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Fitness and strength responses to distinct exercise modes in twins: Studies of Twin Responses to Understand Exercise as a THerapy (STRUETH) study

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Running title: Twins fitness and strength responses to distinct exercise modalities

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KEY POINTS

- Exercise is considered medicine, however the individual degree of responsiveness to a standardised dose of exercise is idiosyncratic.
- Individual responsiveness between distinct exercise modalities and the genetic/environmental contributions to exercise response are not well understood.
- In this novel randomised cross-over design study, monozygotic and dizygotic twins, as pairs, underwent 3 months of resistance and endurance training, separated by a 3 month washout period, to assess training responses in strength and fitness outcomes to dichotomous training modalities, and the genetic/environmental contributions to exercise response.
- Our findings indicate that 1). individual responsiveness differs between exercise modalities; 2). low-responders to one mode may be "rescued" by switching to an alternate mode of exercise; and 3) genes may not play as large a role, as previously estimated from cross-sectional data, for exercise training adaptation.
- This study has implications for those charged with optimising the benefits of exercise by means of individualising the exercise prescription.

Abstract

Exercise response is idiosyncratic, but the degree of responsiveness, concordance in response between modalities and genetic contribution to responsiveness are not well understood. We investigated this using a novel randomised cross-over design of dichotomous exercise interventions in mono-(MZ) and di-zygotic (DZ) twin pairs. We studied strength (1RM) and fitness (VO_2max) responses in 84 same-sex untrained twins (30MZ, 12DZ pairs; 24.9±5.4yr). Twins, as pairs, underwent 3 months of resistance (RES) and endurance (END) training, separated by a 3 month washout period. Training responses and genetic/environmental contributions to responses were assessed. Leg strength 1RM increased following RES but not END (△47±29vs3±26kg; P<0.001), whilst VO_2max increased following END but not RES (△0.25±0.26vs0.04±0.25L.min^{-1}; P<0.001). A higher percentage of individuals responded to RES for strength and to END for VO_2max (P<0.0001). Within-individual responses to each mode weren't correlated (P>0.05). Cross-sectional intraclass correlations were higher for MZ than DZ pairs for all variables, due largely to shared environment. Following training, MZ, but not DZ pairs, were significantly correlated for strength change to RES (rMZ=0.62, P=0.002) and END (rMZ=0.36, P=0.04), and VO_2max change to END (L.min^{-1}, rMZ=0.45, P=0.02) with a mixture of unshared/shared environmental contributions. Our findings indicate that individual responsiveness differs between modalities and low-responders to one mode may be "rescued" by switching to an alternate mode. Additionally, genes may not play as large a role as previously estimated from cross-sectional data for training adaptation, and/or that cross-sectional data do not reflect longitudinal training effects. This study has implications for optimising the individualisation of exercise prescription.

Key words: twins, heritability, genetics, cardiorespiratory fitness, strength

Abbreviations: CRF, cardiorespiratory fitness; VO_2, oxygen uptake; END, endurance training; RES, resistance training; MZ, monozygotic; DZ, dizygotic; 1RM, one-repetition maximum; HR, heart rate; BLa, blood lactate; TTE, time to exhaustion; CX, cross-sectional; A, additive genetic effects; C, common/shared environmental effects; E, Individual/unshared environmental effects; ICC, intraclass correlation; CI, confidence interval.

Introduction

Physical inactivity is responsible for 6–10% of annual global mortality (Lee *et al.*, 2012) and is a modifiable risk factor for several major chronic diseases including cardiovascular disease, diabetes mellitus, obesity and hypertension (Warburton *et al.*, 2006). Despite this, recent studies suggest that up to 20-30% of individuals may fail to exhibit beneficial physiological responses to exercise interventions that accord with guideline recommendations for health (Bouchard *et al.*, 2012). These individuals can be considered "low-responders" for particular health parameters, in relation to the specific type of exercise performed. The idiosyncratic "responsiveness" of cardiorespiratory fitness (CRF; VO_2max) to endurance training (END) has recently been summarised (Ross *et al.*, 2019), with

the conclusion that large inter-individual differences in CRF occur, irrespective of exercise intervention duration (20 weeks to 12 months), frequency, duration, intensity and study population; and that CRF low-response for a given "dose" of exercise occurs even in fully supervised exercise interventions that apply reproducible assessment approaches.

It is generally acknowledged that distinct modalities of exercise induce different physiological adaptations. A common, if oversimplified, example is that END modifies cardiovascular capacity and oxygen uptake (VO_2max), whilst resistance training (RES) principally modifies skeletal muscle function and strength. However, few studies have been designed to directly address inter-individual variation in responsiveness to different exercise modalities. A within-subject cross-over design is an appropriate approach to address the question of whether responsiveness is modality-specific, and whether individuals demonstrate concordant or discordant responses to distinct forms of training. These questions have practical implications for exercise prescription; when an individual is a low-responder for one modality of training, perhaps they may be "rescued" by converting to an alternate mode.

In addition to the low vs high response phenomenon, an associated question relates to genetic contribution to exercise responsiveness. A classical twin study design, utilising both monozygotic (MZ) and dizygotic (DZ) twin pairs, can be used to estimate genetic and environmental contributions to the variance in quantitative traits (Fisher, 1919; Hopper, 1992; MacGregor *et al.*, 2000). A systematic review of VO_2max responses to END training has indicated that a majority of studies have not utilised DZ twin pairs to assess the genetic contribution to adaptation in fitness (Zadro *et al.*, 2017). Studies of the heritability of strength adaptations to training are also scant (Thomis *et al.*, 1998). No study, to our knowledge, has simultaneously trained both twins in a pair (MZ and DZ pairs), with two modalities (RES and END) applied in a randomised cross-over design, to assess the heritability of exercise responsiveness.

The current study therefore utilised a classical twin paradigm, in a randomised cross-over designed study of two dichotomous exercise modalities (RES and END). We hypothesised that exercise responsiveness would be modality-specific in accordance with the principle of training specificity; that individuals would positively respond to at least one modality of training and that responders to one form will also respond to the other (concordance); and that the genetic contribution to variance in traits assessed cross-sectionally would not reflect longitudinal training effects. The results of this study will provide insight into the genetic and environmental contribution to exercise response to distinct modes of training, with implications for determining the optimal approaches to exercise prescription.

Methods

Ethical approval

This study was approved by the University of Western Australia Human Research Ethics Committee (reference number RA/4/7031). Oral and written consent was obtained from each participant prior to participation in the study, which conformed with the Declaration of Helsinki. Full details of the study design and experimental procedures can be found in our protocol paper (Marsh *et al.*, 2020) and in the study registration (ACTRN12616001095459), which was published prior to recruitment and randomisation. A brief summary is provided below.

Participants

We recruited 42 healthy same-sex twin pairs (30 MZ and 12 DZ; aged 24.9 ± 5.4 yr) to participate in the study (see CONSORT, **Error! Reference source not found.**). Recruitment was facilitated by Twins esearch Australia (formerly the Australian Twin Registry, (Murphy *et al.*, 2019)) whereby twin pairs in metropolitan Perth were sent emails, newsletters and mail regarding participation in the study. Other recruitment strategies included advertising in Perth-based newspapers, online and via social media, university email lists, word-of-mouth referral etc. Inclusion criteria included healthy, relatively unfit individuals who did not meet Australian guidelines for physical activity recommendations (<150 min/week), were non-smokers and medication free. Baseline demographic data are displayed in Table 1. A DNA test was administered to determine the zygosity of each twin pair (EasyDNA AU, Springwood, QLD).

Study design

All participants (42 twin pairs; n=84) underwent baseline testing of outcome measures and 34 of these pairs (n=68; 24 MZ and 10 DZ) participated in the training interventions (**Error! Reference ource not found.**). Twin pairs were randomised, together as a pair, to participate in either the 3 month RES or END training intervention (study design in Figure 1). Participants then underwent a 3 month washout period, during which they were instructed to maintain their usual level of activities and usual diet. Participants then crossed over to complete 3 months of their second, alternate, exercise intervention (RES or END). Twins within a pair trained together at matched relative intensities for each exercise modality and completed their exercise interventions in the same time period.

Exercise interventions

The two exercise interventions (RES and END) consisted of 3x 1 h sessions per week for 12 weeks. The programs were progressively overloaded, consisting of specified training phases. Briefly, END utilised 2x running and 1x cycling session per week progressing from 60-90% VO_2max, and RES alternated between upper and lower body each session progressing from 60-90% one-repetition maximum (1RM). Compliance with training sessions was 94% for RES and 95% for the END intervention. Detailed descriptions of the exercise interventions are provided in our protocol paper (Marsh *et al.*, 2020).

Primary outcome measures

A graded exercise test was performed on a treadmill to determine CRF (VO_2max). Heart rate (HR), blood lactate (BLa) and rating of perceived exertion were collected at the end of each 3 min stage and peak oxygen consumption was calculated from the four highest consecutive 15s oxygen uptake values of each stage. Running time to exhaustion (TTE) on the treadmill was also recorded. A 1RM protocol (Spence *et al.*, 2011) was used to measure muscular strength of the major muscle groups of the upper (bench press) and lower (leg press) limbs.

Statistical analysis

Briefly, statistical analyses were performed with SPSS 20.0 (IBM Australia Ltd, New South Wales, Australia) and STATA 11 software (StataCorp, College Station, Texas). Cross-sectional results for each outcome measure refer to baseline entry (week 0) data. Response to training is post minus pre for RES and END training. Differences between cross-sectional (CX) zygosity (Table 1) and the effect of the exercise interventions on each outcome measure (Table 2) were assessed using a linear mixed model which adjusted for twin correlation and relevant measured covariates (i.e. sex and age). Carry-over and order effects were also assessed using a linear mixed model adjusting for twin correlations. A z-test was used to assess the differences in individual responses between exercise interventions (RES vs END), and between concordance vs discordance for each variable.

The classical twin model and analysis is based on the fact that MZ twins theoretically share 100% of their DNA while DZ twins only share 50%. A phenotype that is purely explained by genetics would hold a ratio of 2:1, with correlations of 1 for MZ and 0.5 for DZ pairs (Maia *et al.*, 2002). If the 2:1 ratio remains the same, but the correlations are lower than these values, then both shared and unshared components may be influencing results. This genetic modelling approach has advantages over other heritability estimation methods as extensive variance (i.e. difference between twins) and covariance (i.e. common characteristics between twins) information are deduced (Neale & Cardon, 1992). From this, we can determine what amount and proportion of the variation is due to genes (A, additive genetic effects) and environment. The environmental proportion can be broken down into components either shared (C, common shared environmental effects) or unique (E, individual unshared environmental effects) to twin pairs. A crucial assumption of this model is that C is equal for MZ and DZ pairs, that is, MZ and DZ pairs share their environments to the same extent on average (the "equal environments" assumption (Richardson & Norgate, 2005)). All components represent unmeasured effects, after adjustment for all relevant measured covariates. In STATA, mixed effects models were used to calculate intraclass correlation coefficients (ICC, r) for MZ and DZ twin pairs. The subsequent rMZ and rDZ, and their respective P-values are presented in Table 3. Significant differences between ICC's (rMZ vs rDZ) were assessed using the likelihood-ratio test in STATA to compare mixed effects models constraining covariances for MZ and DZ pairs to be equal with models, allowing different covariances for MZ and DZ pairs (Table 3) (Dominicus *et al.*, 2006). If rMZ were significantly different to rDZ then A, C and E and 95% confidence intervals (CI) were calculated from the estimates of the DZ covariance and the additional MZ covariance, and CI's for A, C and E were estimated using the delta method. When rMZ and rDZ were not significantly different,

then a single model that included all twin pairs but constrained the covariance to be equal for MZ and DZ pairs was used in STATA to calculate C and E components only, and their respective 95% CI's. An additional model which estimated covariance for MZ twins but fixed the DZ covariance to be zero was fitted if the estimated correlations suggested that the equal environments assumption may have been violated and rDZ was approximately 0.

Results

Participant characteristics

Zygosity-based participant demographics, strength and CRF CX data are presented in Table 1. The MZ group had greater body weight (*P*=0.01) and therefore higher body mass index (BMI; *P*=0.01) than the DZ group. Height, strength and CRF measures were not different between zygosities (with the exception of VO_2max normalised to body mass [$ml.kg^{-1}.min^{-1}$; *P*=0.007]). Although there were some differences between the MZ and DZ groups, heritability analysis compares each twin within pairs.

Group means and specificity of training

Training specificity was confirmed for the group means displayed in Table 2 and Figure 2. On average, strength significantly increased following RES but not END training for both leg press (Figure 2A) and bench press. There was an increase following END but not RES for VO_2max (Table 2, Figure 2B) and TTE, and a decrease in resting HR and HR max. There was a decrease in BLa max following RES but not END training. The magnitude of change with training differed significantly between RES and END for leg press, bench press, VO_2max ($L.min^{-1}$ and $ml.kg^{-1}.min^{-1}$), TTE and resting HR. The magnitude of change with training did not differ between interventions (RES vs END) for HR max and BLa max, which are measures of exercise intensity during VO_2max testing.

Individual responses to each exercise intervention are plotted in Figure 2 for leg strength and CRF, showing response rates for each training modality. For strength, positive response rate (>0) to RES and END training were respectively 100% and 51% (*P*<0.0001 for difference between modes) for leg press, and 79% and 28% (*P*<0.0001) for bench press. For CRF, positive response rate to RES and END training was respectively 57% and 86% (*P*<0.0001) for VO_2max ($L.min^{-1}$), 35% and 86% (*P*<0.0001) for TTE, and 40% and 63% (*P*=0.02) for resting HR.

Concordance of exercise response

Concordance graphs are displayed in Figure 3, which presents each individual's response to both RES and END training. Numerical percentages for each quadrant, concordant +/+ or -/-, and discordant +/- or -/+, for RES and END interventions are also presented.

For leg press strength responses to RES and END (Figure 3A), 50% of individuals were positively concordant (+/+) and 50% were discordant (+/-). There were no non-responders in terms of leg press measures in response to either modality. For bench press responses to RES and END (Figure 3B), positive concordance (+/+) was 24%, negative concordance (-/-) was 15%, and discordance was 56% (+/-) and 5% (-/+), respectively.

In terms of VO_2max (L.min^{-1}, Figure 3C), 47% of individuals were positively concordant for both modalities (+/+), 4% were negatively concordant (-/-), whilst discordant percentages for RES and END were 10% (+/-) and 39% (-/+). A similar percentage of individuals were discordant (49%) compared to concordant (51%) for VO_2max (L.min^{-1}; *P*=0.84; Figure 3C). Individual responses to RES and END for TTE (Figure 3D) were 30% (+/+), 8% (-/-), 6% (+/-) and 56% (-/+) respectively, and for resting HR (where a reduction is a positive health response; Figure 3E) were 33% (+/+), 24% (-/-), 30% (+/-) and 13% (-/+).

There were no correlations between response to RES and END training within subjects for leg press strength (r=0.10, *P*=0.45), bench press strength (r=-0.10, *P*=0.42), VO_2max (L.min^{-1}; r=-0.10, *P*=0.22), TTE (r=-0.10, *P*=0.43) or resting HR (r=0.01, *P*=0.93). Therefore, high-response to one mode of training does not necessarily imply high-response to the alternate mode.

Heritability of strength and fitness cross-sectionally and in response to training

Comparison between twin pairs at baseline: Cross-sectional (CX) analysis

The ICC's (r) and proportions of variance calculated for A, C and E are presented in Table 3 and represented in Figure 4 and Figure 5. Cross-sectional rMZ and rDZ were significant for leg press, bench press, and VO_2max in Lmin^{-1}. TTE displayed a significant rMZ but not rDZ. Subsequent analysis revealed a predominant C (shared environment) contribution to each trait for leg press (95% CI 0.68-0.90), bench press (95% CI 0.87-0.97), VO_2max in L.min^{-1} (95% CI 0.25-0.90) and TTE (95% CI 0.57-0.89).

Comparison between the effects of training within twin pairs

For response to exercise training, significant rMZ but not rDZ were present for leg press response to RES and response to END for VO_2max in L.min^{-1}. Subsequent analysis revealed a predominant C (0.64; 95% CI 0.39-0.90) contribution to change in leg press to RES and an even proportion of C (0.43; 95% CI 0.14-0.72) and E (0.57; 95% CI 0.28-0.86) for VO_2max (L.min^{-1}) change in response to END training.

Carry-over effect (was the washout period adequate?)

The washout period of 12 weeks between training interventions was sufficient for all variables; there were no carry-over effects evident as significant differences between the two baseline periods (week 0 vs 24) for any variable when broken down into those who performed RES or END first (*P*>0.05; **Error! Reference source not found.**).

Order effects

Participants were randomised into RES or END, with half the sample completing each mode first (**Error! Reference source not found.**). There was no order effect for magnitude of change in strength ariables to training (P>0.05). For CRF, there was no order effect for the impacts of END training. Although those completing RES first exhibited a lower improvement in VO_2max (L.min^{-1}) in response to RES (0.12 L.min^{-1}, P=0.04), these differences in VO_2max response to RES were small and fell within the calculated technical error of 0.15 L.min^{-1} for CRF on the metabolic cart we used (Parvomedics TrueOne 2400, Salt Lake City, UT).

Discussion

Exercise has beneficial effects on multiple health and fitness outcomes (Warburton *et al.*, 2006), but optimising exercise prescription is challenging, as individual responses are idiosyncratic and differ according to the type of exercise prescribed. In the current study we assessed individual responses to dichotomous modalities of exercise training to determine the proportion of subjects who were low- and high-responders to each modality. Within subjects, we ascertained whether low-responders to one mode may be high-responders to another. Finally, by adopting a novel twin study design utilising MZ and DZ twin pairs who undertook identical exercise programs, we assessed the contribution of genetic and environmental effects (Hopper, 1992) to exercise-induced adaptation. The current study is the first twin design, to our knowledge, to assess the heritability of exercise response to two distinct exercise modalities in a randomised cross-over trial.

The question of whether exercise "responsiveness" is modality-specific was sparked by the results of a recent study comparing RES vs END training (Spence *et al.*, 2011), which suggested modality specificity in the relative proportion of low- vs high-responders. However, this study randomised subjects to parallel groups and results may have been biased by the randomisation process. The current study utilised the same individuals for two dichotomous exercise interventions and assessed individual responsiveness to each modality. We confirmed that responsiveness is modality-specific; a higher percentage of positive responders for RES compared with END for strength, and END compared with RES for CRF. Assessing the individual responsiveness to each modality reveals more than simple consideration of group means, which can mask the variability of the data. By showing all of the individualised data, we illustrate that strength is highly responsive to RES, with 100% of individuals positively responding to leg press, and that CRF is mostly responsive to END, with 86% positively responding. These findings are entirely consistent with the specificity principle of exercise training, but, of interest, ~50% of individuals responded to the non-training specific modality (strength increase following END, and CRF following RES), with some individuals being high-responders. Therefore, whilst utilising modality-specific training to induce strength or fitness results is optimal, the alternate modality can still be a useful tool for inducing adaptation.

By utilising a cross-over design, whereby each subject experienced both modes of exercise, separated by a washout period, our study enabled assessment of concordance/discordance in responsiveness. We found that individuals tend to respond to at least one exercise modality (RES and/or END) for both strength and CRF outcomes. However, there was no correlation between

change in fitness and change in strength within subjects. The findings of our study reinforced those of other cross-over studies that implemented shorter duration exercise interventions. These cross-over studies assessed the response of CRF to: 1) 3 weeks each of END vs interval training (n=21; aged 20.3 yr) concluding that CRF response was not linked between the two modes (Bonafiglia *et al.*, 2016); and 2). 2 weeks each of END vs RES training (n=91; aged 41.5 yr) concluding those who had the lowest CRF response following END improved their CRF following RES (Hautala *et al.*, 2006). The results of our study have progressed the literature as they indicate that individuals who are low-responders to an exercise training modality may be "rescued" by switching to an alternate mode of training. Our findings indicate that, in terms of CRF (VO_2max in L.min^{-1}) response to different modalities; very few people fail to respond altogether (i.e. to either modality 4%); concordance and discordance are roughly 50:50 (but there is no correlation in changes between modes r=-0.10, *P*=0.22); and that non-responders to one modality almost always respond to the other (RES:END = 39:4 ratio; END:RES = 10:4 ratio). It is noteworthy that most of the literature focusses on CRF responses to exercise interventions; strength responses are less widely researched, despite their importance for preserving musculoskeletal integrity with age. For leg strength change, all subjects responded to RES, whereas 50% of subjects respond to END. However, if you were a non-responder to END, you nonetheless responded to RES. These findings suggest that different variables display distinct levels of concordance and discordance and that, even though there is clear evidence for mode-specificity, non-responders to one form of training can be rescued by changing modality.

Previous studies have used twin comparisons to estimate the heritability of phenotypic traits (Bouchard *et al.*, 1986; Fagard *et al.*, 1987; Polderman *et al.*, 2015) such as CRF. Typically, however, these traits are seen as static capacities and the approach has been to assess the outcome, for example CRF, in MZ pairs and calculate heritability. Twin CRF studies conducted cross-sectionally have produced a wide range of heritability estimates, ranging from 0.40 to 0.94 (Fagard *et al.*, 1991; Sundet *et al.*, 1994; Maes *et al.*, 1996; Hopkins *et al.*, 2010; Beunen *et al.*, 2011). It is important to reinforce, however, that CX assessment of fitness does not infer trainability, which is the capacity to modify fitness in response to a training stimulus. In a previous pilot study from our group in a UK paediatric population (11 MZ, 11 DZ, aged 13 yr), we calculated an rMZ of 0.84 (*P*<0.01) and rDZ of 0.44 (*P*=0.07) for baseline VO_2max, with an estimated heritability of 0.8 (Hopkins *et al.*, 2010). But in a smaller sub-study (Hopkins *et al.*, 2012) of 8 weeks of END training (6 MZ, 6 DZ), heritability for exercise training responsiveness was not apparent; neither rMZ nor rDZ were significantly different from 0. Other twin studies assessing the heritability of CRF in response to END training have used MZ twins only (Prud'homme *et al.*, 1984; Boulay *et al.*, 1985; Hamel *et al.*, 1986; Bouchard *et al.*, 1994; Danis *et al.*, 2003) revealing a large range of rMZ of CRF (VO_2max in L.min^{-1}) response to END of 0.44-0.70. Most of these studies were included in a systematic review (Zadro *et al.*, 2017) that concluded a significant pooled rMZ for VO_2max of 0.39. However, as indicated in the Methods section, without the inclusion of DZ twin pairs such as in the present study, the distinction between genetic and environmental contributions cannot be concluded (Hopper, 1992).

The current study utilised a novel and robust approach: we simultaneously trained, at the same relative intensity (according to individual pre-training VO_2max and 1RM results), same-sex twins in pairs, using two dichotomous modalities, in a cross-over study design. We found that, for CRF (VO_2max in L.min^{-1}), CX rMZ and rDZ were both high, with most contribution due to shared

environmental factors (C). However, when the twins were actually exercise trained there was a specificity of training effect where END training produced significant rMZ (but not rDZ) with contributions split between shared and unshared environmental factors (C and E). RES training produced no significant correlations for either zygosity. Previous CX baseline strength assessment studies of twins (Thomis *et al.*, 1998; Ropponen *et al.*, 2004; Maridaki, 2006; Beunen *et al.*, 2011) have revealed a wide range of rMZ of 0.29-0.90. These conflicting results have resulted in strength responses to RES training being labelled as highly environmental, or highly genetic (Thibault *et al.*, 1986; Thomis *et al.*, 1998).

Our findings for strength in the present study, in keeping with our CRF findings, indicate that whilst CX rMZ and rDZ were both high, with most contribution due to shared environmental factors, exercise training responses revealed a specificity effect; RES training produced significant rMZ (but not rDZ) with contributions split between shared and unshared environmental effects (although predominantly shared), whereas END training produced a significant, albeit smaller, rMZ (but not rDZ) with a higher contribution towards unshared than shared environmental effects. Ours is the first study, to our knowledge, to train MZ and DZ twin pairs contemporaneously at matched intensities and using dual modalities. Our findings indicate that different variables exhibit different genetic, shared environmental and unshared environmental components. Cross-sectional analysis (i.e. at baseline) appears to be generally more suggestive of genetic contributions to a capacity than the actual changes associated with training. Our study suggests that shared environmental effects influence the way in which responses to training occur. Shared environmental effects could be due to co-habitation influencing factors such as daily routine, sleep, diet, exercise, school environment, incidental physical activity and/or organised sport participation. More research is needed to determine the contributions of specific environmental factors.

A limitation of the current study is the relatively low number of DZ twin pairs (12 pairs) which may have influenced the likelihood of rDZ being significant. When initially recruiting for the study, twin pairs self-reported their zygosity. However, when they were DNA tested for zygosity, 10 pairs who self-reported as DZ were actually found to be MZ. DNA testing to determine zygosity of twin pairs was therefore a major strength of this study which prevented us misclassifying zygosity, an integral component of all twin studies. Our findings are specific to the young healthy population we recruited and it is possible that older or diseased populations may yield different outcomes and estimates. We selected a younger population to avoid the potential confounding influence of diseases that may impact on exercise participation and/or adaptation. Another strength is that we only included same-sex twin pairs for DZ twins (no male-female pairs). This eliminated any confounding sex-based hormonal influences due to sex-differences (Green *et al.*, 2016). We also utilised twin-based mixed models to determine the contributions of genetics (A), shared (C) and individual (E) environmental factors. The differences seen in the expression of C and E (shared and unshared environment), compared to the CX estimates might suggest that lifelong exposure differs from the impacts of short term interventions.

Conclusions

Our findings indicate that responsiveness to exercise training is modality-specific and that individuals who are low-responders to an exercise training modality may be "rescued" by switching to an alternate mode of training. By adopting a novel twin study design utilising MZ and DZ twin pairs who undertook identical exercise programs at matched intensities, we assessed the contribution of genetic and environmental to exercise-induced adaptation. Our results suggest that genes may not play as large a role as previously estimated from CX data in terms of training adaptation, and/or that CX data do not reflect actual longitudinal training effects. This study has implications for those charged with optimising the benefits of exercise by means of individualising the exercise prescription.

Additional information

Competing interests

None to declare.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

All authors contributed to statistical analysis, interpretation of results, writing the paper, approved the final version of the revised manuscript and agree to be accountable for all aspects of the work. D.G. devised the experiment. L.N., C.M. and H.T. contributed to the study design. C.M. and H.T. completed data analysis, acquisition, and supervised the study data collection. This experiment was performed at The University of Western Australia with the exercise interventions being conducted at the School of Sport Science, Exercise and Health, and testing conducted at the Cardiovascular Exercise Physiology Research Laboratory within this school. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Table 1. Baseline characteristics of participants enrolled in the study

	Monozygotic (MZ)	Dizygotic (DZ)	*P*-value
	n = 60 (30 twin pairs; 17 F, 13 M)	n = 24 (12 twin pairs; 8 F, 4 M)	
Age (yrs)	26.2 (6.2)	23.5 (4.5)	0.11
Height (cm)	174.2 (7.1)	171.8 (7.5)	0.29
Weight (kg)	74.1 (17.9)	62.6 (10.9)	0.01
BMI (kg/m^2)	24.3 (5.1)	21.1 (2.9)	0.01
Leg press (kg)	184.3 (64.4)	157.7 (38.9)	0.08
Bench press (kg)	48.4 (21.3)	39.8 (17.6)	0.07
VO_2max ($L.min^{-1}$)	2.92 (0.78)	2.66 (0.80)	0.32
VO_2max ($ml.kg^{-1}.min^{-1}$)	39.67 (6.26)	42.33 (8.25)	0.007
TTE (s)	950 (318)	1016 (410)	0.52
Resting HR (bpm)	59 (9)	59 (7)	0.85
HR max (bpm)	193 (8.9)	196 (6.8)	0.20
BLa max (mmol.L)	10.2 (3.0)	10.1 (2.9)	0.88

BMI, body mass index; TTE, time to exhaustion; HR, heart rate; BLa, blood lactate. Data are mean (SD).

Table 2. Group mean changes in strength and cardiorespiratory fitness with resistance and endurance training.

	△ RES	△ END	*P*-value
	n = 64	n = 68	(RES vs END)
Muscular strength (1RM)			
Leg press (kg)	47.0 (29.4) ‡	3.0 (26.4)	<0.0001
Bench press (kg)	5.1 (5.0) ‡	-0.4 (3.4)	<0.0001
Cardiorespiratory fitness			
VO_2max (L.min^{-1})	0.04 (0.25)	0.25 (0.26) ‡	<0.0001
VO_2max (ml.kg^{-1}.min^{-1})	0.03 (3.57)	3.61 (3.77) ‡	<0.0001
TTE (s)	-3 (131)	170 (137) ‡	<0.0001
Resting HR (bpm)	-0.1 (0.9)	-3.4 (6.5) ‡	0.009
HR max (bpm)	-1.1 (5.6)	-2.2 (6.3) ‡	0.37
BLa max (mmol.L)	-0.7 (2.4) *	-0.3 (2.7)	0.45

1RM, one-repetition maximum; TTE, time to exhaustion; HR, heart rate; BLa, blood lactate; RES, resistance; END, endurance. Data are mean (SD). **P*<0.05; †*P*<0.01; ‡*P*<0.005 for changes from baseline within condition

Table 3. Intraclass coefficients and heritability ACE contributions for MZ and DZ twins for strength and cardiorespiratory fitness.

		rMZ	rDZ	P rMZ vs rDZ	A	C	E
Muscular strength (1RM)							
Leg press (kg)	CX^{CE}	0.82‡	0.52*			0.79	0.21
	△RES^{C}	0.62‡	0.49			0.64	0.36
	△END^{C}	0.36*	0.28			0.36	0.64
Bench press (kg)	CX^{CE}	0.92‡	0.88‡			0.92	0.08
	△RES^{CE}	0.45*	0.48*			0.46	0.54
	△END	0	0				
Cardiorespiratory fitness							
VO_2max (L.min^{-1})	CX^{ACE}	0.92‡	0.78‡	0.005	0.3	0.63	0.07

	△RES	0.26	0.39			
	△END[C]	0.45[*]	0.18		0.43	0.57
TTE (s)	CX[C]	0.67[‡]	0.24		0.73	0.27
	△RES	0.32	0			
	△END	0.08	0.29			
Resting HR (bpm)	CX	0.12	0.10			
	△RES	0.10	0.74			
	△END	0.18	0			

CX, cross-sectional; RES, resistance; END, endurance; MZ, monozygotic; DZ, dizygotic; A, additive genetic effects; C, common (shared) environmental effects; E, individual (unshared) environmental effects; 1RM, one-repetition maximum; TTE, time to exhaustion; HR, heart rate. *P<0.05; †P<0.01; ‡P<0.005. [ACE] ACE method: Normal method used when rMZ and rDZ, and likelihood ratio test (P rMZ vs rDZ) are all significant; [CE] CE method: A method used to calculate C and E when rMZ and rDZ are not significantly different (using the likelihood ratio test). Assumes that correlation is due to shared environmental effects (C); [C] Revised model C: A new method to calculate revised rMZ, when rDZ is not significant. Only assumes correlation for MZ pairs. Note that the estimate of C from this model has a different meaning and interpretation from the estimate of C from the usual CE model. Note: variance components models were not fitted when neither rMZ nor rDZ were significantly different from 0.

Figure legends

Figure 1. Study design. Twin pairs (1, green; 2, blue) were randomised together to complete 3 months of exercise intervention 1 (resistance [RES] or endurance [END] training), 3 months of a washout period and cross-over to complete 3 months of the alternate modality in exercise intervention 2. Outcome measures including a VO_2max test and 1RM strength test were completed pre-post each exercise intervention (weeks 0, 12, 24 and 36).

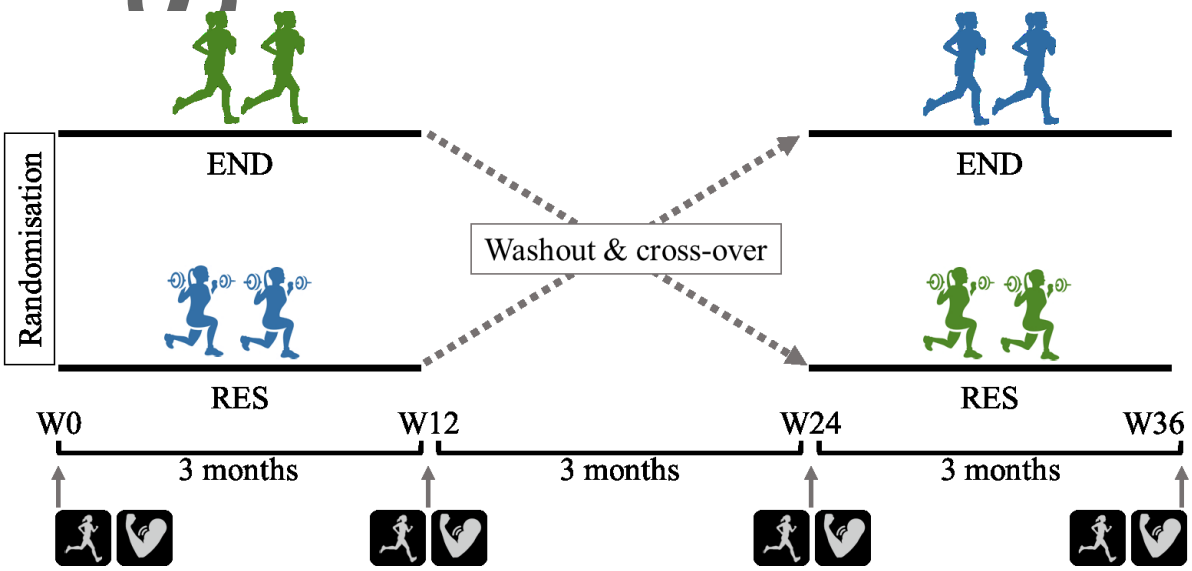


Figure 2. Changes (△) with resistance (RES; blue) and endurance (END; yellow) training for leg press 1RM (top panel, A) and VO_2max (bottom panel, B) in terms of group responses (left), as well as each individuals response to RES (middle) and END (right) training. For a breakdown of each individuals response to both modalities see Figure 3. ‡P<0.005.

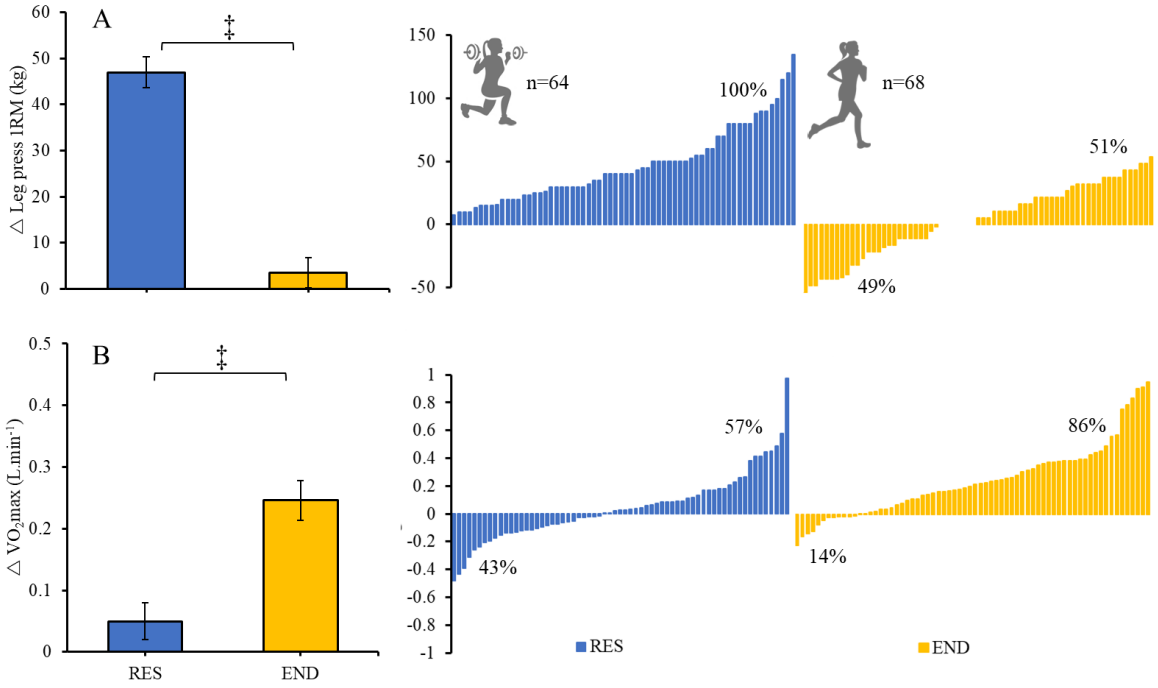


Figure 3. Individual subject (n=64 completed both modes) exercise intervention change score (△) data plotted against one another with response to resistance (RES) and endurance (END) training on the x- and y-axis, respectively. Strength variables (depicted by green dots) are A, leg press 1RM; and B, bench press 1RM. Cardiorespiratory fitness variables (depicted by blue dots) include C, VO_2max; D, time to exhaustion (TTE) and E, resting heart rate (HR). A figure key (F) depicts concordance and discordance for response to RES and END with percentages of responders for each quadrant reported for each variable (A-E).

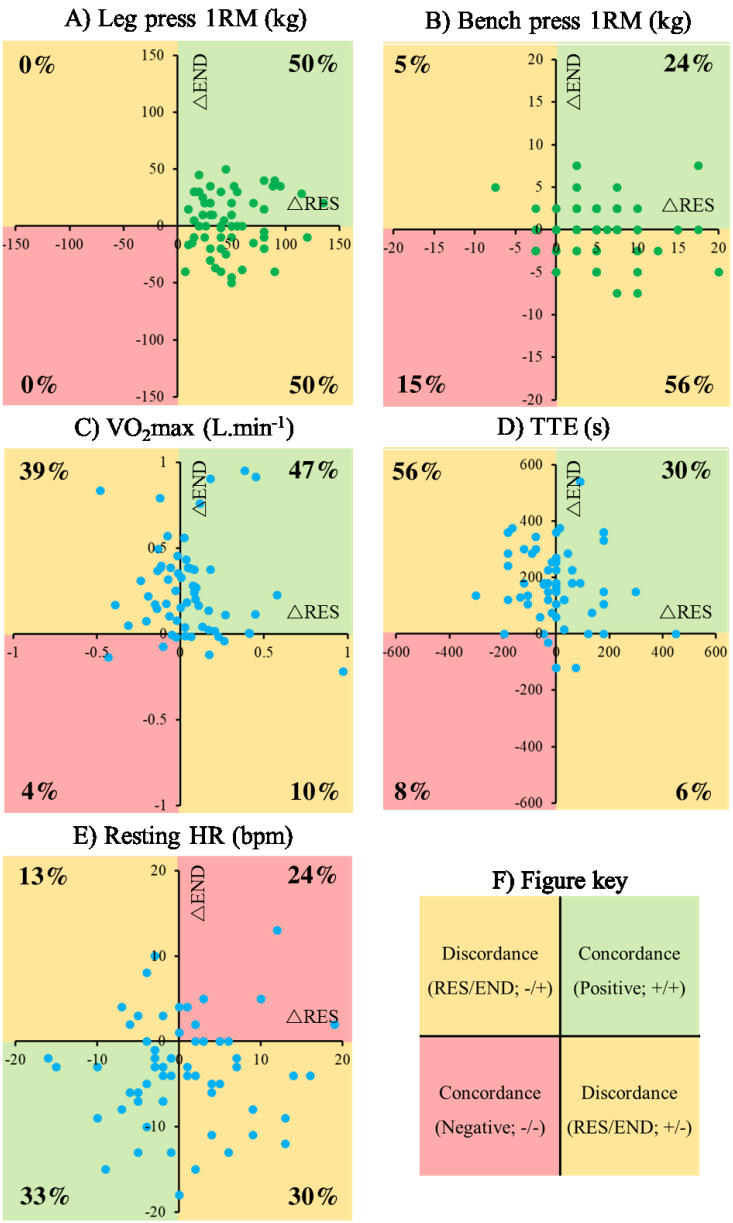


Figure 4. Leg press 1RM results displayed as cross-sectional (panel A), and response (△) to resistance (RES, panel B) and endurance (END, panel C) training. Individual results for twin A and B are represented (left panel) as the higher and lower result within a twin pair, respectively, with each individual within a pair joined by a line. The respective intraclass correlations (r) for monozygotic (MZ) and dizygotic (DZ) twin pairs are above. A boxplot of the absolute differences for each twin pair (Twin A-Twin B) for MZ and DZ, respectively, is displayed (right panel).

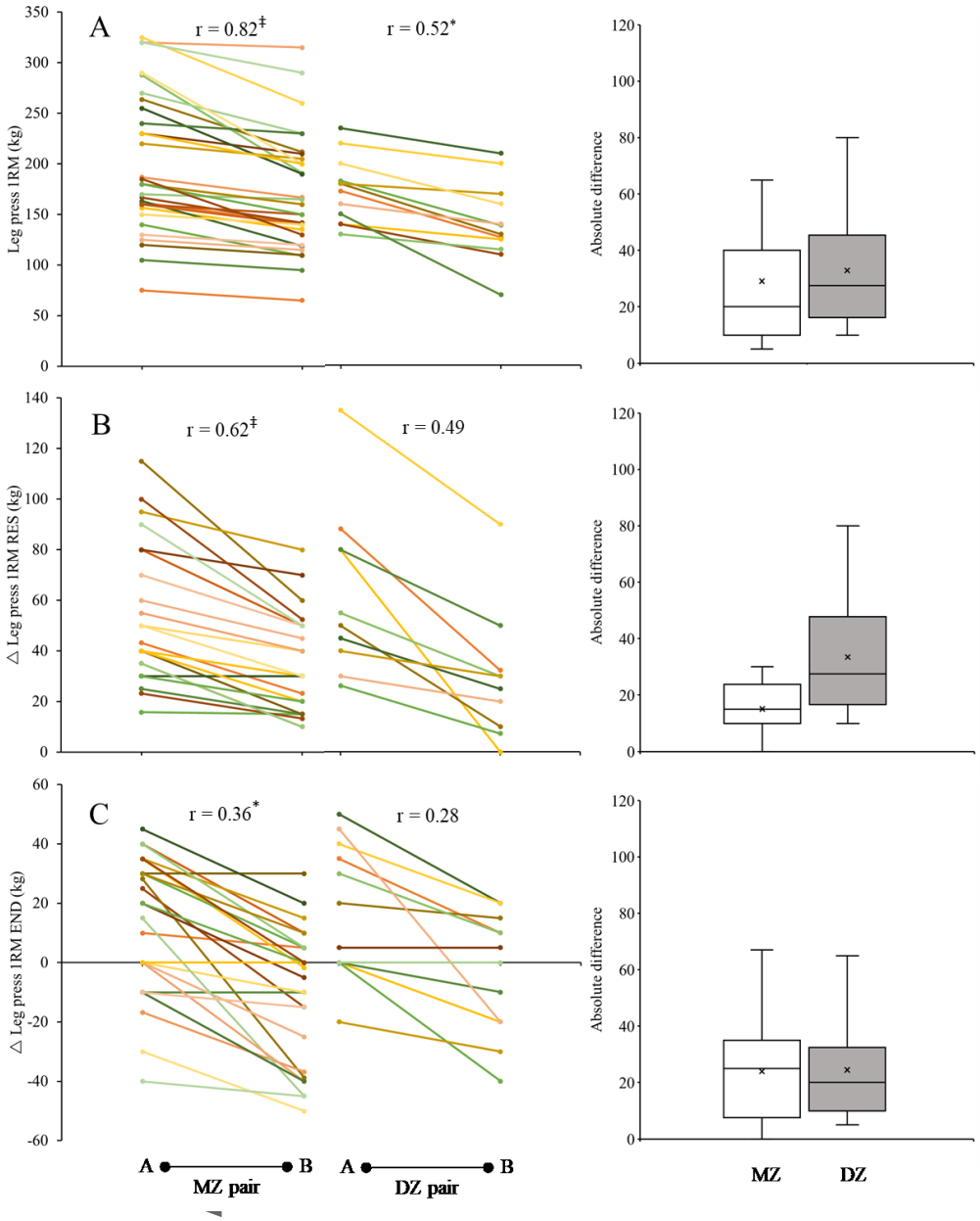
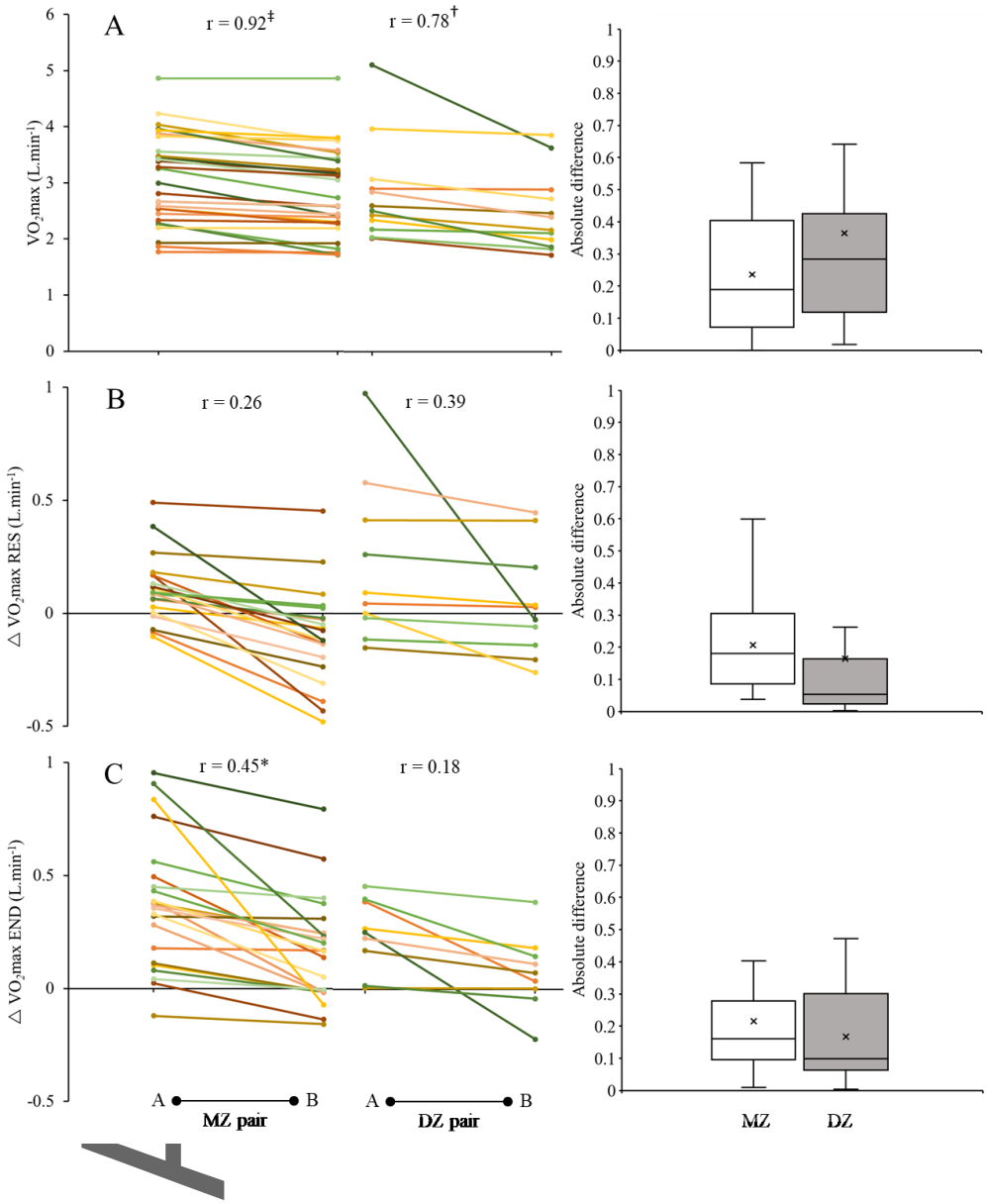


Figure 5. VO_2max ($L.min^{-1}$) results displayed as cross-sectional (panel A), and response (△) to resistance (RES, panel B) and endurance (END, panel C) training. Individual results for twin A and B are represented (left panel) as the higher and lower result within a twin pair, respectively, with each individual within a pair joined by a line. The respective intraclass correlations (r) for monozygotic (MZ) and dizygotic (DZ) twin pairs are above. A boxplot of the absolute differences for each twin pair (Twin A-Twin B) for MZ and DZ, respectively, is displayed (right panel).



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Channa E. Marsh and Hannah J. Thomas are currently completing their PhD at The University of Western Australia under the guidance of Winthrop Professor Daniel J. Green and Dr Louise H. Naylor. This investigation was carried out in the School of Sport Science, Exercise and Health, and testing was conducted at the Cardiovascular and Cerebrovascular Exercise Physiology Research Laboratory. They are interested in using individualised exercise responses to optimise exercise prescription. Channa is specialising in cardiovascular and peripheral vascular structural and functional adaptations to exercise in healthy and athlete populations. Hannah specialises in cerebrovascular and cognitive responses and research investigating the benefits of individualised exercise prescription to cerebrovascular health in clinical populations.

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