, 19)	< 0.05	3 vs. 1
BMI (kg/m^2)			
Group 1	-0.4 (-1.1, 0.3)		
Group 2	-0.7 (-1.3, -0.1)	< 0.05	
Group 3	0.0 (-0.7, 0.6)		
Waist circumference (cm)			
Group 1	0.9 (-1.0, 2.9)		
Group 2	-0.6 (-2.1, 1.0)		
Group 3	0.1 (-1.7, 1.9)		
Fat (%)			
Group 1	-0.1 (-1.5, 1.3)		
Group 2	-0.4 (-1.6, 0.8)		
Group 3	-0.1 (-1.4, 1.2)		
Visceral fat (cm^2)			
Analysis of linear mixed models			

	Estimate	P	P < 0.05 between groups
Group 1	-0.6 (-4.2, 3.0)		
Group 2	-2.5 (-5.4, 0.5)		
Group 3	-0.4 (-3.8, 2.9)		
Fasting glucose (mmol/L)			
Group 1	0.36 (-0.28, 1.00)		
Group 2	-0.26 (-0.81, 0.29)		
Group 3	-0.14 (-0.72, 0.44)		
Fasting insulin (mU/l)			
Group 1	-3.29 (-6.10, -0.47)	< 0.05	
Group 2	-4.14 (-6.58, -1.70)	< 0.05	2 vs. 3
Group 3	0.53 (-2.07, 3.13)		3 vs. 2
HOMA-IR			
Group 1	-0.75 (-1.53, 0.02)		
Group 2	-1.21(-1.88, -0.54)	< 0.05	2 vs. 3
Group 3	0.09 (-0.62, 0.79)		3 vs. 2
HbA1c (mmol/L)			
Group 1	1.5 (-0.8, 3.8)		
Group 2	-0.3 (-3.2, 2.6)		
Group 3	-0.1 (-2.5, 2.3)		
Cholesterol (mmol/L)			
Group 1	-0.14 (-0.64, 0.35)		
Group 2	-0.49 (-0.92, -0.05)	< 0.05	
Group 3	-0.11 (-0.57, 0.35)		
HDL (mmol/L)			
Group 1	-0.01 (-0.16, 0.14)		
Group 2	-0.04 (-0.17, 0.10)		2 vs. 3
Group 3	0.18 (0.04, 0.32)	< 0.05	3 vs. 2
Analysis of linear mixed models			

	Estimate	P	P < 0.05 between groups
LDL (mmol/L)			
Group 1	-0.03 (-0.42, 0.37)		
Group 2	-0.44 (-0.79, -0.09)	< 0.05	
Group 3	-0.13 (-0.49, 0.24)		
Triglycerides (mmol/L)			
Group 1	-0.07 (-0.31, 0.17)		
Group 2	-0.19 (-0.40, 0.02)		
Group 3	-0.05 (-0.28, 0.17)		
Analysis of linear mixed models			

Heart Rate Variability

Reduced HRV has shown to predict multiple poor metabolic outcomes (18,45) and cardiac autonomic balance has been suggested as a worthy target for early prevention of metabolic disorders (46). Reduced HRV, reflecting deterioration of the cardiac parasympathetic innervation predicts cardiovascular risk in type 2 diabetes (20,47–49). Moreover, changes in HRV have been demonstrated in young women with GDM (21,22). Persistent PA and exercise training are associated with activation of the parasympathetic nervous system and increased HRV (50–52), that is opposite to diabetes-induced changes. Some data suggest dose-dependent effect of PA on HRV (53). In our study, only highly individualized exercising accompanied by improvement in CRF increased HRV. Changes in HRV parameters were uniform showing increased parasympathetic activation (reduced mean HR, increased SDNN and RMSSD, reduced SD2/SD1). Concomitant improvement in aerobic fitness and cardiac autonomic function is well supported by the mechanistic studies on cardiovascular adaptation to exercise (54,55). Few studies with a comparative population to ours have demonstrated improvement in CRF and HRV after progressive intense exercise program in obese/overweight apparently healthy men and women (56) and after a moderate-intensity walking program in obese women with or without type 2 diabetes (57). The first study reported also significant improvement in body composition and large inter-individual differences in vagal modulation changes with fat loss. One study in mildly obese apparently healthy women undergoing a moderate walking exercise program reported a decrease in BMI, waist circumference, body fat and total cholesterol and improvement in insulin sensitivity accompanied by increased HRV, but CRF was not determined in this study (58). Heterogeneity between the results may arise from slight differences in study populations, mode and duration of exercise intervention, and relatively small sample sizes. In addition, human heterogeneity in response to even highly standardized training programs, in terms of VO_{2max} as well as HRV indices is a non-controllable confounder both within and between the studies

(59,60). These confounding factors may explain a lack of clear delta-correlation between HRV and CRF in our study, albeit mean HR was lower while SDNN and RMSSD were higher under all conditions post-intervention.

Correlation Analysis

Correlations between the difference observed in CRF and other parameters pre- and post-intervention are shown in Fig. 3. Furthermore, Scatter plot of delta-correlations requiring particular attention (fasting insulin and glucose, HOMA-IR and mean HR at rest) are presented in Fig. 4 for all groups. Group 1 exhibited a surprising positive correlation between HOMA-IR and CRF ($r = 0.89$, $P < 0.05$). In Group 2, delta-correlations were negative between VO_{2max} and HOMA-IR ($r= -0.68$), fasting glucose ($r= -0.69$) and fasting insulin ($r= -0.65$), all $P < 0.05$. In Group 3, change of VO_{2max} correlated significantly with change of BMI ($r= -0.70$), visceral fat ($r= -0.73$), triglycerides ($r=-0.76$), work load ($r = 0.90$) and heart rate at rest ($r= -0.76$) and 60W cycling ($r= -0.70$).

Discussion

Our study question was whether individualized exercise intervention targeting general guidelines of PA or highly individualized exercise intervention targeting increased CRF effects more favorably on metabolism, cardiac autonomic function and fitness of fertile-aged risk women. Our results show that improvement in VO_{2max} and HRV were achieved only by highly individualized intervention whereas a variety of beneficial metabolic changes were seen only in general guideline-targeted intervention group. These changes included weight loss and decrease in BMI, fasting insulin, HOMA-IR, and LDL cholesterol. Considering the 3-month intervention period, the magnitude of these changes was not only statistically but also clinically significant. In the highly individualized intervention group, the only metabolic change observed was an increase in HDL.

Cardiorespiratory Fitness

Improvement in VO_{2max} is related to intensity, duration, and frequency of training. It has been shown that subjects with low VO_{2max} may increase their CRF already from lower intensity training than their more fit counterparts (33) and larger increases have been observed after high intensity training among individuals with lower baseline fitness (34). The mean baseline VO_{2max} in our subjects was 22–28 ml/kg/min, which is placed in the two lowest seventh in age- and gender-related norms of aerobic fitness and described as very poor or poor (35). This finding itself is alarming. According to our results, exercise targeting the minimum of healthy PA recommended by population-targeted guidelines was not enough to improve CRF even in this poor fitness population. One study in accordance with our results found that intensive interval running was superior in improving CRF compared with prolonged running, however, prolonged running was more efficient in decreasing hyperlipidemia and obesity (36). We have showed the effectiveness of

ventilatory-threshold guided exercise prescription in improving VO_{2max} both in healthy subjects and in patients with type 1 diabetes (28). Wolpern et al. presented a similar result in apparently healthy sedentary men and women (27). Recently, Jung et al. showed that both high and moderate intensity training increased CRF when the training continued for 1 year (29). It remains debatable whether our Group 2 would have increased their CRF if the intervention would have been longer.

In large population-based studies exercise capacity is found to be inversely correlated with development of type 2 diabetes and CVD (37,38). In apparently healthy women, low CRF was associated with higher risk for type 2 diabetes independent of age and BMI, and higher CRF engendered a protective effect against type 2 diabetes in overweight/obese women (39). It has been estimated that each 1 metabolic equivalent (3.5 ml/kg/min VO_{2max}) higher CRF is associated with an 8% lower risk of developing diabetes in individuals free of type 2 diabetes at baseline (38,40).In other studies, even smaller increments in CRF were associated with clinically meaningful reductions in type 2 diabetes risk (40). Our highly individualized group increased their VO_{2max} 7% (0.6 metabolic equivalent) from 28 to 30 ml/kg/min.

Exercise And HDL Cholesterol

According to two meta-analyses, effect of exercise training on HDL cholesterol is dependent on the intensity and volume of exercise. Leon and Sanchez (41) found that moderate to hard aerobic intensity training is needed to increase HDL and Kodama et al. (42) determined a minimum exercise volume to be 900 kcal of energy expenditure or 120 min exercise per week. A more recent study evaluating the effect of exercise on HDL function found that high-amount vigorous-intensity exercise training (16 kcal/kg/week at 75% VO_{2max} reserve) was needed to improve HDL cholesterol efflux capacity, which is the major HDL function and is inversely associated with CVD (43). In our study, increase in VO_{2max} and maximal work load in Group 3 indicate intensive training, and could explain the increase in HDL in this group. It is estimated that each time HDL increases 0.026 mmol/l, the cardiovascular risk decreases by 3% for women in apparently healthy populations (44). Increase in HDL in our study Group 3 was 0.18 mmol/l suggesting a reduced risk by 21%.

Exercise Intensity And Insulin Sensitivity

Differences in the level of physical training have been shown to have a regulatory role in controlling insulin action (61). Studies in risk populations undergoing different exercise programs have showed varying results concerning the effect of intervention on glucose metabolism (34,62–64). In accordance with our results is study of Hecksteden et al. who examined a small group (n = 12) of healthy untrained subjects undergoing a maximal exercise test followed by a 4-week supervised training period and found decrease in insulin concentration and HOMA-IR, total cholesterol, LDL cholesterol and triglycerides without change in VO_{2max} (65). Ross et al. randomized 54 premenopausal women with abdominal obesity into three intervention groups with different targets for exercise ± diet and weight loss, and a

control group. During 14-week intervention body weight decreased only in groups targeted to lose weight and CRF increased within the exercise groups only. Insulin sensitivity improved within the exercise + weight loss group alone (66). In our study, Group 1 possessed unorthodox delta-correlation indicating positive correlation between CRF and HOMA-IR. Combined effects of small group size and rank-based correlation may partly explain this bizarre correlation, and induces uncertainty to other correlations. In Group 2, 75% of the subjects were overweight and encouraged to lose weight, which could explain more favorable metabolic changes compared with Group 3 (30% overweight subjects). The correlation studies in Group 2, however, suggest the role of exercise in beneficial changes of glucose metabolism.

Improved CRF Or Anthropo-metabolic Status?

As our results indicate that general guideline- vs. individually focused exercise interventions engender different beneficial outcomes, a question arises whether improvement in CRF or anthropo-metabolic status is more important? There is no easy answer for this question because CRF, anthropometry and metabolism are not disconnected and interchangeable for "head to head" comparison. International risk assessment scores for lifetime risk of coronary heart attack and stroke include metabolic but not physical fitness -related determinants (67) and reports on PA mostly lack metabolic assessment (12). Within physical fitness reports, different measures of both PA and CRF have indicated inverse associations with future cardiovascular events without prioritizing one from another (14,68,69).

Considering that our study population consisted of relatively young women with increased risk of GDM, we find the metabolic changes in Group 2 highly notable. GDM, though first recognized during pregnancy, is a continuum from pre-pregnancy predisposition (genetic, metabolic) via pregnancy complication to type 2 diabetes. Intervening this progress at any point could at least delay if not prevent diabetes and associated CVD. Adherence to a healthy lifestyle before pregnancy is associated with reduced GDM risk (70) and higher levels of PA before and during pregnancy associate with lower risk of developing GDM (6,7). A moderate individualized lifestyle intervention during pregnancy in a similar population with the present study has demonstrated 39% reduction in the incidence of GDM (8). In addition, two large RCT studies examining subjects with impaired glucose tolerance show that lifestyle modification protects against the development of type 2 diabetes even without full compliance to exercise and diet habits (71,72). In this study, change of CRF correlated with a change of central factors of diabetes, e.g. insulin sensitivity and visceral fat, in both Groups 2 and 3 interweaving closely fitness and metabolism.

Dropout

We would like to emphasize one result not specifically focused in our research plan. Our study brought up the gap between ideal of RCT and the real world. Even though randomization in our study was successful the dropout rate was much larger than based on our and other researchers' previous experiences (73,74). In addition, subjects randomized to Group 1 in which no targeted exercise intervention was offered were split into two clearly distinct groups. The dropouts had markedly better CRF and healthier body

composition. Accompanied by the opposite tendency in Group 3, we ended in comparing groups with significant differences in many of those confounding factors we aimed to avoid by choosing randomized study design.

Almost half of our participants decided to finish before the final examinations. The reasons are most probably diverse but markedly biased profiles of those who discontinued and continued especially in Group 1 leads to some conclusions. Dropouts in Group 1 had nearly normal BMI, normal waist circumference and significantly lower visceral fat compared to those who continued in the intervention. In addition, they had higher VO_{2max}. It is well recognized that lifestyle and exercise intervention studies attract subjects interested in health per se and who are motivated to improve their health. Randomization into the control group with no intervention at all may have been disappointment for our Group 1 dropouts. Indeed, this was noticed in personal conversations with the subjects at the time of randomization. The effect of inadequate supervision on adherence to exercise programs has been reported also earlier (75). In contrast to non-obese subjects, obese sedentary women in Group 1 may have considered to benefit from the study even without organized intervention program. This assumption is supported by finding that fasting insulin decreased in Group 1 almost as much as in Group 2. More intensive exercise training in Group 3, in turn, may have resulted in termination in the more obese and unfit women.

Mutsaerts et al. showed a marked underreporting of dropout data in their review on lifestyle intervention studies for overweight and obese women with infertility (73). Roumen et al. who reported a 22% dropout rate in a randomized lifestyle intervention in glucose intolerant obese women found that dropouts had lower VO_{2max}, higher BMI and higher 2-h glucose compared with continuers (74). This is contradictory to our findings (Group 1) and may be at least partly explained by age difference of the study populations (mean 55 y in the study of Roumen et al). Most of our subjects (83%) lived busy life with small children and may have experienced different reasons for discontinuing than elderly subjects.

According to our results, we find adherence in exercise programs as one of the biggest challenges for the future in development of exercise as a medicine.

Strengths And Limitations

Our 3-arm design allowed us to compare two different depths of exercise intervention and have a “control group” which received as minimal-level intervention as possible in a voluntary exercise study. We examined a broad spectrum of cardio-metabolic variables, which enabled us to combine parallel findings to support conclusions in our quite small study population. The main limitation of this study, high dropout rate, is already discussed above. An evident consequence of the reduced sample size is loss of the statistical power. Thus, we consider our study explorative and do not adjust the significance level, albeit multiple analyses were conducted. However, even though high dropout was undesirable, analysis of the continuers and discontinuers revealed interesting data, which can be used to improve further studies.

We did not assess diet in this study. Weight loss during a 3-month period most probably is due to not only increased PA but some dietary changes, as well. The correlation studies suggest a role for exercise in observed metabolic changes and, thus, we find our conclusions justified. In addition, our main outcome was CRF, which is not confounded by possible dietary changes.

Finally, we reached only 12% of invited subjects (65 signed up per 523 recruitment letters sent) without data on the 88% who did not respond our study invitation. Thus, there are limitations in generalizing the data to the presumably heterogenic population of women with a risk of GDM.

Conclusions

In conclusion, our results suggest that the target determines the outcome of exercise intervention of fertile-aged risk women. To improve CRF and cardiac autonomic function the exercise intervention should be highly individualized. PA intervention which focused to achieve general exercise guidelines is not enough to improve CRF over 3-month period but combined with weight loss has beneficial effects on the metabolic profile. Exercising more, and exercising more at a level that is enough to improve CRF is our exercise prescription. Great effort must be put in the future to develop interventions that motivate the participants to adhere and continue in exercise programs long-term.

List Of Abbreviations

CPET Cardiopulmonary exercise test

CRF Cardiorespiratory fitness

ECG Electrocardiogram

GDM Gestational diabetes mellitus

HbA1c Glycated hemoglobin

HDL High-density lipoprotein

HOMA-IR Homeostatic model assessment for insulin resistance

HR Heart rate

HRV Heart rate variability

LDL Low-density lipoprotein

PA Physical activity

RCT Randomized controlled trial

RMSSD Root mean square of successive differences

SD2/SD1 Ratio of Poincaré plot standard deviations

SDNN Standard deviation of beat-to-beat intervals

VO_{2max} Maximal oxygen uptake

Declarations

Ethics approval and consent to participate

Participants gave a written informed consent prior participation and Ethical Board of HUCH approved research project (Dnro 300/E9/06).

Consent for publications

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding authors on a reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MPA was the principal researcher of the study and the writer of the manuscript. VH analyzed data and also drafted and revised the manuscript. All authors contributed to the content and revised and approved the final manuscript.

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Figures

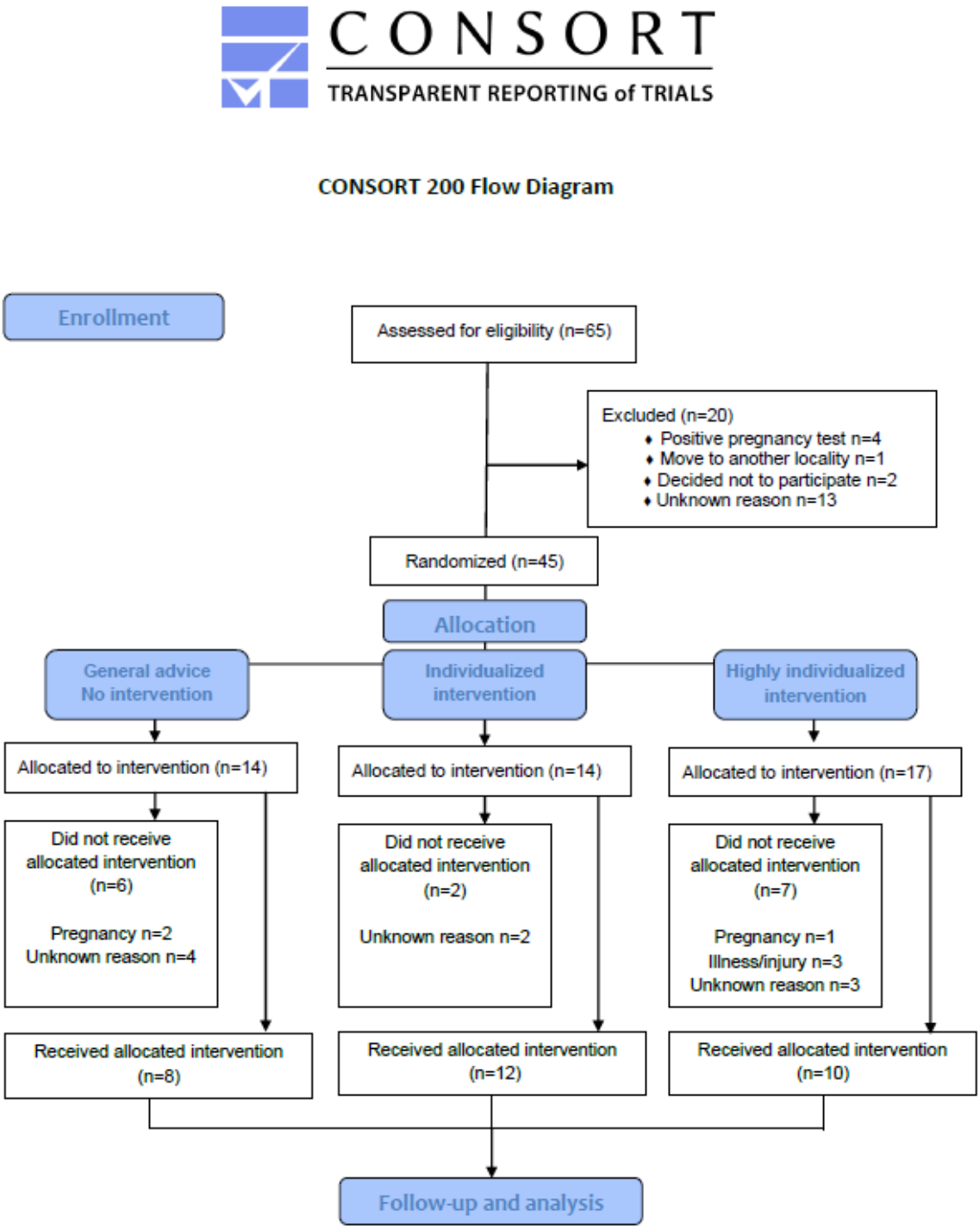

Figure 1

Consort participant flow diagram.

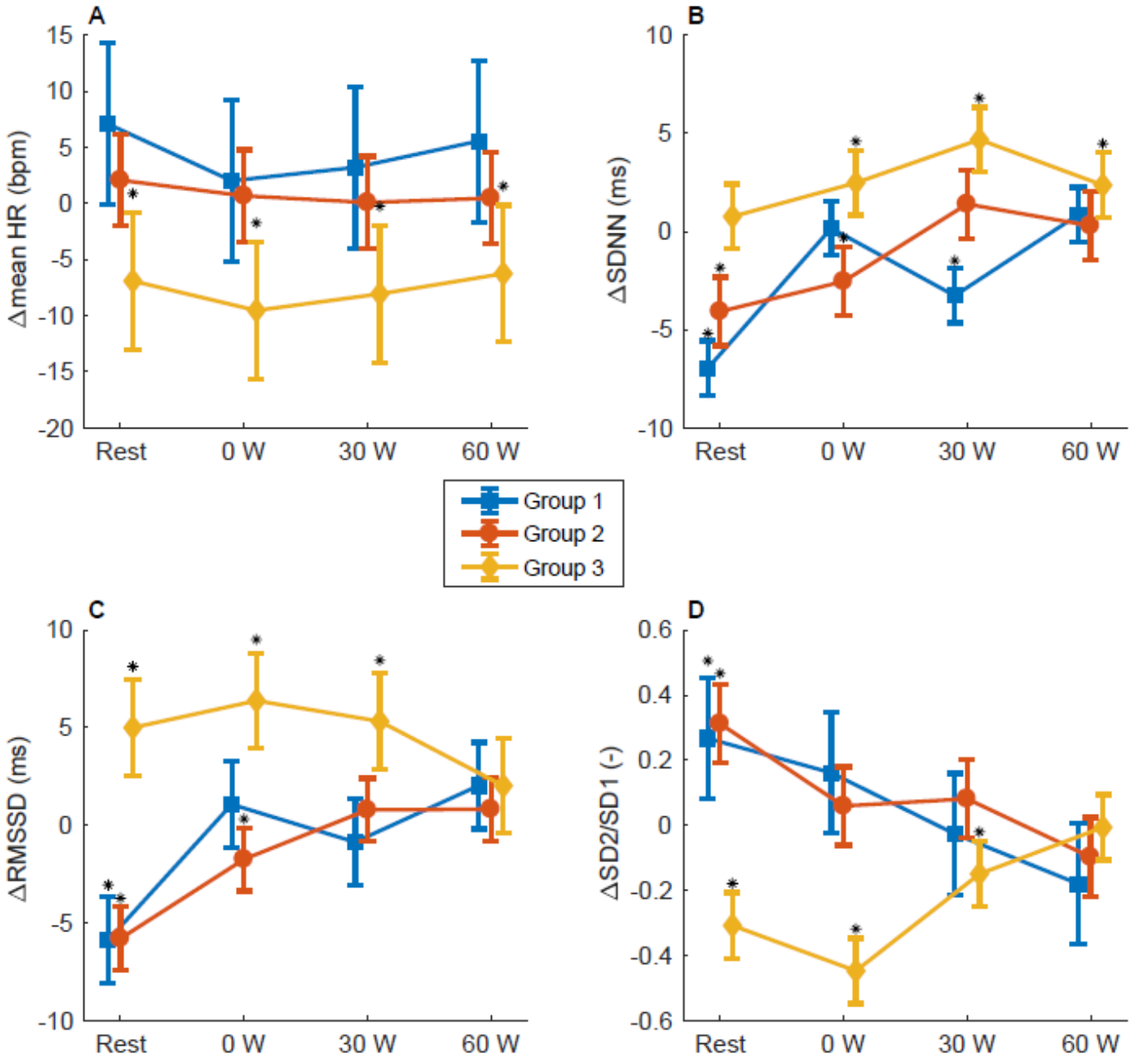

Figure 2

Intervention effects on HRV parameters. Mean (CI 95 %) changes from pre-intervention to post-intervention (Δ=post-pre) in HRV parameters during rest, unloaded (0 W), 30 W and 60 W cycling. Figure shows estimated changes in A. mean heart rate (Δmean HR), B. standard deviation of beat-to-beat intervals (ΔSDNN), C. root mean square of successive differences (ΔRMSSD) and D. Poincaré plot parameter (ΔSD2/SD1). * indicates significant (P<0.05) difference. Group 1 (blue square), Group 2 (red circle) and Group 3 (orange diamond) are presented side by side to maintain explicitness.

	A Group 1 ΔVO_{2max} (95% CI)	B Group 2 ΔVO_{2max} (95% CI)	C Group 3 ΔVO_{2max} (95% CI)
ΔBMI	-0.07 (-0.74, +0.67)	-0.22 (-0.70, +0.41)	-0.70 (-0.92, -0.12)
ΔWaist circumference	+0.05 (-0.68, +0.73)	+0.04 (-0.54, +0.60)	-0.48 (-0.87, +0.27)
ΔFat	-0.38 (-0.86, +0.44)	-0.33 (-0.78, +0.33)	-0.25 (-0.78, +0.50)
ΔVisceral fat	-0.07 (-0.74, +0.67)	-0.45 (-0.81, +0.17)	-0.73 (-0.94, -0.13)
ΔFasting glucose	+0.54 (-0.36, +0.92)	-0.69 (-0.92, -0.11)	+0.07 (-0.67, +0.74)
ΔFasting insulin	+0.50 (-0.41, +0.91)	-0.65 (-0.91, -0.03)	-0.02 (-0.72, +0.69)
ΔHoma-IR	+0.89 (+0.43, +0.98)	-0.68 (-0.92, -0.10)	-0.07 (-0.74, +0.67)
ΔHbA1c	+0.65 (-0.19, +0.94)	-0.32 (-0.98, +0.93)	+0.00 (-0.81, +0.81)
ΔCholesterol	+0.36 (-0.54, +0.87)	+0.52 (-0.22, +0.88)	-0.67 (-0.93, +0.07)
ΔHDL	+0.54 (-0.36, +0.92)	+0.22 (-0.52, +0.77)	-0.38 (-0.86, +0.44)
ΔLDL	+0.46 (-0.44, +0.90)	+0.37 (-0.39, +0.83)	-0.65 (-0.93, +0.11)
ΔTriglycerides	-0.71 (-0.95, +0.08)	+0.35 (-0.41, +0.82)	-0.76 (-0.95, -0.12)
ΔMaximal work	-0.21 (-0.80, +0.58)	+0.20 (-0.42, +0.70)	+0.90 (+0.63, +0.98)
ΔMean HR, rest	+0.49 (-0.54, +0.93)	-0.05 (-0.66, +0.60)	-0.76 (-0.94, -0.24)
ΔMean HR, 0 W	+0.26 (-0.70, +0.88)	-0.19 (-0.73, +0.50)	-0.27 (-0.77, +0.43)
ΔMean HR, 30 W	+0.31 (-0.67, +0.90)	-0.26 (-0.76, +0.44)	-0.59 (-0.89, +0.07)
ΔMean HR, 60 W	+0.37 (-0.63, +0.91)	-0.32 (-0.79, +0.39)	-0.70 (-0.92, -0.12)
ΔSDNN, rest	-0.14 (-0.86, +0.76)	+0.08 (-0.58, +0.67)	+0.37 (-0.34, +0.81)
ΔSDNN, 0 W	-0.60 (-0.95, +0.41)	+0.07 (-0.59, +0.67)	+0.14 (-0.54, +0.71)
ΔSDNN, 30 W	+0.20 (-0.73, +0.87)	+0.25 (-0.45, +0.76)	+0.41 (-0.30, +0.82)
ΔSDNN, 60 W	-0.03 (-0.82, +0.80)	-0.01 (-0.63, +0.63)	+0.61 (-0.03, +0.90)
ΔRMSSD, rest	-0.60 (-0.95, +0.41)	-0.05 (-0.66, +0.60)	+0.36 (-0.35, +0.81)
ΔRMSSD, 0 W	-0.71 (-0.97, +0.23)	-0.10 (-0.69, +0.56)	+0.02 (-0.62, +0.64)
ΔRMSSD, 30 W	-0.31 (-0.90, +0.67)	+0.12 (-0.55, +0.69)	+0.33 (-0.38, +0.80)
ΔRMSSD, 60 W	+0.37 (-0.63, +0.91)	-0.19 (-0.73, +0.50)	+0.45 (-0.25, +0.84)
ΔSD2/SD1, rest	+0.31 (-0.67, +0.90)	+0.21 (-0.48, +0.74)	-0.13 (-0.70, +0.55)
ΔSD2/SD1, 0 W	+0.71 (-0.23, +0.97)	+0.27 (-0.43, +0.77)	-0.05 (-0.66, +0.60)
ΔSD2/SD1, 30 W	+0.31 (-0.67, +0.90)	+0.09 (-0.57, +0.68)	+0.31 (-0.40, +0.79)
ΔSD2/SD1, 60 W	-0.09 (-0.84, +0.78)	+0.37 (-0.34, +0.81)	+0.38 (-0.33, +0.82)

Figure 3

Spearman's rank correlation coefficient between intervention effects on VO2max and other parameters. Spearman's correlation (CI 95 %) between observed changes from pre-intervention to post-intervention (Δ=post-pre) in maximal oxygen uptake (ΔVO2max) and other parameters for A. Group 1, B. Group 2, and C. Group 3. Yellow color indicates significant (P<0.05) correlation between parameters, while orange indicates strong correlation that is close to the significance level (0.05 < P < 0.10).

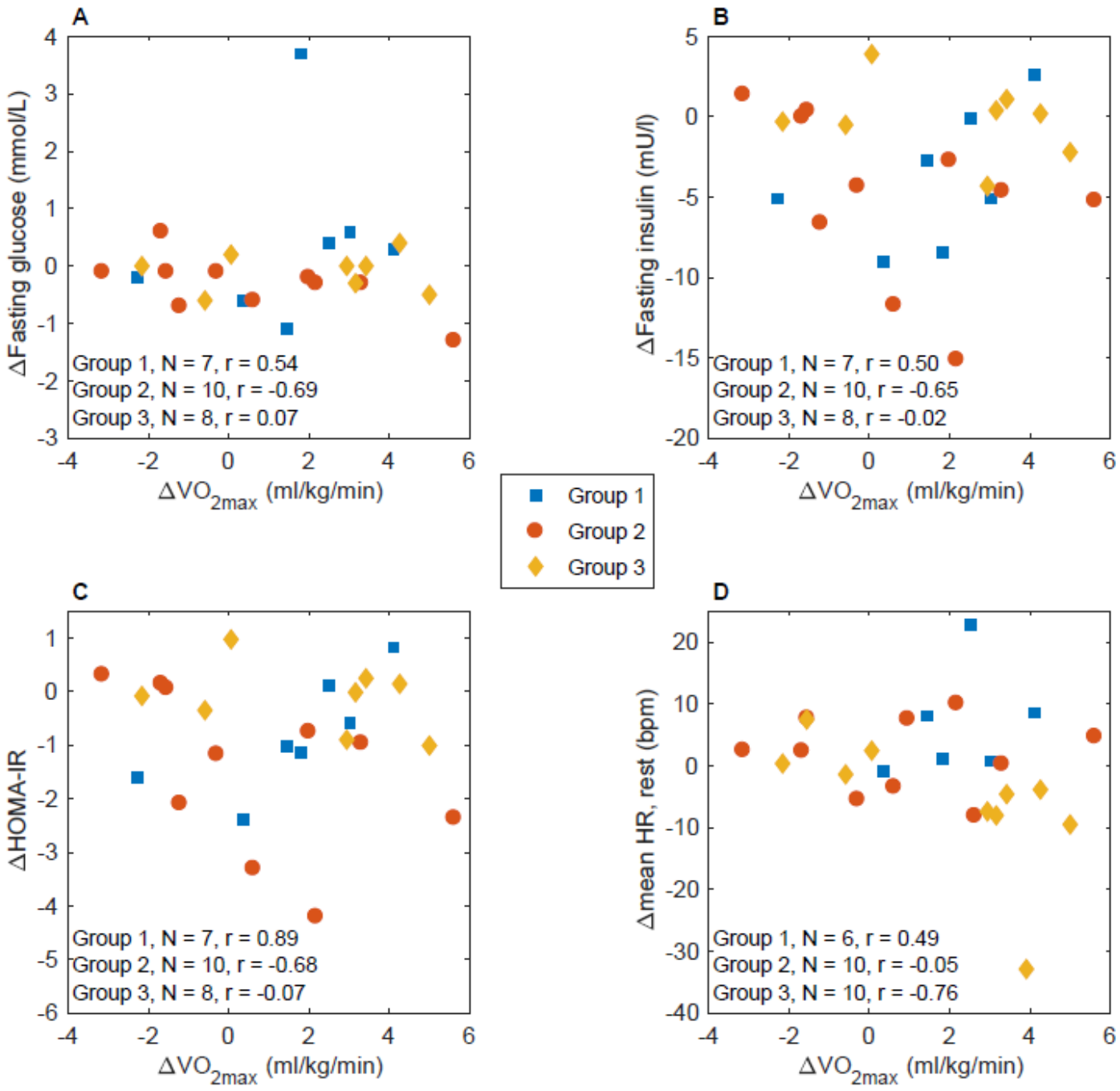

Figure 4

Scatter plot of observed change in parameters. Scatterplot of observed changes from pre-intervention to post-intervention (Δ=post-pre) in A. maximal oxygen uptake (ΔVO2max) and fasting glucose, B. ΔVO2max and fasting insulin, C. ΔVO2max and Homeostatic model assessment for insulin resistance (ΔHOMA-IR) and D. ΔVO2max and mean heart rate (Δmean HR) at rest. Group sizes (N) and corresponding Spearman's correlation (r) for Group 1 (blue square), Group 2 (red circle) and Group 3 (orange diamond) are presented within subplots.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.pdf