Title: Heterogeneous responses of personalised high intensity interval training on type 2 diabetes mellitus and cardiovascular disease risk in young healthy adults

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Abstract

Hypertension, decreased glucose tolerance, adverse lipid profiles and low physical activity levels are associated with increased type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) risk. High intensity interval training (HIIT), a low volume, reduced time, high intensity programme, may be a useful alternative to current government guidelines which specify a minimum of 150 minutes of physical activity per week. We describe a personalised programme of high intensity exercise which provides significant improvements in CVD risk markers. Healthy volunteers undertook 6 weeks of HIIT. T2DM and CVD risk predictors including glucose tolerance, VO_{2max}, blood pressure (BP), and lipids were measured before and after HIIT. HIIT training was associated with beneficial changes in a range of predictors of blood flow and cardiovascular risk. There was a heterogeneous response to HIIT, with some subjects responding with favourable changes and others being non-responders to HIIT. In responders, HIIT was associated with a statistically significant (p=0.023) increase in VO_{2max}, from 45.4 (38.4,52.5) to 56.9 (51.2,65.7) (median (interquartile range)(ml/min/kg)). In responders HIIT resulted in a decrease in systolic BP from 127 (126,129) to 116 (106,122) (mmHg) with p=0.026 and a decrease is diastolic blood pressure from 72 (69,74) to 57 (56,66) with p=0.026. There was also some evidence of a beneficial change in blood lipid and glucose concentrations with HIIT. In conclusion, personalised HIIT has potential as an intervention to improve blood flow and cardiovascular health.

Keywords: Exercise, blood pressure, glucose, lipids, responders

Introduction

Currently, 15 million individuals in the UK are obese with 3.7 million diagnosed diabetes sufferers, and obesity numbers are expected to rise to 26 million by 2030 with T2DM sufferers rising to 5 million by 2025 [29]. This is projected to increase cardiovascular disease (CVD) prevalence which is already the leading cause of death in the UK and worldwide [30]. This is a significant drain on worldwide health services and illustrates that novel interventions are required to prevent and manage this large burden.

Lifestyle interventions such as increased levels of physical activity offer the potential for reduction in cardiovascular risk. Physical activity, particularly in mid-life, is associated with reduced cardiovascular events in later life [14, 25]. Controversy exists over what level of activity is required to reduce risk [18]. Some studies suggest that small increases in activity levels produce measurable health benefits [11] whereas others suggest that high levels of activity are required for any beneficial effects [9, 32]. These beneficial effects include improvements in aerobic capacity, glycaemic control, blood pressure (BP), and lipid profiles, all of which are risk factors for the development of T2DM and CVD [5, 3]. Exercise has a range of effects on hemorheological parameters which may be dependent on the specific exercise regime and acute effects may differ from longer term changes [12, 8]. US and UK government guidelines currently advise that individuals should undertake 150 minutes of continuous moderate exercise (CME) and two muscle-strengthening activities per week to gain appropriate health benefits, however recent evidence suggests that lower frequencies and volumes of high intensity interval training (HIIT) may have similar, or potentially greater, effects in preventing disease risk [10, 15, 28]. Considering that approximately 61% of men and 71% of women fail to meet exercise guidelines in the UK, mainly due to perceived time constraints [15], low volume training protocols such as HIIT may be more attainable for the general population.

HIIT involves repeated brief intervals of intense activity separated by intervals of lower intensity activity or rest, yet protocols vary widely, with intense exercise lasting from 20 seconds to 5 minutes per repetition, with some studies looking at high intensity volumes as low as 3 minutes per week [15, 16]. A more personalised approach to training regimes, with difficulty levels adapting with performance, should maintain motivation [4] and may help improve health benefits. Therefore, HIIT has been the subject of much attention and has been shown to reduce CVD risk in healthy individuals and those with chronic diseases [15, 28]. The mechanisms by which such small volumes of exercise can produce large changes in markers of CVD risk have not been fully elucidated. It is important to note that many studies investigating the effects of HIIT only record the mean responses of the subject cohort, and not individual subjects' responses to HIIT. Recent research has demonstrated that around 10-20% of individuals are non-responders to exercise, meaning that some forms of training may not have beneficial effects in reducing certain disease risk factors [6, 26]. The existence of non-responders to exercise has major implications for the concept of personalised exercise prescription, demonstrating the need for an individual's exercise regime to be at the optimal intensity, frequency and duration to best reduce their individual CVD risk [6].

The aim of this study was to develop individualised HIIT programmes for participants based on initial performance indicators and to determine the response patterns of young, healthy individuals in key cardio-metabolic risk factors to 6 weeks of HIIT programme, in order to examine whether HIIT may be an appropriate disease prevention strategy for all individuals.

Materials and Methods

Subjects

Twenty-three young healthy adults participated in this study; subjects were divided into control (n=10) and test (n=13; n=11 for BP and lipid measurements) groups. The HIIT group undertook 6 weeks of HIIT three times per week for 6 weeks; the control group did not participate in HIIT but continued their normal lifestyle. For both groups an oral glucose tolerance test (OGTT) and VO_{2max} test was performed one week preceding the 6 week trial period (pre-HIIT), and one week following the trial period (post- HIIT). Lipid profiles, systolic and diastolic blood pressure (BP), body fat index (BFI), waist: hip ratio (W:HR) and body mass index (BMI) were measured in both groups. Where designated, subjects were divided into positive responders (beneficial change greater than 2 standard errors of the mean from baseline), and non-responders (no improvement greater than 2 standard errors of the mean from baseline). The study was approved by the Cardiff University School of Biosciences ethics committee. All subjects were fully informed of the experimental procedure prior to giving informed written consent of participation in the study, and subjects were informed that they could withdraw from the study at any time, without needing to provide an explanation.

VO_{2max} test

Subjects performed an exhaustive cycling test to calculate maximum oxygen uptake capacity (VO_{2max}). The test was performed using a cycle ergometer (Seca Cardiotest 100) and subjects were instructed to exercise to their maximum limit. Subjects wore a breathing mask connected to a gas analyser (AD Instruments) which measured oxygen uptake. Subjects warmed up for 5 minutes whilst cycling at 30 watts and maintaining 60rpm; the wattage was then increased by 30 watts every two minutes until the point of exhaustion, where subjects could no longer maintain 60rpm. Maximal aerobic power (in watts) achieved before exhaustion (breaking wattage) was then used as the

starting wattage for HIIT. VO_{2max} was determined by a gas analysis system (AD Instruments) and was determined as the highest value achieved over a 20 second period using LabChart 7.

Oral glucose tolerance test (OGTT)

Subjects refrained from strenuous exercise for 2 days prior to the OGTT and fasted overnight. Fasting blood glucose levels were quantified using an IME-DC glucometer. Subjects then ingested a 75g glucose bolus and blood glucose levels were measured at 30, 60, 90 and 120 minutes following ingestion. Results of the OGTT were used to calculate area under the curve for glucose ($AUC_{0\text{-}120Glucose}$) using the standard trapezoid rule.

Physiological and morphological measurements

Four BP measurements were taken from the upper arm using an automated clinically validated BP monitor (Boots Pharmaceuticals), and the mean value used in analysis. Body mass index (BMI) was calculated as subject weight (kg) divided by height $(M)^2$, and W:HR was recorded to inform of fat deposition. Skinfold thickness was measured, using Harpenden skinfold callipers, at 4 sites: biceps, triceps, waist (suprailiac) and subscapular area. The body fat index (BFI) was then calculated using the Siri formula [24] from the sum of the four skinfold measurements, along with the body density (calculated from standard age and gender matched charts).

High intensity interval training (HIIT) protocol

HIIT consisted of exercising 3 times per week with no more than 2 consecutive days rest, for 6 weeks on cycle ergometers (Seca cardiotest 100, model 545). Each session consisted of a 5 minute warm up, 3 x 1 minute maximum intensity intervals at breaking wattage of the individual, interspersed with a 2 minute working recovery and a 3 minute cool down. Those who completed the 3 intervals on the 1st HIIT session had their wattage adjusted upward by 10% increments based on performance and perceived effort, whilst for those unable to maintain the required >120 rpm for

any interval, wattage was adjusted down in 10% increments based on the same criteria. During the 6 weeks of HIIT if a subject completed 3 intervals maintaining >120 rpm on 2 consecutive sessions, wattage was adjusted upward in 10% increments to ensure maximum intensity was being exerted during each session.

Statistics

Statistical analysis was performed using Excel (windows 7), LabChart 7 reader and Minitab (version 15). Due to the small numbers of samples used , data were assumed to be non-gaussian, hence non-parametric tests were performed; paired data was tested with the 1-sample Wilcoxon, and for more than two sets of data, the Kruskall-Wallis (with post hoc Tukey tests) was used. Statistical significance was accepted when $p<0.05$, all data is shown as median, with interquartile range in brackets, unless otherwise stated.

Results

Despite control subjects not performing HIIT during the 6 week trial period, for consistency, the term 'pre-HIIT' will be used to refer to both HIIT and control subjects' measurements recorded prior to the 6 week trial period. 'Post-HIIT' will refer to HIIT and control subject measurements recorded at the end of the 6 week trial period The effect of HIIT on physiological and biochemical characteristics is summarised in Table 1. There was an increase in the measured maximum aerobic power following HIIT (pre = 217±37 watts to post = 248±64 watts, $p=0.004$) but not in control subjects (pre = 227±64 watts to post = 233±76 watts, $p=0.512$). Two weeks of HIIT in overweight males has previously been shown to reduce BMI and W:HR [31]; these variables were investigated in the young healthy individuals in the present study. There were no significant differences between pre-HIIT and post-HIIT BMI or W:HR in HIIT subjects. This is not surprising given that all subjects were young, healthy individuals and HIIT has a relatively low energy expenditure.

Glucose tolerance response is highly variable

It has been previously demonstrated that HIIT improves glucose tolerance, a component of insulin action [2], and poor glucose tolerance is a risk factor for T2DM. In the present study OGTT plasma glucose levels were used to calculate fasting plasma glucose (FPG), 2 hour plasma glucose and glucose area under the curve (AUC), all of which are indicators of glucose tolerance.

There were no statistically significant differences in FPG, 2 hour plasma glucose, or AUC in the HIIT group pre- to post-HIIT. Glucose AUC following glucose load is a good general indicator of glucose tolerance, with high AUC indicating low glucose tolerance. However, closer analysis indicated there was considerable variation in HIIT subjects' glucose AUC, enabling classification into glucose AUC positive responder and non-responder categories following HIIT [6, 26]; positive responders were classified as having a beneficial change greater than 2 standard errors of the mean from baseline (>49.6 decrease; 8 subjects), whilst the remaining 5 subjects were classified as non-responders. Results of this analysis are summarised in Figure 1. The AUC for the positive responders tended to decrease (p=0.07) whereas in the non-responders the AUC did not decrease although there may have been a small increase, perhaps caused by seasonal variation in AUC (Figure 1).

VO_{2max} response to HIIT is highly variable

Previous studies have shown that HIIT can improve VO_{2max} [10]. HIIT subjects' median VO_{2max} increased from 46.8 to 52.7ml/kg/min, an average increase of 12%, before decreasing 4% from post-HIIT levels to 50.7ml/kg/min after detraining, although these changes were not significant (Table 1).

Although the median VO_{2max} of HIIT subjects did not significantly differ pre-HIIT to post- HIIT, there was considerable variation in individual subjects' HIIT responses. As described above subjects were classified into positive and non-responder groups in VO_{2max} following HIIT. Nine out of thirteen subjects increased their VO_{2max} by over 2 standard errors of the mean in response to HIIT

(>6.1ml/min/kg increase) and were classified VO_{2max} positive responders to HIIT, and the remaining 4 were classified as non-responders. Figure 2 shows the results obtained. The VO_{2max} of positive responders increased significantly following HIIT (p=0.023). The changes in VO_{2max} were significant following HIIT and were also still significant following detraining whilst in non-responders there was a large but non-significant decrease in VO_{2max} post-HIIT (52.1 to 42.83ml/kg/min; p=0.077).

The effect of HIIT on blood pressure in young healthy adults

It has previously been reported that HIIT was effective in reducing mean arterial BP in individuals with metabolic disease [28]; the effect of HIIT on BP was therefore investigated in the young healthy cohort in this study. There were no significant differences between median HIIT subjects' systolic or diastolic blood pressure values before or after HIIT, or following detraining (Table 1).

As with AUC and VO_{2max} results, subjects were classified into BP positive responders, having a beneficial change greater than 2 standard errors of the mean from baseline (>5.9mmHg decrease for SBP and >4.3mmHg decrease for DBP), whilst the remainder of subjects were classified as non-responders to HIIT (Figure 3). There was a large and significant decrease in systolic BP of positive systolic responders pre-HIIT to post-HIIT (127 to 116mmHg; p=0.026). The non-responders experienced a small non-significant increase in systolic BP following HIIT (126 to 136mmHg, p=0795).

For DBP only three out of eleven subjects were positive responders to HIIT, making statistical analysis unreliable; 8 subjects were non-responders to HIIT. Despite this, there was a large difference between pre-HIIT and post-HIIT diastolic BP in positive responders (72 to 57mmHg; p=0.026) which returned to near baseline values on detraining (57 to 67mmHg). There were no changes in diastolic blood pressure in the non-responders (p=0.887)

Changes to blood lipid profile

Total plasma cholesterol levels, triglyceride:high density lipoprotein (TG:HDL) ratio and total cholesterol:HDL (TC:HDL) ratio have been shown to be lipid markers which are predictive of cardiovascular disease. Some evidence exists supporting the role of exercise in improving blood lipid profile [17]. The effect of HIIT on total plasma cholesterol, and TG:HDL and TC:HDL ratios is summarised in table 1. HIIT had no significant effect on total plasma cholesterol ($p=0.610$) or TC:HDL ratio ($p=0.912$). HIIT was associated with statistically significant changes in TG:HDL ratio but the ratio actually tended to increase with HIIT and did not significantly decrease until the detraining period.

The changes in blood lipid profiles associated with HIIT were less heterogeneous that the changes in physiological markers described above. Separation of subjects into positive responders and non-responders did not result in significant changes in total cholesterol ($p=0.059$), TG:HDL ratio ($p=0.10$) or TC:HDL ratio($p=0.371$). The only statistically significant change recorded is a decrease in TG:HDL ratio in the detraining period ($p=0.019$).

Discussion

The present work confirms previous studies showing that individual responses in cardio-metabolic risk factors are highly heterogeneous following exercise [6, 26]. For some individuals HIIT had significant beneficial effects on disease risk markers, demonstrating that lower volumes of exercise than the recommended 150 minutes CME and two strengthening exercise sessions per week may produce health benefits in some individuals.

Glucose tolerance responses to HIIT

High glucose AUC is an indicator of low glucose tolerance and is a risk factor for T2DM; in a recent study glucose AUC was found to be significantly reduced in 16 young men following 6 sessions of HIIT, which each involved 4-6 thirty second cycle sprints [2]. In the present study the median glucose AUC of HIIT subjects tended to decrease but this change was not statistically significant. Subjects demonstrated a heterogeneous response to glucose homeostasis following HIIT training, as with some subjects the AUC decreased markedly following training, but in some subjects HIIT actually resulted in an increase in AUC. When subjects were classified into glucose AUC response categories following HIIT, the 8 glucose AUC positive responders tended to have a decreased AUC following HIIT. Previous studies have attributed HIIT-induced improvements in glucose tolerance to increased muscle GLUT4 content [19, 31], most likely mediated via the AMPK (AMP-activated protein kinase) signalling cascade [20] stimulated by rapid glycogen and energy depletion. In this study five out of thirteen subjects were classified as non-responders and it would be interesting to discover how muscular adaptations may differ in these subjects. It was noted that the pre-HIIT glucose AUC of positive responders was significantly higher than that of non-responders, possibly denoting a greater capacity for positive responders to improve their glucose tolerance with training. Further studies, with increased sample size to increase the statistical power of the study, are required but this study and others [7] suggest that for around 20-30% of people the exercise does not improve glucose tolerance and indeed for around 10% it may have a detrimental effect.

Variability in aerobic capacity responses

A low VO_{2max} is a major predictor of morbidity and mortality, hence manipulation of VO_{2max} via exercise represents a key opportunity for health intervention [26]. In the present study HIIT subjects' VO_{2max} increased by an average 12% following HIIT however this was not statistically significant; this is similar the 9.7% increase reported in young healthy individuals after a similar 6 week HIIT

programme [10]. The value of those categorised as VO_{2max} positive responders significantly increased following HIIT ($p<0.023$).

VO_{2max} improvements following HIIT may partially be the result of increased skeletal muscle mitochondrial biogenesis mediated via the AMPK signalling pathway [10], although Vollaard *et al*. (2009) demonstrated that the magnitude of VO_{2max} response is not always correlated with mitochondrial marker responses. The current study demonstrated that for the majority of subjects HIIT resulted in a significant increase in VO_{2max} but for some subjects this is not the case and in fact in some subjects HIIT actually resulted in a decrease in VO_{2max}. The molecular profile recently developed to predict VO_{2max} response to training may provide greater explanation for the VO_{2max} variability exhibited in this study [27]. VO_{2max} has the greatest impact on future health outcome of all the investigated cardio-metabolic risk factors [26], therefore VO_{2max} improvement following training can be interpreted as an essential element to a successful training programme. HIIT's significant beneficial effect on VO_{2max} in positive responders infers that HIIT is an efficacious protocol for managing morbidity and mortality risk in these individuals.

Systolic and diastolic blood pressure responses

HIIT had no statistically significant effects on median systolic or diastolic BP in the whole test subject cohort or controls. Subjects again demonstrated heterogeneity in the effect of HIIT on blood pressure. In subjects were classified as responders there was a significant decrease in both systolic and diastolic blood pressure. In non-responders no significant changes in blood pressure were recorded and some in some subjects HIIT was actually associated with an increase in blood pressure. It has been previously reported that HIIT was effective in reducing arterial BP in hypertensive subjects [28]. However, these already hypertensive individuals may have a greater capacity to decrease their BP than the young healthy subjects in the present study (median BP of 127/69mmHg). Interestingly the positive diastolic responders to HIIT in this study had a higher median baseline diastolic blood pressure (72mmHg) compared to the non-responders (63mmHg) and there was,

therefore, more potential for exercise intervention to reduce blood pressure. Analysis of the correlation between changes in VO_{2max} and changes in blood pressure offer the potential for a clearer mechanistic understanding of the phenomenon of responders and non-responders and fo the mechanisms by which exercise reduces blood pressure. In this study, however, there is insufficient data to perform this correlation analysis. Potential mechanisms by which HIIT decreases blood pressure may be an increase in peripheral arterial compliance and increased endothelial function, as previously reported [22]. Improvements in compliance may be partially mediated by the high shear stress placed on the arterial wall during HIIT which induces nitric oxide production in the endothelium to promote vasodilation and decrease BP [23].

Lipid profile responses

Obesity and elevated cholesterol levels are highly significant risk factors in CVD [1] and research has highlighted the positive benefits of exercise on lipid profile [21]. In this study, total plasma cholesterol, and TC:HDL median ratios did not significantly change following HIIT. The only statistically significant changes in blood lipids with HIIT reported in the test cohort in the current study is a change in TG:HDL ratio with Tukey method indicating that a decrease in the ratio occurred during the detraining period. A similar change in this ratio has been reported during detraining in postmenopausal women[13]. The decrease in TG:HDL ratio can at least in part be attributed to a drop in TG during detraining. The results suggest that the beneficial effect of training on cardiovascular health may continue for at least six weeks after the training programme finishes.

The TG:HDL ratio, however, significantly decreased during detraining.

Heterogeneity in of responses to HIIT

For many of the factors measured in this study a heterogeneous response to HIIT occurred; some subjects responded to HIIT whereas others were classified as non-responders. Analysis of the

correlation between changes in fitness, measured by $VO_{2max,}$ and improvements in cardiovascular risk offers the potential for some mechanistic understanding of the heterogeneous response described. Correlation analysis could not, however, be performed in this study as the sample size is too small for this type of analysis. It is important to understand the mechanisms that generate the heterogeneous responses to HIIT and this analysis described above would clearly improve this understanding. Enhancing understanding of the mechanisms behind HIIT response patterns may enable the development of genetic predictors of glucose tolerance, BP responses and lipid profiles similar to those already reported for VO_{2max} [26]. It is not definitively known whether non-responders to one form of training would respond more favourably if exposed to an alternative exercise stimulus. Therefore non-responders could be exposed to moderate intensity, endurance or strength training to examine whether these forms of exercise generated the same response patterns as those reported following HIIT. If this was investigated, subjects may be able to find an optimal training regime to maximise health benefits. The minimal time commitment required may mean HIIT could have a place in prescription to those with pre-diabetic conditions, and could become part of the recommendation of physical activity to the general population who 'do not have time' to complete the recommended 150 minutes and two strength training sessions per week.

The heterogeneity of HIIT responses also necessitates that exercise programmes are personalised to the needs and responses of the individual as there is no 'one size fits all' exercise regime. In accordance with the findings of Vollaard *et al.* (2009) response in one risk factor was not found to correlate with response to other risk factors. Therefore, an individual's response in each risk factor would need to be independently assessed and then integrated to generate an overall response profile; if this information was combined with genetic testing to examine any inherent predisposition to cardio-metabolic diseases, one could weigh-up which form of exercise would best manage any innate disease risk. This would enable a more suitable judgement of the appropriateness of HIIT for health risk management in each individual. However, while HIIT may be beneficial to many there

may be a significant proportion of the population to whom it provides no benefit, or even causes an adverse response. Clearly a worsening of glucose tolerance in a pre-diabetic patient is not a desirable outcome. A greater understanding of molecular and genetic mechanisms underlying non- and adverse responses is needed to predict an individual's ability to respond, and enable personalisation of prescription.

Conclusions

In conclusion, there is a heterogeneous response to personalised high intensity interval training with some subjects responding with favourable changes in cardiovascular risk markers. In these subjects HIIT resulted in a significant increase in VO_{2max} which was still increased six weeks after the training programme finished. In responders, HIIT resulted in beneficial changes in both systolic and diastolic blood pressure and changes in diastolic blood pressure were still present six weeks after training. There is also some evidence that HIIT is associated with beneficial changes in some blood lipid parameters. Personalised high intensity interval training has potential as an intervention to improve blood flow and cardiovascular health.

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Tables

Table 1. Physiological and biochemical characteristics of the HIIT at baseline (pre-HIIT) and post-HIIT . Data presented as median and interquartile range. Differences between medians determined by 1-sample Wilcoxon or Kruskal Wallis test with significant differences from pre-HIIT indicated by *, determined by Tukey method . **BP**: blood pressure (mmHg); **VO_{2max}** (ml/min/kg); **FPG**: fasting plasma glucose (mmol/L); **2-h PG**: 2-hour plasma glucose (mmol/L); **AUC**: area under the curve (arbitrary units); **TC**: total cholesterol (mmol/L); **TG**: triglyceride (mmol/L); **HDL**: high density lipoprotein cholesterol(mmol/L). n=13 for all variables except BP and lipid measurements where n=11.

Variable	A	B	C		A	B	C
	HIIT group values			P value (Kruskall Wallis)			**P value (1-sample Wilcoxon)**
	Pre-HIIT	**Post-HIIT**	**Detraining**		**Controls - Pre**	**Controls - Post**	
FBG	4.3 (4.4, 5.1)	4.7 (4.5, 5.0)	4.6 (4.2, 5.0)	0.741	4.85 (4.68, 5.20)	4.65 (4.48, 4.80)	0.285
2-h PG	6.0 (5.0, 6.7)	5.3 (5.1, 6.3)	5.4 (5.0, 6.3)	0.834	5.60 (5.20, 6.45)	5.05 (4.60, 6.80)	0.407
Glucose AUC	837 (689, 857)	770 (695, 780)	759 (687, 847)	0.441	784 (681, 890)	749 (676, 865)	0.610
VO_{2max}	46.8 (43.0, 54.7)	52.7 (48.0, 61.6)	50.7 (46.7, 55.1)	0.323	37.1 (33.3, 59.3)	49.5 (29.9, 55.1)	0.673
Systolic BP	127 (120, 136)	123 (106, 138)	125 (110, 137)	0.835	128 (111, 135)	121 (112, 130)	0.093
Diastolic BP	69 (62, 74)	62 (57, 74)	67 (57, 72)	0.626	69 (66, 73)	70 (60, 77)	0.767
Plasma TC	4.6 (3.7, 4.8)	4.2 (4.1, 4.5)	4.5 (3.6, 4.7)	0.610	3.9 (3.6, 4.5)	3.80 (3.55, 4.30)	0.944
TC:HDL ratio	3.0 (2.8, 3.5)	3.2 (3.0, 3.9)	3.2 (3.0, 3.5)	0.912	3.7 (3.0, 4.1)	3.6 (2.8, 4.3)	0.272
TG:HDL ratio	0.69 (0.54, 1.33)	0.78 (0.64, 0.90)	0.49 (0.43, 0.54)*	0.019	0.90 (0.75, 1.11)	0.75 (0.54, 1.37)	0.721

Table 2. TC:HDL and TG:HDL ratios of the HIIT positive and non-responder groups pre- and post-HIIT. . Data presented as median and interquartile range. Differences between medians determined by 1-sample Wilcoxon. **TC**: total cholesterol (mmol/L); **TC:HDL**, total cholesterol: high density lipoprotein cholesterol ratio; **TG:HDL**, triglyceride:high density lipoprotein cholesterol ratio.

Variable	A	B	E	C	D	F
	Positive responders			Non-responders		
	Pre-HIIT	Post-HIIT	Positive responders p value	Pre-HIIT	Post-HIIT	Non-responders p values
Plasma TC	4.6 (3.9, 4.5)	4.2 (4.0, 4.3)	0.059	4.6 (3..7, 4.8)	4.5 (4.2, 5.3)	0.106
TG:HDL	1.33 (1.03,1.53)	0.86 (0.56, 1.18)	0.10	0.59 (0.50, 0.69)	0.76 (0.64, 0.83)	0.108
TC:HDL	4.4	3.6	0.371	3.0 (2.8, 3.2)	3.2 (3.1, 3.7)	0.024

Figure captions

Fig. 1. Changes in glucose AUC pre- and post-HIIT as classified into responder groups based on HIIT response. Bars represent median with interquartile range. Differences between medians determined by Kruskal Wallis test where p= 0.07 for responders and p= 0.298 for non-responders.

Fig. 2. **Changes in VO_{2max} pre-HIIT, post-HIIT and after detraining according to response. Bars represent median with interquartile range.** Differences between medians determined by Kruskal Wallis test where p= 0.023 for responders and p= 0.077 for non-responders. Significant differences from Pre-HIIT indicated by *, determined by Tukey method.

Fig. 3. **Systolic (A) and diastolic (B) blood pressure of positive and non-responders. Bars represent median with interquartile range.** Differences between medians determined by Kruskal Wallis test where p= 0.026 for responders and p= 0.795 for non-responders for systolic blood pressure and p=0.026 for responders and p=0.887 for non-responders for diastolic blood pressure. Significant differences from Pre-HIIT indicated by *, determined by Tukey method.

Figures

Fig. 1. Changes in glucose AUC pre- and post-HIIT as classified into responder groups based on HIIT response. Bars represent median with interquartile range. Differences between medians determined by Kruskal Wallis test where p= 0.07 for responders and p= 0.298 for non-responders.

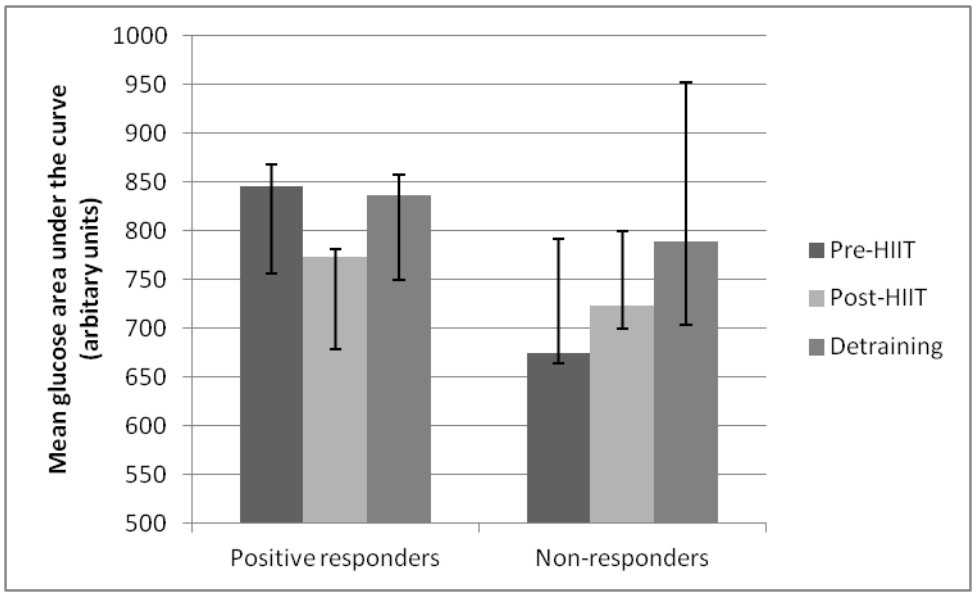


Fig. 2. Changes in VO_{2max} pre-HIIT, post-HIIT and after detraining according to response. Bars represent median with interquartile range. Differences between medians determined by Kruskal Wallis test where p= 0.023 for responders and p= 0.077 for non-responders. Significant differences from Pre-HIIT indicated by *, determined by Tukey method.

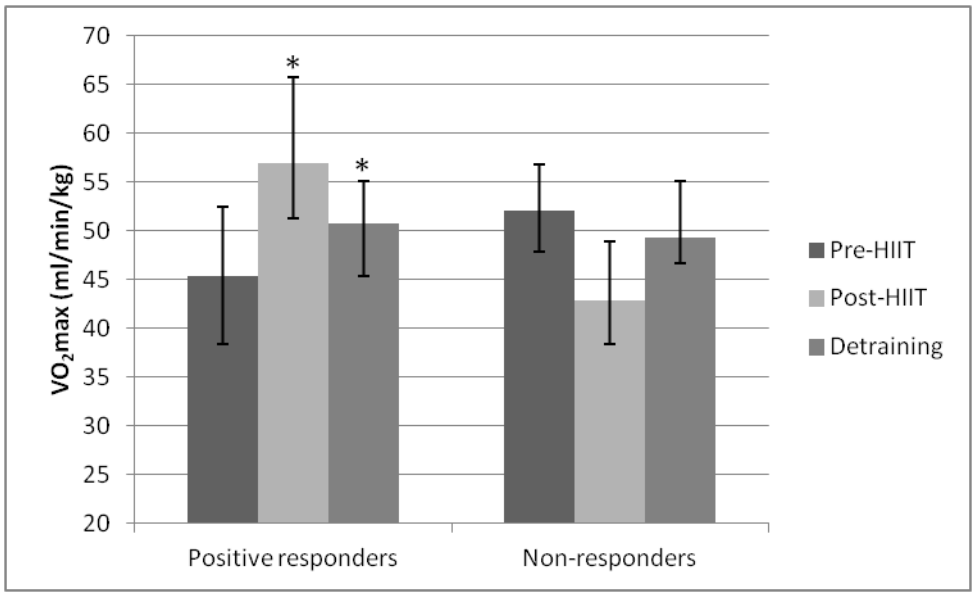
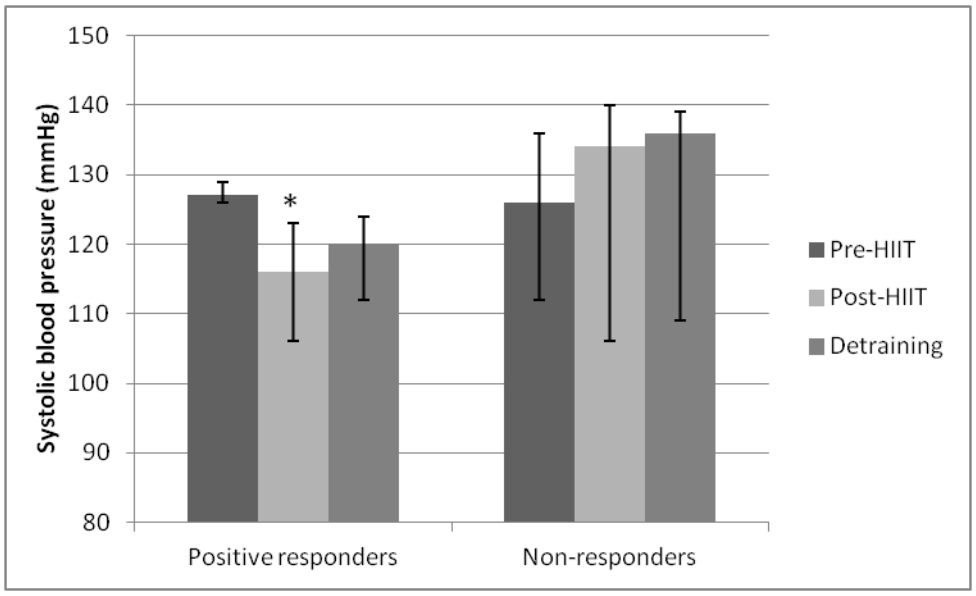


Fig. 3. Systolic (A) and diastolic (B) blood pressure of positive and non-responders. Bars represent median with interquartile range. Differences between medians determined by Kruskal Wallis test where p= 0.026 for responders and p= 0.795 for non-responders for systolic blood pressure and p=0.026 for responders and p=0.887 for non-responders for diastolic blood pressure. Significant differences from Pre-HIIT indicated by *, determined by Tukey method.

A. Systolic blood pressure



B. Diastolic blood pressure