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The effects of adding high intensity of effort resistance training to routine care in persons with type II diabetes: an exploratory randomised comparative interrupted time-series study

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For correspondence: james.fisher@solent.ac.uk
Twitter: @jamessteeleii @DrJpfisher

Jürgen Giessing[1], Björn Eichmann[1], Wolfgang Kemmler[2], Wayne L. Westcott[3], Richard Winett[4], Kevin Busuttil[5], James Steele[5], James P. Fisher[5]

[1]Institute of Sport Science, University of Koblenz-Landau, Landau, Germany
[2]Institute of Medical Physics, Friedrich-Alexander University, Erlangen-N¨urnberg, Erlangen, Bavaria, Germany
[3]Quincy College, Quincy, MA, USA
[4]Virginia Tech University, Blacksburg, USA
[5]Faculty of Sport, Health and Social Science, Solent University, East Park Terrace, Southampton, UK

ABSTRACT

Aims: The aims of this study were to consider the effects of supervised, low volume, high intensity of effort resistance training compared to continued routine care in persons with type II diabetes. *Methods:* This study utilized a randomized comparative interrupted time-series design. All participants completed baseline testing (T0) and then participated in an educational training intervention regarding management of their diabetes. They were followed up for six months during which they received routine care before being retested (T1). Following this they were randomly allocated to either continue with routine care (CON), or to receive the high intensity of effort resistance training intervention (HIT). The intervention lasted for six months after which participants from both groups were retested again (T2). After this all participants were followed up for a further 12 months before being finally tested (T3). Data was available from 57 participants who completed the whole duration of the study (HIT, n = 29; CON, n = 28) for (i). anthropometric outcomes (body mass, waist circumference, and BMI), (ii). body composition

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outcomes (body fat mass, body fat percentage, muscle mass, and visceral fat mass), (iii). water and blood outcomes (total body water, phase angle, HbA1c, and fasted blood glucose), and (iv). subjective wellbeing (WHO-5). ***Results:*** During the initial 6-month time epoch significant improvements were noted for waist circumference, body fat mass, muscle mass, body fat percentage, muscle mass percentage, visceral fat mass, HbA1c, fasted blood glucose, and subjective wellbeing. During the successive 6- and 18-month periods data suggest that many of these positive changes during the initial 6-months were negated or reversed for CON. In contrast participants engaging in HIT continued to show positive changes for waist circumference, body fat mass, muscle mass, body fat percentage, muscle percentage, and visceral fat. For blood markers and wellbeing, HbA1c continued to decrease, fasted blood glucose decreased, and subjective wellbeing continued to increase. These positive responses were still evidence and significantly different compared to CON after the 12-month follow-up. ***Conclusion***: The results of this exploratory pragmatic trial suggest that the addition of high intensity of effort RT alongside routine care can have a positive impact on a range of outcomes in type 2 diabetics having undergone prior routine care.

KEYWORDS: body composition, fat mass, HbA1c, muscle mass, strength training, subjective wellbeing

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Introduction

Resistance training (RT) has been acknowledged to produce a plethora of physiological- as well as psychological- health benefits (Fisher, et al. 2017). These are in addition to the notable increases in muscular strength and hypertrophy, which are independently strong predictors of longevity and quality of life (Ruiz, et al. 2008; Srikanthan, et al. 2014). As such publications have discussed these health benefits and appropriately stated “resistance training is medicine” (Westcott, 2012). Westcott continues, discussing increased metabolic rate and fat loss resulting from RT as central in fighting obesity, and as such, highlighting RT as an effective intervention to combat type 2 diabetes (T2D). Further publications have supported that resistance training can be essential in the management and prevention of type 2 diabetes (T2D) (Irvine, et al. 2009). For example, Strasser, et al. (2010) reported decreases in glycosylated hemoglobin (HbA1c) - essential in the management of T2D. Further research has demonstrated a reduced rate of T2D in persons engaging in RT compared to those who do not (Shiroma, et al. 2017), as well as improved muscle quality and insulin sensitivity resulting from RT in persons suffering with T2D (Brooks, et al. 2006). Finally, muscular improvements resulting from RT support enhanced glucose transport in addition to improved mitochondrial oxidative capacity, both of which are identified as important favorable adaptations for persons with T2D (Pesta, et al. 2017).

Despite the numerous health benefits, RT participation and adherence remains surprisingly low. In 2008 it was reported that only 6% of American adults met the government recommendations for muscle strengthening exercise (Loustalat, et al. 2013). However, whilst data suggests this has increased to ~34% in males and ~25% in females for the UK and USA, these numbers are still low (Nuzzo, 2020). Further, these data represent *muscle strengthening activities* which typically includes yoga and heavy gardening – exercise which is unlikely to be as effective as RT (Steele, et al. 2017). The most common barriers to long-term RT adherence are time constraints and perceived difficulty (Trost et al., 2002; Winett et al., 2009), and as such a growing body of research is investigating and showing support for more time efficient and uncomplicated approaches (Fisher, et al. 2017).

In considering persons with T2D, a recent publication of a case study suggests that very-low volume RT (2 sets of 4 exercises performed 2 x / week) performed over 15 weeks, improved the health and quality of life in a diabetic and hypertensive female (e.g. reduced blood glucose, systolic and diastolic blood pressure, and heart rate at rest, as well as improvements in body mass index, cardiorespiratory fitness, and a reduction in the amount of antihypertensive and anti-diabetic medications; Seguro, et al. 2020). Furthermore, empirical research has reported similar adaptations and HbA1c responses for different loading schemes (50% versus 75% 1RM; Yang, et al. 2017), and a recent meta-analysis and systematic review compared *hypertrophy* RT (e.g., 70-85% 1-repetition maximum; RM, for 1-3 sets of 8-12 repetitions) to *muscular endurance* RT (e.g., <70% 1RM, for 2-4 sets of 10-25 repetitions) as therapeutic interventions for persons with T2D. The authors again reported similarly favorable adaptations, suggesting load is not the primary driver for adaptation (Acosta-Manzano, et al. 2020). These publications support existing research in asymptomatic persons that training volume and load are variables secondary to intensity of effort for catalyzing positive adaptations (Fisher, et al, 2017b; Schoenfeld, et al. 2017). Indeed, following a large review, Röhling, et al. (2016) reported that the improved molecular signaling pathways leading to glucose transport into the cell, and modulation of inflammatory processes as a result of exercise, appear to be primarily determined by intensity of effort.

With the above in mind, it is surprising that there exists a relative dearth of literature considering low-volume, high effort RT in persons with T2D. As such the aims of this study were to consider the effects of supervised high intensity of effort RT performed twice a week for six months.

Methods

Study design

This study utilized a randomized comparative interrupted time-series design. Comparative interrupted time-series designs typically are used in causal inference from observational data where policies/interventions have been implemented in one sample group but not another. The assumed counterfactual in this design is that the slope and level of the outcomes would have changed similarly in the intervention group compared to the non-intervention group. Normally however, group assignment is not randomized. In this study however, we randomized which of the participants were to receive the intervention thus strengthening the ability to draw causal inferences.

A schematic of the study design is presented in figure 1. Participants were recruited and tested at baseline (T0) before participating in an educational training intervention regarding management of their diabetes. They were followed up for six months during which they received routine care before being retested (T1). Following this they were randomly allocated to either continue with routine care (Control), or to receive the high intensity of effort resistance training intervention (HIT). The intervention lasted for six months after which participants from both groups were retested again (T2). After this all participants were followed up for a further 12 months before being finally tested (T3).

This study was exploratory in nature and was not explicitly designed for a specific *a priori* power or level of precision for estimates. The study was conducted pragmatically and recruited form the pool of participants already engaged with the educational training at the diabetes centre of Vinzentius Hospital in Landau, Germany. Our aim was to explore the use of the high intensity of effort resistance training intervention, in addition to providing estimates of effects on outcomes.

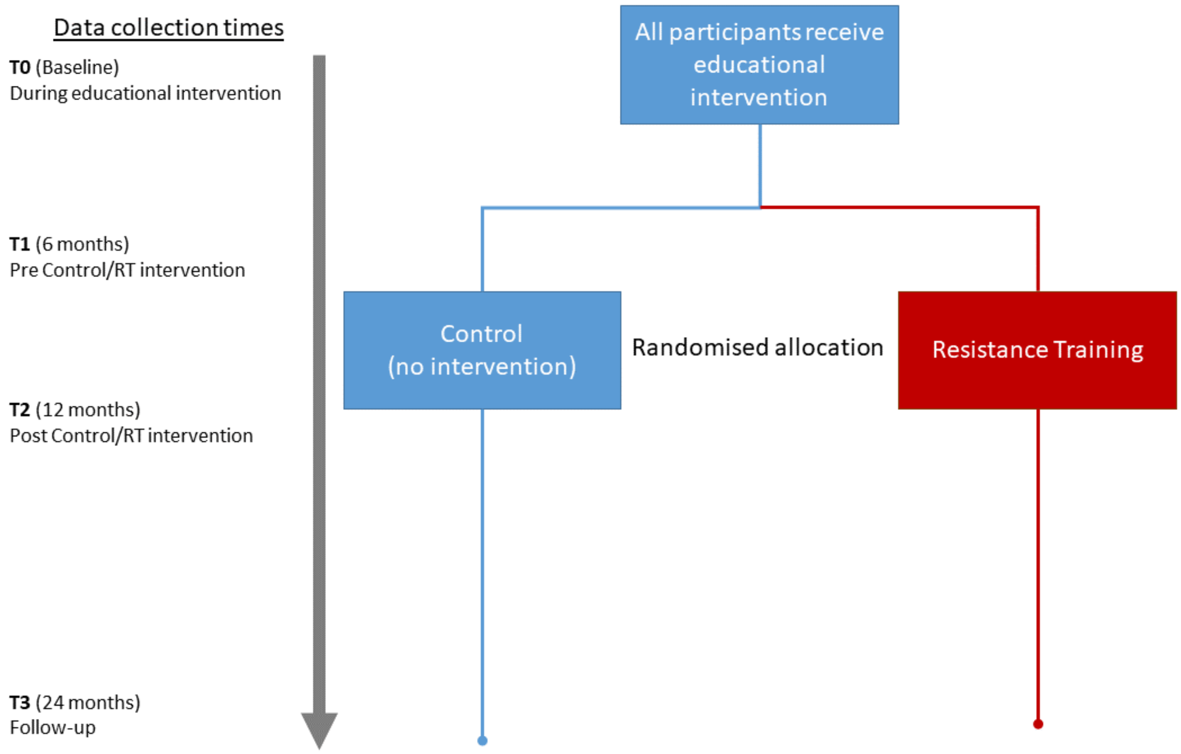


Figure 1. Study design schematic

Participants

Participants were invited to participate in the study from type 2 diabetics undertaking an educational course/schooling for diabetics at Vinzentius Hospital in Landau, Germany where the diabetes centre offers regular courses for type 1 and type 2 diabetics. One hundred and seventy-two people initially expressed interest in participating and underwent screening for inclusion/exclusion criteria. Participants in the study had to be at least 18 years of age with a diagnosis of type 2 diabetes and a National Glycohemoglobin Standardization Program (NGSP) haemoglobin A1c (HbA1c) value of at least 6.3 percent and fasted blood glucose value of at least 100 mg/dl. Excluded from the study were patients with amputations of upper and/or lower extremities, diabetics with very severe visual impairment, diabetics with a pacemaker, and those patients who suffered from co-morbidities which did not allow regular physical activity. All participants were required to get a prior medical check-up and an attestation by their doctor that allowed them to participate in an exercise programme. After screening 60 participants were included in the study and provided informed consent. At T1 participants were assessed for interest and medical clearance from their doctor to participate in the resistance training intervention. Those participants who were suitable were randomised in a counterbalanced fashion to either receive the 6 months intervention or continue receiving routine care as controls. During the study duration one participant dropped out of the intervention group and two participants dropped out of the control. Thus, complete data was available from 57 participants who completed the whole duration of the study (HIT, n = 29; CON, n = 28). Participant characteristics at baseline are available in table 1.

Table 1. Participant characteristics

Characteristic	**N = 57**[1]
Sex (% male)	40 (70%)
Age (years)	62 (52, 73)
Height (cm)	170 (165, 178)
Body mass (kg)	92 (80, 103)
BMI (kg.m^2)	31.8 (27.9, 34.9)
Waist circumference (cm)	107 (99, 115)
Body fat mass (kg)	28 (21, 34)
Muscle mass (kg)	60 (51, 67)
Body fat (%)	31 (26, 36)
Muscle (%)	66 (60, 70)
Visceral fat mass (kg)	15.0 (12.0, 17.0)
Total body water (%)	48.0 (45.6, 51.4)
Phase angle (degrees)	5.80 (5.30, 6.40)
NGSP HbA1c (%)	8.30 (7.90, 8.90)
Fasted Blood Glucose (mg/dl)	129 (122, 139)

Table 1. Participant characteristics

Characteristic	N = 57[1]
WHO-5 (points)	44 (28, 60)

[1] Statistics presented: n (%); median (IQR)

Routine Care

Type 2 diabetics at Vinzentius Hospital in Landau, Germany are offered a weeklong educational course/schooling for management of their diabetes. The inpatient and outpatient courses are certified by the German Diabetes Society (DDG) and are offered by a team consisting of a diabetologist, a psychologist, a podologist/chiropodist, a nutritionist, a physiotherapist, and a diabetes consultant. Within these training days the diabetics were educated about different topics: nutrition, treatment options for diabetes, diabetes medication, sequelae, physical activity and exercise. In addition to these theoretical basics, there were practical training days in which the focus was on experiencing and learning practical skills in everyday life: assessing the effect of meals on blood glucose with confidence, measuring blood glucose correctly, how to inject insulin, mastering hypoglycaemia safely, and controlling blood glucose during exercise and work. After the initial weeklong training all participants continued to receive routine care from their doctors in private practice.

High Intensity of Effort Resistance Training Intervention

The intervention was comprised of supervised high intensity of effort resistance training performed twice a week for six months (26 weeks) from T1 until T2. The control group did not participate in the intervention. Training took place on fixed days, both Mondays and Thursdays, between 9:00am and 11:00am or between 15:00pm and 17:00pm based on participant availability. However, once assigned to a group training time, participants remained within that group through the duration of the intervention. This was clearly explained to participants because of the diurnal variation of blood glucose metabolism (Mancilla, et al. 2020). Each training session was performed using Ergofit-POWER LINE 4000 resistance machines which enabled training to be automatically recorded and evaluated using the built in Vitality System 6.0. The advantage of this digital training control is that both the range of movement and the movement speed could be programmed. The stored recommendations were displayed visually on a monitor on each device, so that everyone's seat adjustment was visible on the screen as well as the repetition duration (seconds) and ROM of each repetition. A full body routine was programmed using the Ergofit-

POWER LINE 4000 resistance machines including chest press, seated row, reverse fly, shoulder press, elbow flexion, elbow extension, knee extension, knee flexion, lumbar extension, and abdominal flexion. The order of the exercises could be self-determined by each subject, as long as multi-joint exercises (chest press, seated row, shoulder press, reverse fly) were to be trained before single-joint exercises (elbow flexion, elbow extension, knee extension, knee flexion, lumbar extension, and abdominal flexion). Participants initially performed a single set of repetitions for each exercise using a load permitting approximately 8 to 12 repetitions to be performed until reaching a set endpoint equating to their self-determined repetitions maximum (sdRM; i.e. when they estimate that, if attempted, they would fail to complete the next repetition). Upon reaching this point, participants rested for between 10-29 seconds and then attempted further repetitions until reaching their sdRM. This was then repeated one more time. A rest of interval of $\leq$29 seconds was permitted since breaks of <30 seconds are considered intra-serial breaks (e.g. a single-set with rest-pause repetitions), compared to breaks of >30 seconds, which are generally considered inter-serial breaks (e.g. multiple sets). Total time for the resistance workout was 30-45minutes. Repetitions were performed using a duration of at least 5 seconds (i.e., 2 seconds concentric, 1 second pause, 2 seconds eccentric). Load was progressed by 5% once participants could complete more than 12 repetitions in their first set of each exercise. The load to be used for every exercise was stored on the subject's chip card which linked to the Vitality System 6.0. Only repetitions that were performed slowly enough (i.e. at least 5 seconds - 2 seconds concentric, 1 second pause, 2 seconds eccentric) and over the full range of motion were recorded by the computer system; if performance was inadequate in terms of either, the repetition was not counted. After completion, each training session was stored on the chip card and could be checked by each test person at a permanently installed PC station (Vitality Coach) in the fitness studio, which was accessible at any time.

Outcome Measures

Anthropometric outcomes included body mass, BMI, and waist circumference. Body composition outcomes including body fat (both mass in kg and %), muscle (both mass in kg and %), visceral fat mass (%), in addition to total body water (%) and phase angle (degrees) were measured using bioelectrical impedance analysis (Tanita MC-180MA). Blood samples were taken by trained medical staff at Vinzentius hospital to assess both NGSP HbA1c (%) and fasted blood glucose (mg/dl). Participants also completed the WHO-5 questionnaire to assess subjective wellbeing. All training sessions were supervised by the same research assistant who also did all the BIA, questionnaire, and measurement tests and who knew the members of both groups and was familiar with the individual training progress the members of the training group had achieved. All tests were performed at the same time as the previous tests.

Statistical Analysis

As noted, this study was treated as exploratory. Thus, analyses of the data generated from our participants was performed such that inferential statistics were treated as highly unstable local descriptions of the relations between model assumption and data in order to acknowledge the inherent uncertainty in drawing generalised inferences from single and small samples (Amrhein et al., 2019). For all analyses we opted to avoid dichotomising the existence of effects and therefore did not employ traditional null hypothesis significance testing, which has been extensively critiqued (Amrhein et al., 2019b; McShane et al., 2019). Instead, though we present *p* values, we consider the implications of all results compatible with these data, from the lower limit to the upper limit of compatibility (confidence) interval estimates for parameters, with the greatest interpretive emphasis placed on the point estimate for parameters. All analysis was conducted in R (v 4.0.2; R Core Team, https://www.r-project.org/) and all data and code utilised is presented in the supplementary materials (https://osf.io/5bd4y/).

Linear mixed models were used to examine the main effects of 'time', 'group', and 'time x group' upon all outcomes as dependent variables. Routine care (i.e., CON) was the reference for 'group' effects. In essence a longitudinal growth model was fit with time in months treated as a continuous variable, and random intercepts and slopes for time for individual participants. The assumptions of this model are reasonable given the study design and data generating process. Essentially, individual participants have approximately linear trends over time given routine care; the introduction of the intervention will break this linear trend, initially with an offset to the intercept, and then with a different slope as time continues. Further, given that the intervention was delivered between 6 and 12 months, we employed linear splines with knots selected at these timepoints using the 'lspline' package (Bojanowski et al., 2017). This enabled us to produce linear parameter estimates for 'time' and 'time x group' interactions in a piecewise manner facilitating interpretation of the effects over each epoch. As noted, this is essentially a sort of comparative interrupted time-series, but the interruption is when randomised assignment to the intervention occurs, and at the point in which the intervention ended. This model allows us to interpret the coefficient for time as what we would expect the slope to be for routine care, the group coefficient as the intercept offset that occurs with randomisation (i.e., between group difference in values at 6 months due to randomisation alone), and then the interaction as the effects of the intervention over time compared with routine care (i.e., the effect of HIT compared to CON on the slope for time). However, unlike traditional interrupted time series analyses we do not need to make any assumptions about the trajectory for routine care as some participants (CON) actually continued along that path. The linear mixed model was fit using the 'lme4' package (Bates et al., 2015) and Maximum Likelihood Estimation. The models for each dependent variable (dv) in Pinheiro-Bates-modified Wilkinson-Rogers notation (Wilkinson and Rogers, 1973; Pinheiro and Bates, 2000) and specifying the linear spline for the fixed effect of time using the lspline package notation was:

```
dv ~ lspline(time, c(6,12)) * group + (time | participant)
```

Model predicted values were extracted and summary tables were produced using the 'sjPlot' package (Lüdecke, 2020). Data visualisation included plotting individual raw data adjusted for individual random intercepts and the model predicted values.

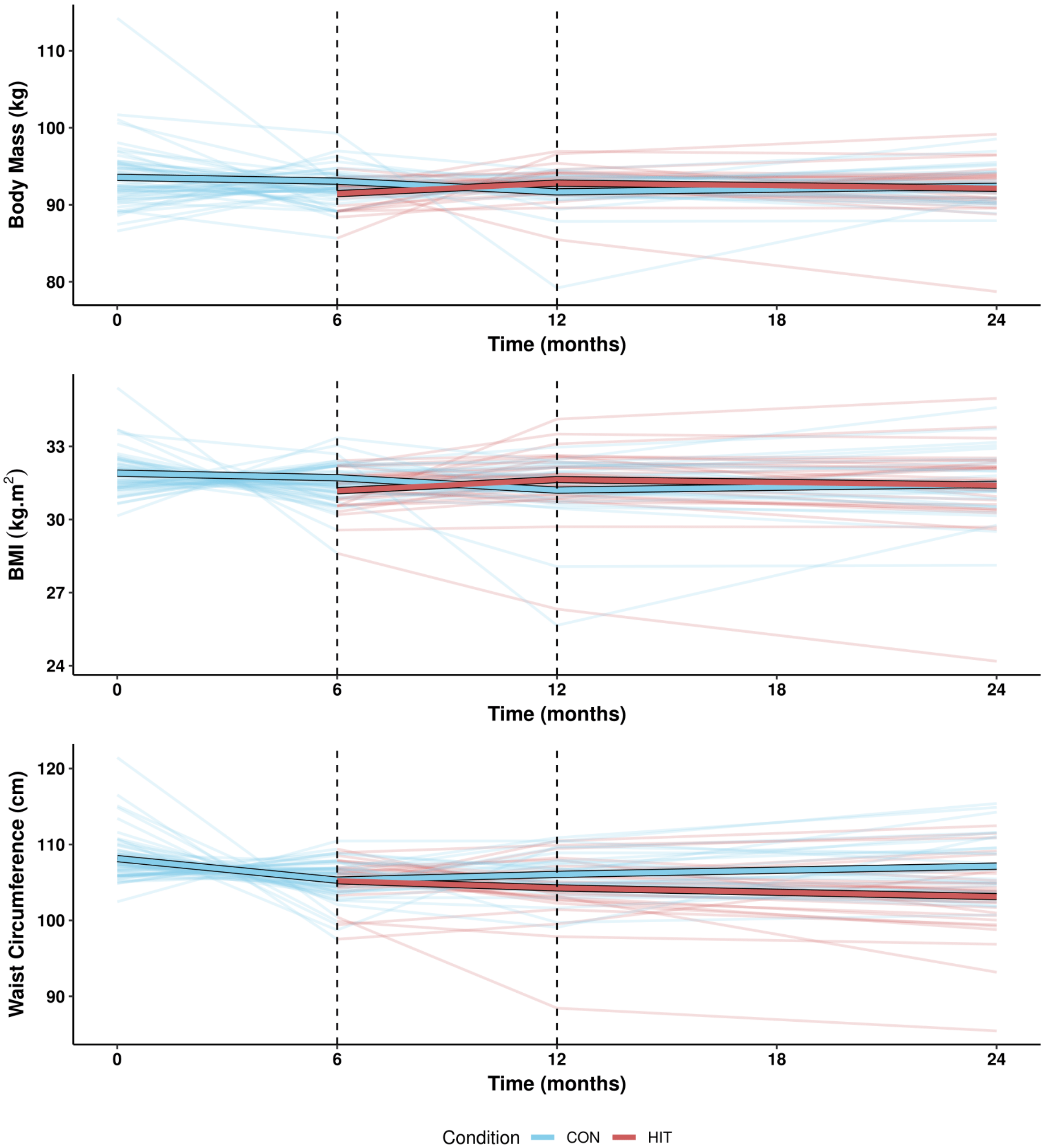
Results

Anthropometric Outcomes

Both body mass and BMI appeared relatively stable over time across both routine care and from introduction of the HIT intervention. There was a minimal time x group interaction effect for the second time epoch only whereby the slope for the HIT intervention was positive compared to the negative slope for CON (Time [2nd degree] * Group [HIT]: $\beta_{Body\ Mass}$ = 0.46 kg [95%CI 0.03 kg to 0.90 kg], β_{BMI} = 0.16 kg.m^2 [95%CI 0.04 kg.m^2 to 0.28 kg.m^2]). Waist circumference appeared to initially decrease over the first- time epoch for CON (Time [1st degree]: $\beta_{Waist\ Circumference}$ = -0.47 cm [95%CI -0.76 cm to -0.19 cm]) and, though from visual inspection of the data (figure 2) it appeared to increase over the second- and third- time epochs for CON while continuing to decrease over both for HIT, interaction effects were imprecise and included zero. Table 2 presents the full model summaries for all anthropometric outcomes and figure 2 presents the model predicted values with random intercept adjusted individual participant values.

Table 2. Mixed model summaries for anthropometric outcomes.

	Body Mass (kg)			BMI (kg.m^2)			Waist Circumference (cm)		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	93.56	88.33 – 98.80	**<0.001**	31.90	30.40 – 33.40	**<0.001**	108.14	104.55 – 111.73	**<0.001**
Time [1st degree]	-0.08	-0.39 – 0.23	0.606	-0.03	-0.12 – 0.05	0.469	-0.47	-0.76 – -0.19	**0.001**
Time [2nd degree]	-0.23	-0.55 – 0.08	0.142	-0.08	-0.17 – 0.00	0.052	0.13	-0.16 – 0.41	0.387
Time [3rd degree]	0.06	-0.10 – 0.22	0.447	0.02	-0.03 – 0.07	0.428	0.09	-0.07 – 0.25	0.263
Group [HIT]	-1.63	-4.24 – 0.97	0.218	-0.54	-1.25 – 0.18	0.139	-0.08	-2.49 – 2.32	0.946
Time [2nd degree] * Group [HIT]	0.46	0.03 – 0.90	**0.038**	0.16	0.04 – 0.28	**0.009**	-0.28	-0.69 – 0.12	0.169
Time [3rd degree] * Group [HIT]	-0.12	-0.34 – 0.10	0.293	-0.04	-0.11 – 0.03	0.266	-0.19	-0.41 – 0.04	0.102
Random Effects									
σ^2	12.59			0.85			9.89		
τ_{00}	377.25 $_{id}$			31.03 $_{id}$			173.82 $_{id}$		
τ_{11}				0.01 $_{id.Time}$			0.04 $_{id.Time}$		
ρ_{01}				-0.18 $_{id}$			0.08 $_{id}$		
ICC	0.97			0.97			0.95		
N	57 $_{id}$			57 $_{id}$			57 $_{id}$		
Observations	228			228			228		
Marginal R^2 / Conditional R^2	0.001 / 0.968			0.002 / 0.974			0.015 / 0.947		



Note: Thick lines are model predicted values, thin lines are individual raw data adjusted for random intercepts

Body Composition Outcomes

Body fat mass, body fat percentage, muscle mass percentage, and visceral fat mass all appeared to initially improve over the first time epoch for CON (Time [1st degree]: $\beta_{Body\ Fat\ Mass}$ = -0.27 kg [95%CI -0.46 kg to -0.08 kg]; $\beta_{Body\ Fat\ \%}$ = -0.26 % [95%CI -0.39 % to -0.12 %]; $\beta_{Muscle\ Mass\ \%}$ = 0.25 % [95%CI0.10 % to 0.39 %]; $\beta_{Visceral\ Fat\ Mass}$ = -0.11 kg [95%CI -0.19 kg to -0.02 kg];) and, though from visual inspection of the data (figure 2) it appeared to then either remain stable or revert towards baseline slightly over the second and third time epochs for CON while continuing to improve over both for HIT, interaction effects were imprecise and included zero with the exception of for body fat percentage whereby the slope for the HIT intervention was more clearly negative compared to the positive slope for CON (Time [2nd degree] * Group [HIT]: $\beta_{Body\ Fat}$ % = -0.22 % [95%CI -0.42 % to -0.03%]). Muscle mass also showed an improvement over the initial time epoch for CON (Time [1st degree]: $\beta_{Muscle\ Mass}$ = 0.18 kg [95%CI 0.08 kg to 0.28 kg]), which interestingly reversed for CON during the second time epoch (Time [2nd degree]: $\beta_{Muscle\ Mass}$ = -0.20 kg [95%CI -0.30 kg to -0.10 kg]), and stabilised during the third epoch of follow-up (Time [3rd degree]: $\beta_{Muscle\ Mass}$ = -0.04 kg [95%CI -0.09 kg to 0.02 kg]). However, there was a clear interaction effect during the second epoch whereby the slope for the HIT intervention was clearly positive compared to the negative slope for CON (Time [2nd degree] * Group [HIT]: $\beta_{Muscle\ Mass}$ = 0.44 kg [95%CI 0.30 kg to 0.57 kg], and the increases during the second epoch where similarly maintained into the third epoch of follow-up for HIT (Time [3rd degree] * Group [HIT]: $\beta_{Muscle\ Mass}$ = 0.00 kg [95%CI -0.07 kg to 0.08 kg]). Table 3 presents the full model summaries for all body composition outcomes and figure 3 presents the model predicted values with random intercept adjusted individual participant values.

Table 3. Mixed model summaries for body composition outcomes

	Body Fat Mass (kg)			Muscle Mass (kg)			Body Fat (%)			Muscle (%)			Visceral Fat Mass (kg)		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	30.03	26.94 – 33.13	**<0.001**	60.37	57.36 – 63.39	**<0.001**	31.37	29.29 – 33.45	**<0.001**	65.21	63.22 – 67.19	**<0.001**	14.81	13.57 – 16.05	**<0.001**
Time [1st degree]	-0.27	-0.46 – -0.08	**0.006**	0.18	0.08 – 0.28	**<0.001**	-0.26	-0.39 – -0.12	**<0.001**	0.25	0.10 – 0.39	**0.001**	-0.11	-0.19 – -0.02	**0.015**
Time [2nd degree]	0.04	-0.15 – 0.24	0.648	-0.20	-0.30 – -0.10	**<0.001**	0.12	-0.02 – 0.26	0.088	-0.04	-0.18 – 0.11	0.592	0.06	-0.02 – 0.15	0.159
Time [3rd degree]	0.08	-0.03 – 0.19	0.142	-0.04	-0.09 – 0.02	0.172	0.06	-0.02 – 0.13	0.123	-0.08	-0.15 – 0.00	0.055	-0.00	-0.05 – 0.05	0.924
Group [HIT]	-0.29	-1.89 – 1.31	0.722	-1.30	-2.13 – -0.48	**0.002**	0.31	-0.83 – 1.46	0.591	-0.30	-1.51 – 0.91	0.625	-0.07	-0.77 – 0.63	0.845
Time [2nd degree] * Group [HIT]	-0.06	-0.33 – 0.21	0.660	0.44	0.30 – 0.57	**<0.001**	-0.22	-0.42 – -0.03	**0.023**	0.14	-0.07 – 0.34	0.181	-0.11	-0.23 – 0.01	0.067
Time [3rd degree] * Group [HIT]	-0.10	-0.25 – 0.06	0.219	0.00	-0.07 – 0.08	0.969	-0.06	-0.17 – 0.04	0.230	0.08	-0.02 – 0.19	0.123	0.02	-0.06 – 0.09	0.672
Random Effects															
σ^2	4.22			1.19			2.27			2.60			0.80		
τ_{00}	132.01_{id}			128.00_{id}			59.37_{id}			53.43_{id}			21.02_{id}		
τ_{11}	$0.03_{id.Time}$			$0.00_{id.Time}$			$0.01_{id.Time}$			$0.01_{id.Time}$			$0.01_{id.Time}$		
ρ_{01}	-0.10_{id}			-0.13_{id}			0.02_{id}			0.01_{id}			-0.16_{id}		
ICC	0.97			0.99			0.96			0.95			0.96		
N	57_{id}			57_{id}			57_{id}			57_{id}			57_{id}		
Observations	228			228			228			228			228		
Marginal R^2 / Conditional R^2	0.005 / 0.969			0.003 / 0.991			0.010 / 0.964			0.009 / 0.954			0.006 / 0.964		

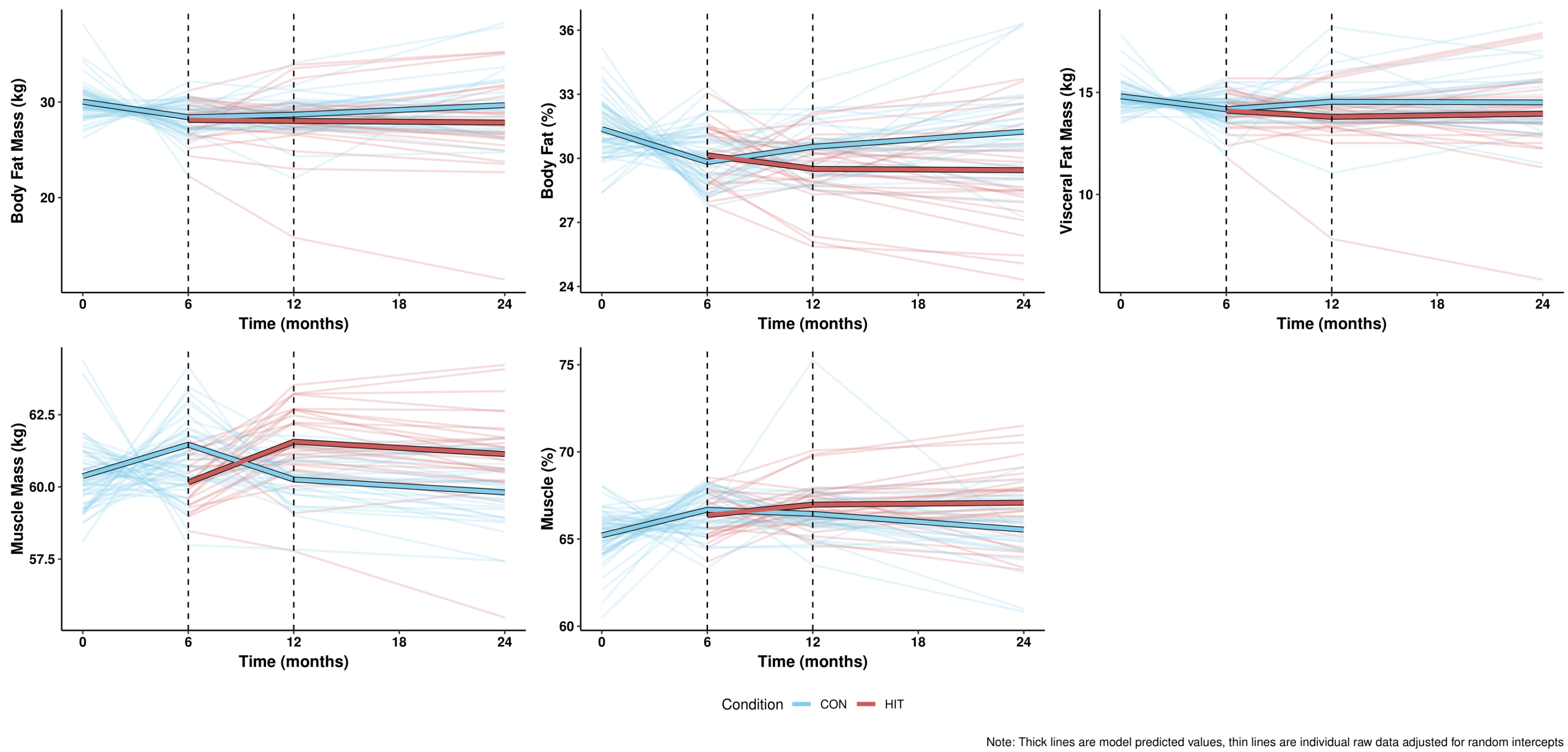


Figure 3. Body composition outcomes (top left = body fat mass; top middle = body fat percentage; bottom left = muscle mass; b ottom middle = muscle percentage; top right = visceral fat mass) individual raw data adjusted for individual random intercepts and the model predicted values.

Water and Blood Outcomes

Both total body water and phase angle appeared relatively stable over time across both routine care and from introduction of the HIT intervention. There was a minimal time effect for the first time epoch for CON for total body water (Time [1st degree]: $\beta_{Total\ Body\ Water}$ = 0.21 % [95%CI 0.05 % to 0.38 %]). NGSP HbA1c and fasted blood glucose both showed clear reductions during the first (Time [1st degree]: $\beta_{NGSP\ HbA1c}$ = -0.15 % [95%CI -0.17 to -0.13 %]; $\beta_{Fasted\ Blood\ Glucose}$ = -2.00 mg/dl [95%CI -2.39 mg/dl to -1.61 mg/dl]) and second time epochs (Time [2nd degree]: $\beta_{NGSP\ HbA1c}$ = -0.04 % [95%CI -0.06 to -0.01 %]; $\beta_{Fasted\ Blood\ Glucose}$ = -0.64 mg/dl [95%CI -1.05 mg/dl to -0.23 mg/dl]) with a stabilisation of levels over the third epoch of follow-up (Time [3rd degree]: $\beta_{NGSP\ HbA1c}$ = -0.00 % [95%CI -0.02 to 0.01 %]; $\beta_{Fasted\ Blood\ Glucose}$ = 0.12 mg/dl [95%CI -0.10 mg/dl to 0.35 mg/dl]). However, for NGSP HbA1c there was an interaction effect during the second epoch whereby the slope for the HIT intervention was more negative compared to the slope for CON (Time [2nd degree] * Group [HIT]: $\beta_{NHSP\ HbA1c}$ = -0.04 % [95%CI -0.08 % to -0.01 %], and this greater decrease during the second epoch was similarly maintained into the third epoch of follow-up for HIT (Time [3rd degree] * Group [HIT]: $\beta_{NHSP\ HbA1c}$ = 0.01 % [95%CI -0.01 % to 0.03 %). Table 4 presents the full model summaries for all water and blood outcomes and figure 4 presents the model predicted values with random intercept adjusted individual participant values.

Table 4. Mixed model summaries for water and blood outcomes												
	Total Body Water (%)			**Phase Angle (degrees)**			**NGSP HbA1c (%)**			**Fasted Blood Glucose (mg/dl)**		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	48.33	46.86 – 49.80	**<0.001**	5.87	5.66 – 6.08	**<0.001**	8.34	8.16 – 8.52	**<0.001**	129.18	126.63 – 131.72	**<0.001**
Time [1st degree]	0.21	0.05 – 0.38	**0.010**	-0.00	-0.04 – 0.04	0.967	-0.15	-0.17 – -0.13	**<0.001**	-2.00	-2.39 – -1.61	**<0.001**
Time [2nd degree]	0.03	-0.13 – 0.20	0.696	0.03	-0.01 – 0.08	0.154	-0.04	-0.06 – -0.01	**0.007**	-0.64	-1.05 – -0.23	**0.003**
Time [3rd degree]	-0.02	-0.11 – 0.07	0.649	-0.02	-0.04 – 0.01	0.166	-0.00	-0.02 – 0.01	0.496	0.12	-0.10 – 0.35	0.283
Group [HIT]	-0.37	-1.73 – 0.98	0.589	0.07	-0.26 – 0.39	0.691	-0.03	-0.21 – 0.16	0.788	1.06	-2.04 – 4.16	0.501
Time [2nd degree] * Group [HIT]	0.09	-0.14 – 0.32	0.422	0.04	-0.03 – 0.10	0.255	-0.04	-0.08 – -0.01	**0.013**	-0.21	-0.79 – 0.36	0.463
Time [3rd degree] * Group [HIT]	-0.01	-0.14 – 0.12	0.913	-0.00	-0.03 – 0.03	0.882	0.01	-0.01 – 0.03	0.259	-0.03	-0.34 – 0.29	0.866
Random Effects												
σ^2	3.08			0.24			0.08			19.94		
τ_{00}	27.64 $_{id}$			0.40 $_{id}$			0.37 $_{id}$			72.87 $_{id}$		
τ_{11}	0.02 $_{id.Time}$			0.00 $_{id.Time}$			0.00 $_{id.Time}$			0.11 $_{id.Time}$		
ρ_{01}	0.13 $_{id}$			-0.56 $_{id}$			-0.86 $_{id}$			-0.54 $_{id}$		
ICC	0.90			0.62			0.83			0.79		
N	57 $_{id}$			57 $_{id}$			57 $_{id}$			57 $_{id}$		
Observations	228			228			228			228		
Marginal R^2 / Conditional R^2	0.012 / 0.901			0.038 / 0.638			0.379 / 0.892			0.299 / 0.849		

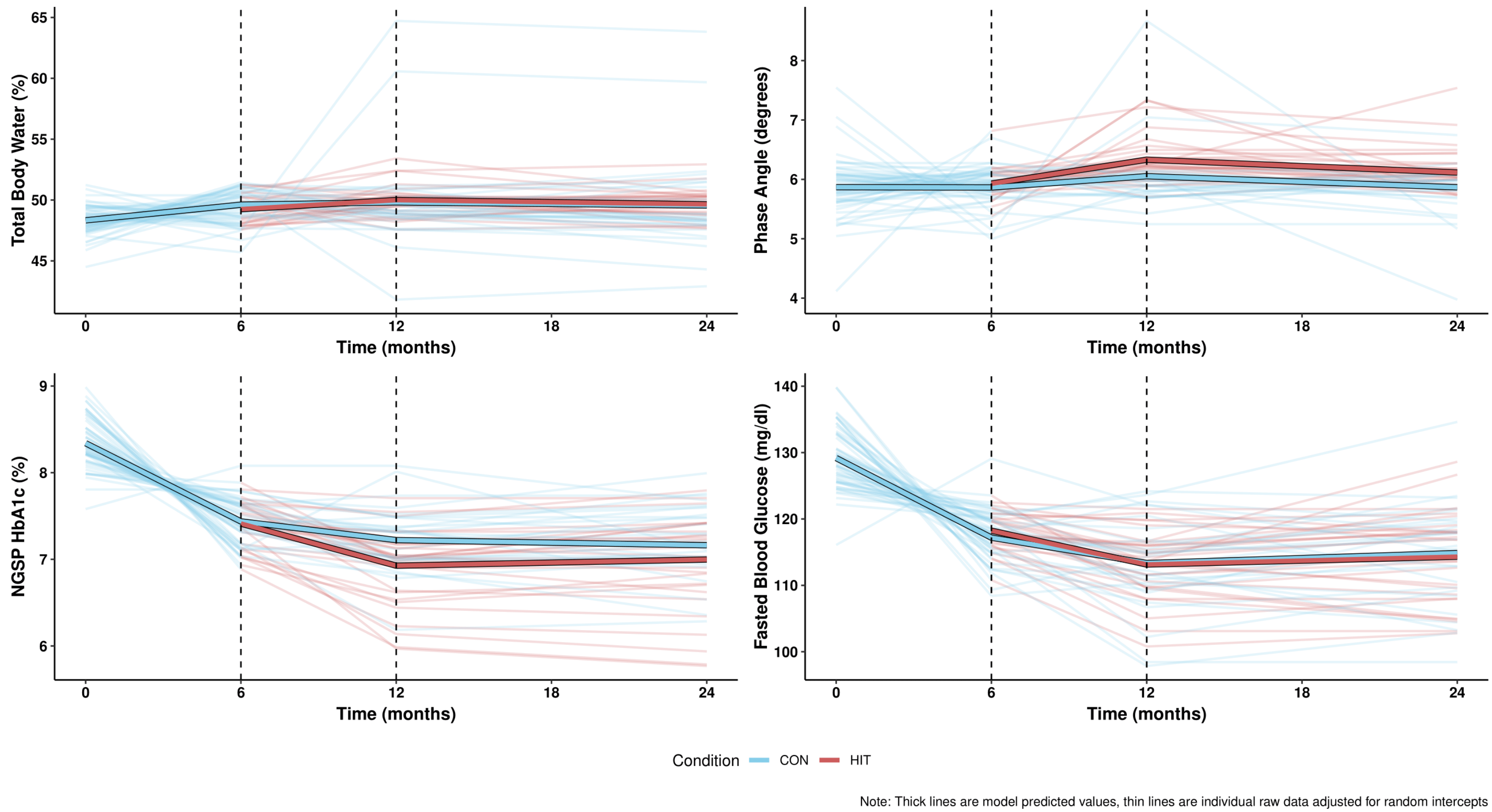


Figure 4. Water and blood outcomes (top left = total body water; top right = phase angle; bottom left = NGSP HbA1c; bottom right = fasted blood glucose) individual raw data adjusted for individual random intercepts and the model predicted values.

Subjective Wellbeing

Subjective wellbeing measured using the WHO-5 showed a small improvement over the first time epoch for CON (Time [1^{st} degree]: $\beta_{WHO\text{-}5}$ = 0.97 points [95%CI 0.37 points to 1.57 points]) remaining fairly stable thereafter. However, there was a clear interaction effect during the second time epoch whereby the slope for HIT was clearly positively greater compared to CON (Time [2nd degree] * Group [HIT]: $\beta_{WHO\text{-}5}$ = 2.82 points [95%CI 1.96 points to 3.67 points], and this greater decrease during the second epoch was similarly maintained into the third epoch of follow-up for HIT (Time [3^{rd} degree] * Group [HIT]: $\beta_{WHO\text{-}5}$ = -0.02 points [95%CI -0.47 points to 0.42 points). Table 5 presents the full model summary for the WHO-5 and figure 5 presents the model predicted values with random intercept adjusted individual participant values.

Table 5. Mixed model summary for WHO-5

	WHO-5 (points)		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	45.40	40.04 – 50.77	**<0.001**
Time [1st degree]	0.97	0.37 – 1.57	**0.002**
Time [2nd degree]	-0.32	-0.93 – 0.29	0.298
Time [3rd degree]	-0.23	-0.55 – 0.09	0.162
Group [HIT]	2.05	-2.88 – 6.99	0.412
Time [2nd degree] * Group [HIT]	2.82	1.96 – 3.67	**<0.001**
Time [3rd degree] * Group [HIT]	-0.02	-0.47 – 0.42	0.914
Random Effects			
σ^2	46.48		
$\tau_{00\ id}$	363.42		
$\tau_{11\ id.Time}$	0.09		
$\rho_{01\ id}$	-0.32		
ICC	0.89		
N_{id}	57		
Observations	228		
Marginal R^2 / Conditional R^2	0.147 / 0.903		

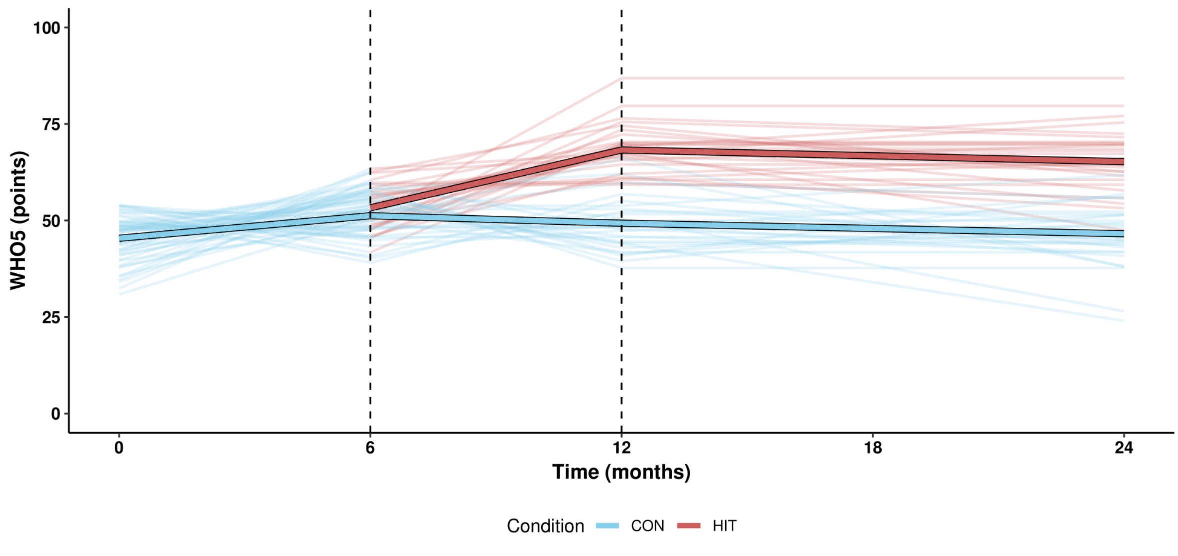


Figure 5. WHO-5 individual raw data adjusted for individual random intercepts and the model predicted values.

Discussion

The present study appears to be the first to consider the effects of low-volume, high effort RT in persons with T2D to in addition to undertaking routine care.

Routine Care

The first point for discussion is the value of the routine care alone. During the initial 6-month time epoch all participants received routine care which included education about diabetes, nutrition, and exercise. Through this period significant improvements were noted; waist circumference decreased by ~2.82cm, body fat mass decreased by ~1.62kg, muscle mass increased by ~1.08kg, body fat percentage dropped by ~1.56%, muscle percentage increased by ~1.5%, visceral fat mass decreased by ~0.66kg, HbA1c decreased by ~0.9%, fasted blood glucose decreased by ~1.2mg/dl, and finally subjective wellbeing increased by ~5.82 points. These data suggest support for the efficacy of educational practices for persons diagnosed with diabetes. Interestingly, previous research has compared hospital attendance for routine care to that of general practitioner care in the UK (Hayes and Harries, 1984). Notably, even though the patients attending the hospital-based diabetic clinic received no special attention and saw a variety of doctors, their outcomes were more favourable than those seeing their general practitioner. In the present study an initial weeklong educational course was provided by Vinzentius Hospital, following which participants received routine care from their doctors in private practice. Of course, considering the lack of non-intervention control group during the first-time epoch (or throughout this pragmatic trial) it is difficult to infer causality with respect to the effects of this routine care. It may merely reflect the natural history of the disease progression resultant from patients attending hospital settings (Hayes and Harries, 1984). Thus, of greater interest is the comparison during the second epoch to the HIT intervention.

RT Intervention vs. control

Whilst there is some suggestion of effectiveness of the initial 6-months of routine care, the second time epoch during which half of the sample continued with only having received this intervention gives some insight into the continuation or maintenance of these positive changes. In the routine care group, over the successive 18 months; waist circumference increased by ~1.86cm, body fat mass increased by ~1.2kg, muscle mass decreased by ~1.68kg, body fat percentage increased by ~1.44%, muscle percentage decreased by ~1.2%, and visceral fat increased by ~0.36kg. For blood markers and wellbeing, HbA1c continued to decrease by ~0.24% over the following 6 months and remained stable after the 12-month follow-up, fasted blood glucose continued to decrease by ~3.84mg/dl over the following 6 months but increased by ~1.44mg/dl after the 12-month follow-up, and subjective wellbeing decreased by ~1.92 after 6 months and by a further ~2.76 points at the 12-month follow-up. These data suggest that many of the positive changes during the initial 6-months were negated or reversed over the successive 6- and 18-month periods. Again, it is unclear whether this reflects perhaps the natural time course of disease progression, regression to the mean artifacts, or a waning impact over time of the initial educational intervention.

However, in contrast participants engaging in supervised high effort RT for 6-months showed the following changes; waist circumference decreased by a further ~0.9cm during the RT intervention, and by a further ~1.2cm after the 12-month follow-up, body fat mass decreased by a further ~0.36kg during the RT intervention, muscle mass increased by ~0.96kg following the RT intervention and 12-month follow-up, body fat percentage decreased by ~0.6% following the RT intervention, muscle percentage increased by ~0.6% following the RT intervention and 12-month follow-up, and visceral fat decreased by ~0.18kg following the RT intervention and 12-month follow-up. For blood markers and wellbeing; HbA1c continued to decrease by ~0.48% during the RT intervention and an increase of ~0.12% following the 12-month follow-up, fasted blood glucose decreased by ~5.1mg/dl during the 6-month RT intervention, but had also increased (by ~1.08mg/dl) at the 12-month follow-up, and subjective wellbeing continued to increase during the 6-month RT intervention (~15 points), but decreased by ~3 points over the successive 12-months.

A lack of consistency across studies in the outcome measures used makes comparison to existing research difficult. However, the changes identified have been considered in relation to the threshold for a clinically relevant change. Furthermore, comparison to the present body of literature has been considered where possible. For example, at 24 months after baseline waist circumference had decreased from 108.14cm to 107.18cm and 104.12cm for the control and RT conditions, respectively. However, whilst participants in the RT intervention are on a more favourable trajectory, the changes don't appear to be clinically meaningful, that is to say that patients from neither condition reduced their waist circumference sufficiently to move from the highest quintile for waist circumference (≥102.7cm), and thus the highest relative risk of death (2.05) (Pischon, et al. 2008). In addition, participants in the high intensity of effort resistance training group showed a decrease in fat mass of ~1.98kg, equating to ~2.1% of their body mass. Whilst, Donnelly, et al. (2009) suggested that a reduction of 3-5% of body weight indicates a reduction in health risk in overweight and obese populations, the authors also highlight that increases in muscle mass are indicative of reductions in health risk...

Furthermore, Castaneda, et al. (2002) considered the effects of 16 weeks of RT 3x/week, reporting decreases of 1.1% in HbA1C (8.7 to 7.6%) and increases in lean muscle mass of 1.2kg. In a further small sample of Indian participants following a RT protocol 2x/week for 8 weeks, HbA1c decreased by 1.3% (from 7.5 to 6.2%; Arora, et al. 2009). The RT group discussed herein showed similar decreases of ~1.1% in HbA1C (from 8.3 to 7.2%), however following 6 months of routine care muscle mass had increased to a similar extent (1.1kg) and increased by a further 1kg with the addition of a 6-month RT intervention. Perhaps most importantly, these positive changes to HbA1c and muscle mass were evidenced 24 months from the initial measurements, and whilst a lack of additional data points cannot identify to what extent these values fluctuated throughout this time period, it is important to recognise that typically people make short-term positive adaptations which plateau or might even be reversed over a longer time epoch. Certainly, research has demonstrated diminishing returns and a plateau in strength adaptations in participants engaging in RT over a prolonged time period (Steele, et al. 2021). Previous research has reported excessive muscle loss in community dwelling older adults (Park, et al. 2009), and so there is a great importance of retaining and even increasing muscle mass, specifically as a storage cite for glycogen (Jensen, et al. 2011). Furthermore, the regular participation in exercise and RT is shown to deplete glycogen stores as well as increase the expression of the sodium-dependent glucose co-transporter system (e.g., an insulin-independent glucose transporter) is activated and enhanced by resistance training (Castaneda, et al. 2006), and so, postprandial carbohydrate consumption is preferentially stored by repletion of glycogen within the muscles (Jensen, et al. 2011). Finally, it is worth highlighting that declining muscle mass and muscle strength are associated with progressive mobility impairment and a reduction in physical activity (McGlory, et al. 2018). The increase in strength and muscle mass plays an important role in the performance of physical activity of any kind, which appears to play a role in maintaining glycaemic control (McGlory, et al. 2018).

A further important finding from this study is the positive changes to mental state as a result of the RT intervention. The WHO-5 questionnaire, scored out of 100, asks questions unrelated to medical condition or exercise habits but rather related to feelings of being cheerful and in good spirits, calm and relaxed, active, and vigorous, fresh and rested, and whether *"…life has been filled with things that interest me…"* (Topp, et al. 2015). The WHO-5 has been discussed as a screening tool for depression (where a score $\leq$50), and even identified that persons scoring <50 have significantly higher mortality rate compared to scoring $\geq$50 (Topp, et al. 2015). At the beginning of the study participants scored 45/100 which increased to ~51 by the end of the routine care. In the CON group this gradually decreased over the successive 18 months to a score of 47/100. However, following 6 months of RT, participants increased their score by ~15 points, and at the 24-month follow-up had a score of 63 on the WHO-5. An improvement exceeding 10 points on the WHO-5 is considered to be the threshold for a clinically relevant change (Topp, et al. 2015) and so this improvement is likely to have been a meaningful effect. Previous studies assessing quality of life and general wellbeing (using the SF-36, and 22-item GWBS; which measure similar aspects), also report positive responses following a RT intervention (Seguro, et al. 2020; Arora, et al. 2009). This validates our present findings and is promising to know that RT can demonstrate improvement in mental wellbeing in persons suffering from diabetes.

Limitations

Whilst the findings of the present study are important, we should acknowledge the potential limitations of the methods used. Primarily, our pragmatic design, whilst utilising randomisation in the context of an interrupted time-series to allow for causal inference, was limited to only being able to consider the causal effects of the addition of high intensity of effort RT to routine care *after* having received routine care for 6 months prior. Inference regarding the causal effects of routine care alone should be very cautious given possible confounding by things such as natural time course of disease progression and regression to the mean artifacts. We should also note that the trial is explicitly exploratory, and thus inferences should be drawn cautiously considering the convenience sample used. Further, a lack of data surrounding lifestyle and exercise habits for the 12-months following cessation of the second time epoch (i.e., from the end of the RT intervention). Previous studies have shown that even where accessible, participants concluding a supervised high-effort resistance training intervention show poor engagement in unsupervised RT (Steele, et al.

2017; Van Roie, et al. 2015), and in response, show a decline of the initial physical improvements. Whilst this appears likely in the present study, a lack of data precludes us from drawing inferences about the exercise habits of participants and their subsequent impact on longer-term maintenance.

Conclusions

The results of this exploratory pragmatic trial suggest that the addition of high intensity of effort RT alongside routine care can have a positive impact on a range of outcomes in type 2 diabetics having undergone prior routine care. The addition of the RT intervention appeared to result in positive changes to body composition including reduced body fat and increased muscle mass, in addition to improvements HbA1C, and meaningful changes in subjective wellbeing and quality of life. Future work should look to scale up and conduct a fully powered trial to examine the effects of high intensity of effort RT alongside routine care.

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Data and Supplementary Material Accessibility

All materials, data, and code are available on the Open Science Framework project page for this study https://osf.io/5bd4y/

Author contributions

JG, BE, and WK conceived of the study; JG and BE collected the data; JS carried out statistical analyses; all authors were meaningfully involved in interpreting data, and drafting and critically revising the manuscript for intellectually important content.

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