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REVIEW ARTICLE

High Responders and Low Responders: Factors Associated with Individual Variation in Response to Standardized Training

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Abstract The response to an exercise intervention is often described in general terms, with the assumption that the group average represents a typical response for most individuals. In reality, however, it is more common for individuals to show a wide range of responses to an intervention rather than a similar response. This phenomenon of 'high responders' and 'low responders' following a standardized training intervention may provide helpful insights into mechanisms of training adaptation and methods of training prescription. Therefore, the aim of this review was to discuss factors associated with inter-individual variation in response to standardized, endurance-type training. It is well-known that genetic influences make an important contribution to individual variation in certain training responses. The association between genotype and training response has often been supported using heritability estimates; however, recent studies have been able to link variation in some training responses to specific single nucleotide polymorphisms. It would appear that hereditary influences are often expressed through hereditary influences on the pre-training phenotype, with some parameters showing a hereditary influence in the pre-training phenotype but not in the subsequent training response. In most cases, the pre-training phenotype appears to predict only a small amount of variation in the subsequent training response of that phenotype. However, the relationship between pre-training autonomic activity and subsequent maximal oxygen uptake response appears to show relatively stronger predictive potential. Individual variation in response to standardized training that cannot be explained by genetic influences may be related to the characteristics of the training program or lifestyle factors. Although standardized programs usually involve training prescribed by relative intensity and duration, some methods of relative exercise intensity prescription may be more successful in creating an equivalent homeostatic stress between individuals than other methods. Individual variation in the homeostatic stress associated with each training session would result in individuals experiencing a different exercise 'stimulus' and contribute to individual variation in the adaptive responses incurred over the course of the training program. Furthermore, recovery between the sessions of a standardized training program may vary amongst individuals due to factors such as training status, sleep, psychological stress, and habitual physical activity. If there is an imbalance between overall stress and recovery, some individuals may develop fatigue and even maladaptation, contributing to variation in pre–post training responses. There is some evidence that training response can be modulated by the timing and composition of dietary intake, and hence nutritional factors could also potentially contribute to individual variation in training responses. Finally, a certain amount of individual variation in responses may also be attributed to measurement error, a factor that should be accounted for wherever possible in future studies. In conclusion, there are several factors that could contribute to individual variation in response to standardized training. However, more studies are required to help clarify and quantify the role of these factors. Future studies addressing

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such topics may aid in the early prediction of high or low training responses and provide further insight into the mechanisms of training adaptation.

1 Introduction

1.1 Individual Variation in Response to Standardized Training

In the exercise science literature, it remains conventional to report only the group mean and standard deviation for exercise or training responses even though ~32 % of normally distributed measurements fall more than 1 standard deviation from the mean [1]. This variation in response around the mean alludes to the inter-individual variation in exercise and training responses that are ubiquitously observed but only specifically addressed in a comparatively small number of studies. To be specific, parameters for which inter-individual variation in training response have been highlighted include maximal oxygen uptake (VO_{2max}) [2–12], resting heart rate (HR) [9], exercise HR [4, 9], exercise systolic blood pressure [4], the aerobic threshold [13], the anaerobic threshold [9, 13], resting muscle glycogen [8], muscle enzyme activity [2, 8, 14], and total work done in a performance trial of fixed duration [8].

At each end of a range of individual responses are individuals who show exceptionally large responses (high responders) and individuals who show exceptionally small responses (low responders) to a training intervention. However, individuals who show a low training response in one parameter (e.g., VO_{2max}) do not necessarily show a low training response in other parameters (e.g., submaximal HR) [8, 9], making the concept of high responders versus low responders an even more complex one. Given that training response can be detected in a myriad of outcome measurements, discussing inter-individual variation in training response on a measurement-by-measurement basis would be an overwhelming task. Therefore, as a starting point, the aim of the current review was to discuss, in broad terms, factors that may be associated with inter-individual variation (henceforth simply referred to as 'individual variation') in response to standardized, endurance-type training. It is envisaged that increased understanding of these factors could provide helpful insight into mechanisms of training adaptation and help to inform strategies for training prescription.

2 Genotype, Heredity, and Baseline Phenotype

The link between genetic variation and heterogeneous training responses was first investigated in the mid 1980s by comparing the within-pair and between-pair training responses of monozygotic twins [2, 13, 15, 16]. There was less variation within pairs of twins than between pairs of twins for several response phenotypes, suggesting that certain training responses were indeed genotype-dependent [2, 13, 15]. However, these findings were somewhat limited by small participant numbers (5–10 twin pairs).

In response to the need for a much larger study, a five-laboratory consortium recruited more than 90 Caucasian families and more than 40 African American families (both parents and three or more adult offspring) and studied their responses to a 20-week, standardized endurance training program—an undertaking known as the HERITAGE Family Study [17]. The study examined the cardiovascular and metabolic responses to exercise training and examined genetic influences on training adaptation from the perspective of major gene effects [18, 19], specific polymorphisms [20, 21], heritability [22–26], and familial aggregation [23, 27]. For clarity, heritability includes both shared genetic and shared familial environmental influences and is reported as a maximal estimate based on the correlations between family members who share genetic variance (parent–offspring and siblings) and family members who do not (spouses). Conversely, familial aggregation is determined by comparing variance within and between family units.

The following sections focus in further detail on genetic influences in the form of genotype and heritability estimates. Due to the challenges of investigating heritability and training response (e.g., need for large sample sizes, recruitment of family units), the findings of the HERITAGE study feature prominently in the reported heritability estimates. However, heritability estimates may vary with the model of analysis [24] as well as with factors such as race [22], the relative intensity of the exercise response measurement [24], and the duration of the training program [2]. Furthermore, the mode of training and the training load would also be expected to affect heritability estimates [28]. It follows that in Sects. 2.2–2.4, reported instances of variance explained by genotype or heritable factors should be viewed as examples rather than as established effects.

2.1 Genotype and Training Response

Gene variants associated with certain training response phenotypes are gradually being identified. For example, it has previously been shown that ~50 % of the variance in VO_{2max} response to training could be explained by variance in 21 single nucleotide polymorphisms (SNPs) [20] and ~36 % of the training response in exercise HR at 50 W could be explained by nine SNPs [21]. Other training response phenotypes that may be associated with specific gene variants include peak power output, the anaerobic

threshold, and running economy (see review by Bray et al. [29]).

Nevertheless, several findings have yet to be replicated elsewhere and many aspects of the relationship between genotype and training response remain unclear. For example, it is not known whether the genetic variance associated with variation in training response remains consistent across different exercise modes, training program structures, and training program durations [28]. Furthermore, it is unclear whether genomic predictors of training response are the same in healthy and at-risk or diseased populations. In light of this uncertainty, the clinical value of genomic predictors of exercise response for individualized exercise prescription remains under debate [30–33].

2.2 Hereditary Factors and Baseline Phenotype

Many exercise-related parameters have a considerable hereditary or familial influence in the untrained or 'baseline' state (Fig. 1). For example, hereditary factors may explain up to 50 % of the variance in VO_{2max} [34], up to 58 % of the variance in oxygen uptake (VO_2) at the ventilatory threshold [22], and up to 59 % of the variance in HR when exercising at 50 W in the untrained state [35]. Furthermore, there appears to be significant familial aggregation of the maximal enzyme activities for the phosphagen, glycolytic, and oxidative pathways in the untrained state [27]. Hereditary influences and specific gene variants have also been linked to a number of other exercise-related phenotypes including fat-free mass, forced expiratory volume, and muscle strength (see review by Puthucheary et al. [36]).

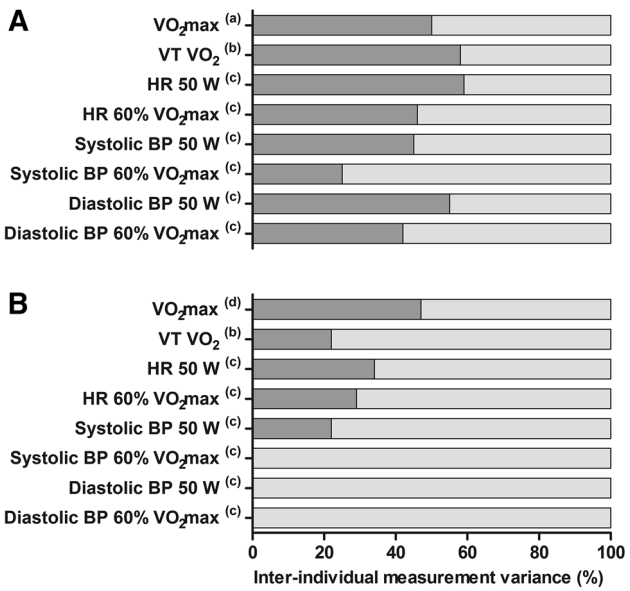

Fig. 1 Maximum heritability (*dark gray bars*) and minimum environmental influence on inter-individual variation in measurement variance from the HERITAGE Family Study [17]. **a** Baseline measurements, **b** baseline-corrected training response. *BP* blood pressure, *HR* heart rate, VO_2 oxygen consumption, VO_{2max} maximum oxygen uptake, *VT* ventilatory threshold. [a]Bouchard et al. [34], [b]Gaskill et al. [22], [c]An et al. [35], [d]Bouchard et al. [23]

2.3 Baseline Phenotype and Training Response

In some cases, there may be little relationship between the pre-training value of a measurement and the magnitude of the subsequent training response. For example, baseline values explained only ~1 % of the training-induced change in high-density lipoprotein cholesterol levels and in VO_{2max} in the HERITAGE study [4], and a weak relationship between initial VO_{2max} and VO_{2max} training response has also been reported on other occasions [3, 6, 37].

Conversely, there are other parameters for which much stronger relationships between baseline values and training response have been established. For example, in the HERITAGE study, baseline HR at 50 W accounted for ~40 % of the variation in the training-induced change in HR at 50 W [4]. In a similar way, baseline systolic blood pressure at 50 W accounted for 32 % of the variation in the training-induced change in systolic blood pressure at 50 W [4]. In these cases, the relationship between baseline parameters and subsequent training responses may be related to the capacity for improvement. In other words, individuals with more 'favorable' values at baseline (e.g., lower submaximal HR) may potentially show a low subsequent training response if a 'ceiling effect' limits further improvement in that parameter.

In keeping with the view that baseline parameters may influence subsequent training responses, there are a small number of examples in which authors have used baseline measurements as well as factors such as age and sex in multiple regression models to predict training response [4, 5, 9, 38]. Further details of these studies appear in Table 1. Although it is difficult to form conclusions based on such a small number of studies, it would appear that factors such as age, sex, and the baseline value of a measurement explain only a small amount of the subsequent training response for VO_{2max} and the individual anaerobic threshold (11–16 %) and a somewhat larger amount of variation in exercise HR and blood pressure training responses (21–47 %).

However, growing evidence suggests that markers of autonomic activity, measured at baseline, could predict subsequent training responses [5, 38–41]. For example, Hautala et al. [5] and Boutcher et al. [38] found that resting HR variability measured in the untrained state was able to explain ~30 % of the variation in VO_{2max} response to a subsequent training program. Furthermore, both Hedelin et al. [39] and Buchheit et al. [40] reported that resting HR

Table 1 Multiple regression models to predict training response from baseline phenotypes in untrained individuals

Predicted variable	Participants	Training program	Predictive variable/model	Variance explained (R^2) (%)	References
ΔVO_2max	$n = 17$ (M and F)	3 sessions/week for 50 weeks	Age, gender, compliance, and baseline VO_{2max}	16	Scharhag-Rosenberger et al. [9]
	$n = 720$ (M and F)	3 sessions/week for 20 weeks	Age, gender, race and baseline VO_{2max}	11	Bouchard and Rankinen [4]
	$n = 39$ (M)	6 sessions/week for 8 weeks	Nocturnal heart rate variability	27	Hautala et al. [5][a]
	$n = 16$ (F)	3 sessions/week for 12 weeks	Resting heart rate variability	34	Boutcher et al. [38]
Δ exercise heart rate	$n = 18$ (M and F)	3 sessions/week for 50 weeks	Age, gender, compliance and baseline exercise heart rate	21	Scharhag-Rosenberger et al. [9]
Δ heart rate at 50 W	$n = 720$ (M and F)	3 sessions/week for 20 weeks	Baseline heart rate 50 W, gender, race, and age	47	Bouchard and Rankinen [4]
Δ HDL-C	$n = 720$ (M and F)	3 sessions/week for 20 weeks	Baseline HDL-C, gender, and race	2	Bouchard and Rankinen [4]
Δ systolic blood pressure at 50 W	$n = 720$ (M and F)	3 sessions/week for 20 weeks	Systolic blood pressure at 50 W and gender	33	Bouchard and Rankinen [4]
Δ individual anaerobic threshold (W)	$n = 15$ (M and F)	3 sessions/week for 50 weeks	Age, gender, compliance, and baseline individual anaerobic threshold	11	Scharhag-Rosenberger et al. [9]

Δ pre–post training change, *F* females, *HDL-C* high-density lipoprotein cholesterol, *M* males, VO_{2max} maximum oxygen uptake

[a] Hautala et al. [5] used relative change in the predictive variable whereas the other authors appear to have used absolute change

variability was associated with subsequent improvements in performance among trained individuals.

With further investigation, it may be possible to establish which variable or combination of variables could be used to predict relatively high or low training responses for a particular training response parameter. However, unlike existing studies, these investigations should also consider whether predictive models or variables are practically meaningful and not just statistically significant.

2.4 Hereditary Factors and Baseline-Corrected Training Response

To gain a clearer understanding on the role of genetics in training response, over and above the influence of baseline phenotype, outputs from the HERITAGE study have reported heritability estimates and/or familial aggregation for baseline-corrected training responses (Fig. 1) [22–24, 35]. For example, in the HERITAGE study, heritable factors were able to explain up to 47 % of the VO_{2max} training response [23], 22 % of the ventilatory threshold training response [22], 34 % of the HR at 50 W training response [35], and 22 % of the systolic blood pressure and 50 W training response [35] when corrected for baseline influences. However, no significant hereditary influences or familial aggregation were detected for the training-induced change in diastolic blood pressure at 50 W [35], fiber-type proportion [27], and muscle capillarization [27]. This implies that, aside from the potential influence of baseline phenotype (discussed in Sect. 2.3), the latter training responses were determined primarily by environmental factors.

Some of the afore-mentioned training response heritability estimates from the HERITAGE study are in accordance with earlier observations in monozygotic twins by Prud'homme et al. [13]. These authors reported within-pair similarities of 55 % and 18 % for VO_{2max} and ventilatory threshold training responses following a 20-week standardized training program. In addition, the authors showed a reduced hereditary influence on training responses at higher exercise intensities (ventilatory threshold response vs. anaerobic threshold response), a finding in keeping with observations from the HERITAGE study [24].

2.5 Genetics, Baseline Phenotype, and Training Response: Mechanistic Links

In a brief note on mechanistic perspectives, preliminary evidence suggests that high or low response to training may be mediated through the expression profile of certain RNAs at baseline [42] and/or the expression profile of certain micro RNAs in response to training [43]. These and other observations linking molecular factors to individual variation in training response have been discussed in further detail by Timmons [44]. Furthermore, the importance of molecular characteristics points to epigenetic modulation

as a primary mediator of individual variation in training responses and the reader is referred to several recent reviews linking physical activity (and other lifestyle factors) to epigenetic modulation [45–48].

3 Homeostatic Stress of Each Training Session

The overall homeostatic stress of an exercise bout is determined by the interaction of factors such as exercise intensity and duration and serves as a 'stimulus' to initiate adaptive responses. For example, at the muscular level, adaptation to exercise training is the accumulated effect of specific transcriptional and translational 'micro-adaptations' that occur after each exercise bout [49]. It follows that variation in the acute exercise stimulus received may partially explain individual variation the training responses accumulated over time.

With this in mind, it is appropriate that many authors reporting individual variation in response to training have taken care to ensure that the training received can be considered approximately equal among participants. To be specific, training was prescribed at a relative intensity [e.g., percentage maximal HR (%HR_{max})] with a fixed session duration and frequency and was often supervised [3, 6, 8–10, 50]. Although training prescribed according to relative exercise intensity is designed to produce a comparable homeostatic stress among individuals, it is, nevertheless, challenging to standardize all the components of an exercise stimulus simultaneously. It follows that inter-individual differences in the homeostatic stress of each training session may occur if the method of prescribing relative exercise intensity was not sufficiently effective [10].

Studies that have reported individual variation in response to training have generally prescribed relative exercise intensity as a percentage VO_{2max} (%VO_{2max}) or a %HR_{max} [3, 6–8, 23]. However, these methods of prescribing exercise intensity have been criticized on the basis of large inter-individual variation in blood lactate responses [51–53] and time to exhaustion [53] at a fixed %VO_{2max} or %HR_{max} of moderate-to-high intensity. It has been argued that individual variation in blood lactate response is indicative of individual variation in the 'metabolic stress' of the exercise bout and that, for this reason, the use of %VO_{2max} or %HR_{max} does not standardize the relative intensity of the exercise bout effectively [8, 51–54]. Metabolic stress is closely associated with the activation of certain signaling pathways [55, 56], and therefore individual variation in the metabolic stress of each training session may well contribute to individual variation in the adaptive responses incurred over time.

Gaskill et al. [57] provided some evidence of this effect when the authors retrospectively analyzed the effect of training intensity relative to the ventilatory threshold on pre- versus post-training changes in the ventilatory threshold and in VO_{2max} among HERITAGE study participants. The HERITAGE study training sessions were initially prescribed at 55 % VO_{2max} and progressed to 75 % VO_{2max} over the course of the 20-week training intervention. At the initial training intensity of 55 % VO_{2max}, baseline ventilatory threshold values ranged from 34 to 83 % VO_{2max}, indicating large individual variation in the training intensity relative to the ventilatory threshold [57]. Variation in training intensity relative to the ventilatory threshold was subsequently shown to account for 26 % of the improvement in VO_2 at the ventilatory threshold with higher relative intensities associated with greater improvements in ventilatory threshold VO_2. Conversely, there was no significant relationship between training intensity relative to the ventilatory threshold and improvements in VO_{2max}. This implies that individual variation in training intensity relative to threshold values does not necessarily make a detectable contribution to the individual variation in VO_{2max} response reported in the HERITAGE study [4] or elsewhere [2, 3, 5–10]. Although Gaskill et al. [57] described the lack of effect as "surprising," it could be speculated that the influence of intensity relative to threshold values on training responses could be less prominent in training responses where a relatively high proportion of variation can be explained by genetic factors (e.g., VO_{2max} training response [20]).

Authors that have criticized the use of %VO_{2max} and %HR_{max} for exercise intensity prescription have argued that training prescribed relative to threshold measurements would be better suited to eliciting a similar relative exercise stress among individuals [8, 51–54] and the afore-mentioned findings of Gaskill et al. [57] would appear to support this premise. However, few studies [11] have reported individual variation in training responses following training relative to threshold measurements and reduced individual variation in training response following threshold-related training versus training at a %VO_{2max} or %HR_{max} has yet to be established [58]. Nevertheless, it is reasonable to conclude that individual variation in the homeostatic stress of each training session is likely to make a significant contribution to individual variation in training responses after a standardized training program. It follows that the method of relative exercise intensity prescription may require careful consideration, taking into account the main outcomes targeted for improvement after the training intervention. For example, the findings of Gaskill et al. [57] suggest that exercise prescribed relative to a threshold measurement may reduce individual variation in the ventilatory threshold training response but not necessarily in VO_{2max} training response.

4 Recovery and 'Readiness to Train'

In general, the time taken to return to resting homeostasis after a training session is associated with the overall homeostatic stress or 'training load' of the session [59–61]. For example, Stanley et al. [61] recently demonstrated that vagal-related heart variability required less than 24 h, 24–48 h, or more than 48 h to return to pre-exercise levels following low-intensity exercise, threshold-intensity exercise, and high-intensity exercise, respectively.

In a standardized program, training sessions prescribed using a fixed relative intensity and duration should, in theory, produce a similar homeostatic stress among individuals. Nevertheless, this may be difficult to achieve in practice [62] and differences in the homeostatic stress of training might contribute to variation in recovery time in some instances. Furthermore, there are several other factors over and above this possible influence that could modulate recovery and adaptive responses between training sessions, including fitness level/training status, sleep, psychological stress, and habitual physical activity.

While it is not necessarily requisite for resting homeostasis to be completely restored between training sessions [61], general trends of recovery from previous training sessions and 'readiness' for subsequent training sessions may affect the magnitude of the training response incurred [63]. With this in mind, some of the factors that may affect recovery and readiness to train are discussed in further detail in the following sections.

4.1 Training Status

It is well-established that a higher fitness level or training status is associated with more rapid post-exercise recovery [61, 64–69]. For example, higher training status is associated with faster parasympathetic reactivation [61, 68, 69] and more efficient regulation of metabolism [64–67] in the post-exercise period. Although most studies involving standardized training programs recruit participants with a similar training status at baseline [6, 8–11], variation in training status or fitness level may contribute to variation in recovery between training sessions in certain cases.

4.2 Sleep and Stress

Variation in the ability to recover between training sessions may also arise from lifestyle factors such as psychological stress and sleep [70]. Concerning the role of psychological stress, two studies have reported that higher psychological/life event stress at baseline was associated with smaller improvements in power- or strength-related outcomes following a subsequent training program [71, 72]. Furthermore, a recent novel investigation by Stults-Kolehmainen and Bartholomew [73] found that higher life event stress was associated with slower recovery of muscle function in the 60 min following a strenuous exercise bout. On the possible role of sleep in training adaption, Samuels presented case studies relating sleep disturbances to poor training tolerance and fatigue in athletes and observed that "ongoing sleep debt is likely a critical factor affecting post-exercise recovery, performance and susceptibility to the overtraining syndrome" [74].

Although these afore-mentioned studies targeted the potential influence of either psychological stress or sleep, increased psychological stress and inadequate sleep are often closely associated [75–77] and the relative influence of these factors on training adaptation may be difficult to differentiate. Increased psychological stress and/or inadequate sleep are associated with a variety of physiological and neurological effects including increased sympathetic tone, decreased parasympathetic tone, altered endocrine function, and altered carbohydrate metabolism [78–80]. There is, as yet, no clear understanding of which specific mechanisms could link increased psychological stress or inadequate sleep to impaired training adaptation. However, one factor that is likely to play a significant role is the increased circulating cortisol associated with psychological stress [81] and with sleep debt [80]. In wound-healing studies, the inhibitory effect of glucocorticoids on pro-inflammatory cytokines has been linked to delayed wound healing [82] and it has been suggested that a similar mechanism may contribute to delayed muscle recovery after a damage-inducing exercise bout [73]. In a slightly different approach, Dattilo et al. [80] have hypothesized that increased cortisol levels, along with decreased testosterone levels and decreased insulin-like growth factor-1, may link sleep debt to impaired muscle recovery. To be specific, the authors have reasoned that these hormonal changes produce a catabolic environment within the muscle, promoting loss of muscle mass and inhibiting anabolic processes in the post-exercise period.

Increased psychological stress and inadequate sleep may also contribute to low training responses through a lower training load. For example, stress and/or inadequate sleep is associated with fatigue [76, 83] and increased susceptibility to infection [84, 85] factors, which may in turn result in missed training sessions or a reduced effort during exercise. Nevertheless, Stults-Kolehmainen and Bartholomew [73] found no relationship between baseline psychological stress and the effort expended during a strenuous exercise bout and it is likely that these influences are more apparent under 'self-governing' conditions than in research studies, where training loads and minimum compliance are often pre-determined.

4.3 Habitual Physical Activity

Whereas psychological stress and inadequate sleep may predict lower training responses, recent work from Hautala et al. [12] showed an association between higher levels of habitual physical activity and larger improvements in certain training response parameters. The authors used accelerometers to quantify daily physical activity in healthy volunteers completing a standardized 8-week endurance training program and found that habitual "light" physical activity (min/day) predicted 28 % of individual variation in VO_{2max} training responses [12]. However, habitual physical activity at "moderate," "high," or "very high" intensities was not related to VO_{2max} training response and physical activity measures did not predict any of the variation in ventilatory threshold training response [12].

A possible mechanism linking greater habitual light physical activity to larger improvements in VO_{2max} (following a standardized training program) is not clear, although the authors [12] speculated that light physical activity may aid recovery between training sessions by stimulating metabolism. However, habitual light physical activity showed relatively high variation within the study participants (64.6 $\pm$ 32.9 min/day) and it is also possible that light physical activity was associated with variation in other factors (e.g., psychological stress) rather than exerting a direct influence on VO_{2max} training responses. Future studies could shed further light on these relationships by reporting associations between habitual physical activity, psychological stress, sleeping patterns, and training responses within the same participant group.

4.4 Fixed Versus Flexible Training Prescription

In many of the studies highlighting individual variation in response to training, the frequency and intensity of the training sessions was pre-determined [6, 8–11] and did not allow for individual variation in the time taken to recover from each session. Under these circumstances, some individuals may be in a more favorable state to adapt to subsequent training than others due to afore-mentioned factors such as sleep, psychological stress, and habitual physical activity. However, it could be argued that the influence of most 'readiness to train' factors could be summed up as the influence of a 'fixed' approach to training prescription.

An alternative to fixed training prescription is to prescribe training in a flexible, 'individualized' manner, using monitoring tools to assess an individual's day-to-day 'readiness to train' [86–89]. In novel investigations from Kiviniemi et al. [86, 87], moderately active individuals were divided into a group that completed a pre-determined schedule of training and a group whose training was guided by day-to-day changes in HR variability. In the latter group, an increase or no change in morning HR variability resulted in a high-intensity training session being prescribed for that day, whereas a decrease in morning HR variability resulted in the participants either resting or training at a lower intensity on that day. The authors [86, 87] subsequently demonstrated that training guided by day-to-day changes in HR variability resulted in larger or equivalent improvements in VO_{2max} and maximal workload in moderately active individuals than a pre-determined schedule of training.

In a similar approach, Capostagno et al. [88] assigned trained cyclists to a "structured" high-intensity training group or a flexible training group, in which high-intensity sessions were prescribed according to day-to-day responses to a standardized submaximal monitoring test. In keeping with the findings of Kiviniemi et al. [86, 87], it was observed that the flexible group showed a larger overall improvement in 40 km time trial performance at the group level and a larger number of improved 40 km time trial performances at the individual level than the structured training group. Furthermore, the authors [88] reported that different individuals in the flexible group completed the training sessions in the same time, a longer time, or a shorter time than individuals in the structured training group and reasoned that the timing of high-intensity training sessions could partially explain differences in training response.

Although further studies comparing fixed versus flexible training prescription would be beneficial, larger improvements following flexible training prescription [86–88] would suggest that this approach decreases the likelihood of poor training responses and may even result in less individual variation in training responses. It falls beyond the scope of the current review to discuss which day-to-day monitoring tool or measurement would best inform flexible, individualized training prescription; suffice to say, the state of the autonomic system appears to provide key insight into an individual's state of recovery and/or adaptive potential [41, 61, 89]. With this in mind, the reader is directed to several recent reviews on the topic of using HR indices to monitor changes in training status [89–91].

5 Nutritional Status

It is increasingly evident that endogenous and exogenous substrate availability can modulate the transcriptional and translational response to an exercise bout [92, 93], suggesting that variation in the typical timing and composition of dietary intake may also contribute to individual variation in certain training responses. For example, ingestion of carbohydrates or a carbohydrate–protein mixture attenuates

the messenger RNA expression of genes involved in lipid metabolism [94] and protein degradation [95], respectively. In addition, several studies have demonstrated significant differences in training adaptation following short-term dietary interventions (e.g., training with low muscle glycogen levels) (see review by Hawley et al. [93]). Nevertheless, the mechanisms linking acute, substrate-related differences in gene regulation and accumulated training adaptations remain under investigation and it is not clear what magnitude of variation in typical nutritional status would be required to make a meaningful contribution to individual variation in training responses.

6 Measurement Error and Smallest Worthwhile Change

When reporting individual responses to training, it has been common to highlight the extent of individual variation by reporting the absolute range of responses and/or using bar graphs to depict rank-ordered individual responses [4, 6, 10–12]. However, two factors that have typically been omitted when presenting these results are the measurement error and the smallest worthwhile change associated with the measurement.

The measurement error, or within-subject reliability of a measurement, encompasses both technical error and normal biological variation and may vary with factors such as participant characteristics, the testing protocol, and the time period between tests [96, 97]. When comparing pre- versus post-training values, individual changes that fall within the typical error of a measurement may be as a result of noise in the measurement and cannot necessarily be interpreted as individual variation in training responses. In other words, it could be argued that individual changes that do not exceed the typical error of the measurement could all be categorized as 'non-response' to the associated training intervention [9, 88]. When individuals show increases or decreases larger than the typical error of the measurement, it could be argued that two individual responses that differ by less than the typical error of the measurement are not necessarily different. In essence, considering only the absolute value of each individual response creates the impression that all responses with different absolute values are different from one another. However, in reality, it is likely that one individual's response is meaningfully different from some—but not all—of the other individual responses in a participant group. It follows that measurement error may 'explain' a certain amount of individual variation in responses.

Although the typical error of the measurement is a useful threshold for identifying 'real' changes, the smallest detectable change is not necessarily equivalent to the smallest worthwhile change from a clinical- or performance-related perspective. The smallest worthwhile change in a measurement is often not known and some authors have justified the use of a particular value for smallest worthwhile change [98, 99] or used Cohen's effect sizes to calculate an appropriate value [100–102]. In futures studies, it may be beneficial to view individual responses in the context of the smallest worthwhile change in the measurement rather than on the basis of larger or smaller responses relative to the rest of the group alone. Although this approach is inevitably more complex than simply reporting a range of individual responses, it would help to differentiate clinically relevant individual variation from 'absolute' individual variation.

7 Clinical Perspectives

At the opposite end of the spectrum to 'high responders' are a small proportion of individuals who show little improvement, or even some deterioration, in certain outcomes after exercise training. This phenomenon, discussed in further detail below, is of particular concern given that certain individuals may fail to attain the anticipated health benefits of regular exercise training.

7.1 Non-Response to Training

'Non-responders' is a terms that has been used to describe individuals who show a worsened or unchanged response after training [7] or, more accurately, individuals whose training response does not exceed the day-to-day variation of that particular measurement [9]. The presence of at least some non-responders for VO_{2max} training response is a common occurrence following endurance training in previously untrained individuals [3, 4, 6–9]. However, as authors have included more measurements of training response, rather than measuring VO_{2max} alone, it has become apparent that non-responders for VO_{2max} are not necessarily non-responders in other markers of training adaptation. For example, Scharhag-Rosenberger et al. [9] found that after a year of endurance training, 4 of 18 participants had training-induced changes in exercise HR and the individual anaerobic threshold but no change in VO_{2max}, whereas three different participants improved their VO_{2max} and individual anaerobic threshold but showed no change in exercise HR. The authors described this phenomenon as "individual patterns of non-response."

Individual patterns of non-response have also been demonstrated at a molecular level. For example, Vollaard et al. [8] showed that some individuals with no change in aerobic enzyme activity post-training were among the highest responders for VO_{2max}. Finally, interesting work

from Hautala et al. [6] showed that individuals who failed to improve their VO_{2max} in response to endurance training were able to improve their VO_{2max} in response to resistance training. This finding suggests that individual patterns of non-response may vary by training mode.

It seems logical that lack of improvement in parameters related to cardiovascular disease risk (e.g., resting HR [103]) could be synonymous with failure to reduce overall cardiovascular risk. However, we are not aware of any studies that have monitored the long-term health status of individuals who had particularly low responses following a standardized training program. Indeed, to do so would be a complex undertaking given that non-responders for one training response parameter are not necessarily non-responders for other training response parameters [8, 9]. Timmons [44] has suggested that there is a "hierarchy of health benefits from exercise training," whereby increasing aerobic fitness is of greater significance for long-term health than improvements in metabolic regulation. Nevertheless, longitudinal studies specifically incorporating individuals with poor responses to exercise training would help to confirm whether or not this is the case.

7.2 Adverse Response to Training

Although individuals who show no improvement in certain parameters after training may be a concern for coaches or health professionals, an even greater concern are individuals who show a categorically adverse response in certain training response parameters. The prevalence of adverse responses was recently investigated by Bouchard et al. [104] in a combined sample of 1,687 men and women from six different training studies. The authors defined an adverse response as a change greater than or equal to double the within-subject typical error of measurement, in an adverse direction (i.e., an increase or decrease indicative of a deterioration in health status rather an improvement in health status). Examples of adverse changes for typical measurements include $\geq$10 mmHg increase in systolic blood pressure, $\geq$0.42 mmol/L increase in triglyceride levels, $\geq$24 pmol/L increase in fasting insulin levels, and $\geq$0.12 mmol/L decrease in high-density lipoprotein cholesterol levels. Based on these criteria, 12 % of the participants were adverse responders for systolic blood pressure, 10 % for triglyceride levels, 8 % for fasting insulin levels, and 13 % for high-density lipoprotein cholesterol levels [104]. In total, 31 % of the sample showed one adverse metabolic response, 6 % showed two adverse responses, and 0.8 % showed three or four adverse responses.

The six studies from which the total sample was composed were heterogeneous with respect to participant age, health status, and training methods. Nevertheless, the prevalence of adverse responses appeared to be consistent across the different participant groups [104]. Adverse metabolic responses were not related to a smaller increase in VO_{2max}. Furthermore, the incidence of adverse metabolic responses was not different in subgroups who had performed different training volumes [104]. With this in mind, factors associated with adverse training responses constitutes an important topic for future research. Furthermore, as was the case for non-responders (see Sect. 7.1), the significant of adverse response to exercise training for long-term health does not appear to have been investigated.

7.3 Possible Interventions for Low Training Response

We are not aware of any studies that have had the specific aim of applying an intervention to individuals with a poor initial training response. Nevertheless, based on the current review, possible interventions for 'low responders' could include increased exercise intensity relative to threshold measurements [57], a change of training mode [6], and flexible training prescription based on day-to-day monitoring [86–88]. Furthermore, wherever possible, both the initial identification of 'low responders' and the evaluation of subsequent interventions should incorporate the measurement error and the smallest worthwhile change of the chosen outcome measurement(s).

8 Summary and Conclusion

Although it is conventional to focus on the group mean response following a particular training intervention, individual responses typically show considerable variation, including particularly 'high responders' and particularly 'low responders' or 'non-responders' for a certain training response parameter [4, 8, 11]. A high responder for one form of training response (e.g., change in submaximal HR) may not necessarily be a high responder for a different form of training response (e.g., change in VO_{2max}) [8, 9], implying that the same individual could potentially be described as both a 'responder' or a 'non-responder,' depending on the outcome variable of interest.

Rather than focusing on one outcome measurement in particular, this review discussed genetics/heredity, baseline phenotype, the homeostatic stress of each training session, training status, psychological stress, sleep, habitual physical activity, a fixed versus flexible approach to training prescription, and nutrition as factors that could contribute to individual variation in training response, in a broad sense. In each case, the discussion included a rationale as to why a particular factor would be expected to contribute to individual variation in response to training. Nevertheless,

studies linking each factor to individual variation in training response were often few in number and/or designed with different research questions in mind. Therefore, further evidence supporting the role of each factor is required. A better understanding of non-genetic determinants of training responses (e.g., homeostatic stress of each training session, sleep, nutritional status) would be particularly beneficial given that these factors could potentially be managed for optimal training effect. Finally, future investigations addressing individual variation in training responses would do well to identify high and low responses in the context of measurement error and smallest worthwhile change in the measurement, so as to allow for a more practical interpretation of this complex phenomenon.

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References

1. Cohen L, Holliday M. Inferential statistics. In: Statistics for education and physical education. London: Harper; 1979.
2. Hamel P, Simoneau JA, Lortie G, et al. Heredity and muscle adaptation to endurance training. Med Sci Sports Exerc. 1986;18:690–6.
3. Kohrt WM, Malley MT, Coggan AR, et al. Effects of gender, age, and fitness level on response of VO_2max to training in 60–71 yr olds. J Appl Physiol. 1991;71:2004–11.
4. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. Med Sci Sports Exerc. 2001;33:S446–51.
5. Hautala AJ, Mäkikallio TH, Kiviniemi AM, et al. Cardiovascular autonomic function correlates with the response to aerobic training in healthy sedentary subjects. Am J Physiol Heart Circ Physiol. 2003;285:H1747–52.
6. Hautala AJ, Kiviniemi AM, Mäkikallio TH, et al. Individual differences in the responses to endurance and resistance training. Eur J Appl Physiol. 2006;96:535–42.
7. Sisson SB, Katzmarzyk PT, Earnest CP, et al. Volume of exercise and fitness nonresponse in sedentary, postmenopausal women. Med Sci Sports Exerc. 2009;41:539–45.
8. Vollaard NBJ, Constantin-Teodosiu D, Fredriksson K, et al. Systematic analysis of adaptations in aerobic capacity and submaximal energy metabolism provides a unique insight into determinants of human aerobic performance. J Appl Physiol. 2009;106:1479–86.
9. Scharhag-Rosenberger F, Walitzek S, Kindermann W, et al. Differences in adaptations to 1 year of aerobic endurance training: individual patterns of nonresponse. Scand J Med Sci Sports. 2012;22:113–8.
10. McPhee JS, Williams AG, Degens H, et al. Inter-individual variability in adaptation of the leg muscles following a standardised endurance training programme in young women. Eur J Appl Physiol. 2010;109:1111–8.
11. Karavirta L, Häkkinen K, Kauhanen A, et al. Individual responses to combined endurance and strength training in older adults. Med Sci Sports Exerc. 2011;43:484–90.
12. Hautala AJ, Martinmaki K, Kiviniemi A, et al. Effects of habitual physical activity on response to endurance training. J Sports Sci. 2012;30:563–9.
13. Prud'homme D, Bouchard C, Leblanc C, et al. Sensitivity of maximal aerobic power to training is genotype-dependent. Med Sci Sports Exerc. 1984;16:489–93.
14. McPhee JS, Williams AG, Perez-Schindler J, et al. Variability in the magnitude of response of metabolic enzymes reveals patterns of co-ordinated expression following endurance training in women. Exp Physiol. 2011;96:699–707.
15. Després J-P, Bouchard C, Savard R, et al. Adaptive changes to training in adipose tissue lipolysis are genotype dependent. Int J Obes. 1984;8:87–95.
16. Thibault MC, Simoneau JA, Côté C, et al. Inheritance of human muscle enzyme adaptation to isokinetic strength training. Hum Hered. 1986;36:341–7.
17. Bouchard C, Leon AS, Rao DC, et al. The HERITAGE Family Study. Aims, design, and measurement protocol. Med Sci Sports Exerc. 1995;27:721–9.
18. An P, Borecki IB, Rankinen T, et al. Evidence of major genes for exercise heart rate and blood pressure at baseline and in response to 20 weeks of endurance training: the HERITAGE Family Study. Int J Sports Med. 2003;24:492–8.
19. An P, Borecki IB, Rankinen T, et al. Evidence of major genes for plasma HDL, LDL cholesterol and triglyceride levels at baseline and in response to 20 weeks of endurance training: the HERITAGE Family Study. Int J Sports Med. 2005;26:414–9.
20. Bouchard C, Sarzynski MA, Rice TK, et al. Genomic predictors of the maximal O_2 uptake response to standardized exercise training programs. J Appl Physiol. 2011;110:1160–70.
21. Rankinen T, Sung YJ, Sarzynski MA, et al. Heritability of submaximal exercise heart rate response to exercise training is accounted for by nine SNPs. J Appl Physiol. 2012;112:892–7.
22. Gaskill SE, Rice TK, Bouchard C, et al. Familial resemblance in ventilatory threshold: the HERITAGE Family Study. Med Sci Sports Exerc. 2001;33:1832–40.
23. Bouchard C, An P, Rice TK, et al. Familial aggregation of VO_2max response to exercise training: results from the HERITAGE Family Study. J Appl Physiol. 1999;87:1003–8.
24. Pérusse L, Gagnon J, Province MA, et al. Familial aggregation of submaximal aerobic performance in the HERITAGE Family Study. Med Sci Sports Exerc. 2001;33:597–604.
25. Rice TK, An P, Gagnon J, et al. Heritability of HR and BP response to exercise training in the HERITAGE Family Study. Med Sci Sports Exerc. 2002;34:972–9.
26. Rice TK, Després J-P, Pérusse L, et al. Familial aggregation of blood lipid response to exercise training in the health, risk factors, exercise training, and genetics (HERITAGE) Family Study. Circulation. 2002;105:1904–8.
27. Rico-Sanz J, Rankinen T, Joanisse DR, et al. Familial resemblance for muscle phenotypes in the HERITAGE Family Study. Med Sci Sports Exerc. 2003;35:1360–6.
28. Bouchard C. Genomic predictors of trainability. Exp Physiol. 2012;97:347–52.
29. Bray MS, Hagberg JM, Pérusse L, et al. The human gene map for performance and health-related fitness phenotypes: the 2006–2007 update. Med Sci Sports Exerc. 2009;41:35–73.
30. Roth SM. Perspective on the future use of genomics in exercise prescription. J Appl Physiol. 2008;104:1243–5.
31. Thomis M. Commentary on viewpoint: perspective on the future use of genomics in exercise prescription. J Appl Physiol. 2008;104:1251.
32. Hawley JA. Commentary on viewpoint: perspective on the future use of genomics in exercise prescription. J Appl Physiol. 2008;104:1253.

33. Roth SM. Last word on viewpoint: perspective on the future use of genomics in exercise prescription. J Appl Physiol. 2008;104:1254.
34. Bouchard C, Daw EW, Rice TK, et al. Familial resemblance for VO_2max in the sedentary state: the HERITAGE Family Study. Med Sci Sports Exerc. 1998;30:252–8.
35. An P, Pérusse L, Rankinen T, et al. Familial aggregation of exercise heart rate and blood pressure in response to 20 weeks of endurance training: the HERITAGE Family Study. Int J Sports Med. 2003;24:57–62.
36. Puthucheary Z, Skipworth JR, Rawal J, et al. Genetic influences in sport and physical performance. Sports Med. 2011;41:845–59.
37. Skinner JS, Jaskólski A, Jaskólska A, et al. Age, sex, race, initial fitness, and response to training: the HERITAGE Family Study. J Appl Physiol. 2001;90:1770–6.
38. Boutcher SH, Park Y, Dunn SL, et al. The relationship between cardiac autonomic function and maximal oxygen uptake response to high-intensity intermittent-exercise training. J Sports Sci. 2013;31:1024–9.
39. Hedelin R, Bjerle P, Henriksson-Larsén K. Heart rate variability in athletes: relationship with central and peripheral performance. Med Sci Sports Exerc. 2001;33:1394–8.
40. Buchheit M, Chivot A, Parouty J, et al. Monitoring endurance running performance using cardiac parasympathetic function. Eur J Appl Physiol. 2010;108:1153–67.
41. Hautala AJ, Kiviniemi AM, Tulppo MP. Individual responses to aerobic exercise: the role of the autonomic nervous system. Neurosci Biobehav Rev. 2009;33:107–15.
42. Timmons JA, Knudsen S, Rankinen T, et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. J Appl Physiol. 2010;108:1487–96.
43. Davidsen PK, Gallagher IJ, Hartman JW, et al. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. J Appl Physiol. 2011;110:309–17.
44. Timmons JA. Variability in training-induced skeletal muscle adaptation. J Appl Physiol. 2011;110:846–53.
45. Pareja-Galeano H, Sanchis-Gomar F, García-Giménez JL. Physical exercise and epigenetic modulation: elucidating intricate mechanisms. Sports Med. 2014;44(4):429–36.
46. Ntanasis-Stathopoulos J, Tzanninis JG, Philippou A, et al. Epigenetic regulation on gene expression induced by physical exercise. J Musculoskelet Neuronal Interact. 2013;13:133–46.
47. Sanchis-Gomar F, Garcia-Gimenez JL, Perez-Quilis C, et al. Physical exercise as an epigenetic modulator: Eustress, the "positive stress" as an effector of gene expression. J Strength Cond Res. 2012;26:3469–72.
48. Alegría-Torres JA, Baccarelli A, Bollati V. Epigenetics and lifestyle. Epigenomics. 2011;3:267–77.
49. Flück M. Functional, structural and molecular plasticity of mammalian skeletal muscle in response to exercise stimuli. J Exp Biol. 2006;209:2239–48.
50. Skinner JS, Wilmore KM, Krasnoff JB, et al. Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. Med Sci Sports Exerc. 2000;32:157–61.
51. Dwyer J, Bybee R. Heart rate indices of the anaerobic threshold. Med Sci Sports Exerc. 1983;15:72–6.
52. Meyer T, Gabriel HH, Kindermann W. Is determination of exercise intensities as percentages of VO_2max or HRmax adequate? Med Sci Sports Exerc. 1999;31:1342–5.
53. Scharhag-Rosenberger F, Meyer T, Gässler N, et al. Exercise at given percentages of VO_2max: heterogeneous metabolic responses between individuals. J Sci Med Sport. 2010;13:74–9.
54. Katch V, Weltman A, Sady S, et al. Validity of the relative percent concept for equating training intensity. Eur J Appl Physiol Occup Physiol. 1978;39:219–27.
55. Coyle EF. Physical activity as a metabolic stressor. Am J Clin Nutr. 2000;72:512S–20S.
56. Baar K. The signaling underlying FITness. Appl Physiol Nutr Metab. 2009;34:411–9.
57. Gaskill SE, Walker AJ, Serfass RA, et al. Changes in ventilatory threshold with exercise training in a sedentary population: the HERITAGE Family Study. Int J Sports Med. 2001;22:586–92.
58. McLellan TM, Skinner JS. The use of the aerobic threshold as a basis for training. Can J Appl Sport Sci. 1981;6:197–201.
59. Kaikkonen P, Hynynen E, Mann T, et al. Can HRV be used to evaluate training load in constant load exercises? Eur J Appl Physiol. 2010;108:435–42.
60. Kaikkonen P, Hynynen E, Mann T, et al. Heart rate variability is related to training load variables in interval running exercises. Eur J Appl Physiol. 2012;112:829–38.
61. Stanley J, Peake JM, Buchheit M. Cardiac parasympathetic reactivation following exercise: implications for training prescription. Sports Med. 2013;43:1259–77.
62. Mann T, Lamberts RP, Lambert MI. Methods of prescribing relative exercise intensity: physiological and practical considerations. Sports Med. 2013;43:613–25.
63. Lamberts RP, Swart J, Capostagno B, et al. Heart rate recovery as a guide to monitor fatigue and predict changes in performance parameters. Scand J Med Sci Sports. 2010;20:449–57.
64. Tomlin DL, Wenger HA. The relationship between aerobic fitness and recovery from high intensity intermittent exercise. Sports Med. 2001;31:1–11.
65. Short KR, Sedlock DA. Excess postexercise oxygen consumption and recovery rate in trained and untrained subjects. J Appl Physiol. 1997;83:153–9.
66. Sedlock DA, Lee M-G, Flynn MG, et al. Excess postexercise oxygen consumption after aerobic exercise training. Int J Sport Nutr Exerc Metab. 2010;20:336–49.
67. Hagberg JM, Hickson RC, Ehsani AA, et al. Faster adjustment to and recovery from submaximal exercise in the trained state. J Appl Physiol. 1980;48:218–24.
68. Buchheit M, Millet GP, Parisy A, et al. Supramaximal training and postexercise parasympathetic reactivation in adolescents. Med Sci Sports Exerc. 2008;40:362–71.
69. Sugawara J, Murakami H, Maeda S, et al. Change in postexercise vagal reactivation with exercise training and detraining in young men. Eur J Appl Physiol. 2001;85:259–63.
70. Kenttä G, Hassmén P. Overtraining and recovery. A conceptual model. Sports Med. 1998;26:1–16.
71. Bartholomew JB, Stults-Kolehmainen MA, Elrod CC, et al. Strength gains after resistance training: the effect of stressful, negative life events. J Strength Cond Res. 2008;22:1215–21.
72. Ruuska PS, Hautala AJ, Kiviniemi AM, et al. Self-rated mental stress and exercise training response in healthy subjects. Front Physiol. 2012;3:51.
73. Stults-Kolehmainen MA, Bartholomew JB. Psychological stress impairs short-term muscular recovery from resistance exercise. Med Sci Sports Exerc. 2012;44:2220–7.
74. Samuels C. Sleep, recovery, and performance: the new frontier in high-performance athletics. Phys Med Rehabil Clin North Am. 2009;20:149–59.
75. Kashani M, Eliasson A, Vernalis M. Perceived stress correlates with disturbed sleep: a link connecting stress and cardiovascular disease. Stress. 2012;15:45–51.
76. De Lange AH, Kompier MAJ, Taris TW, et al. A hard day's night: a longitudinal study on the relationships among job demands and job control, sleep quality and fatigue. J Sleep Res. 2009;18:374–83.

77. Demarzo MMP, Stein PK. Mental stress and exercise training response: stress–sleep connection may be involved. Front Physiol. 2012;3:178.
78. McEwen BS. Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. Metabolism. 2006;55:S20–3.
79. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999;354:1435–9.
80. Dattilo M, Antunes HK, Medeiros A, et al. Sleep and muscle recovery: endocrinological and molecular basis for a new and promising hypothesis. Med Hypotheses. 2011;77:220–2.
81. Fukuda S, Morimoto K. Lifestyle, stress and cortisol response: review I: mental stress. Environ Health Prev Med. 2001;6:9–14.
82. Christian LM, Graham JE, Padgett DA, et al. Stress and wound healing. Neuroimmunomodulation. 2006;13:337–46.
83. Akerstedt T, Knutsson A, Westerholm P, et al. Mental fatigue, work and sleep. J Psychosom Res. 2004;57:427–33.
84. Yang EV, Glaser R. Stress-induced immunomodulation and the implications for health. Int Immunopharmacol. 2002;2:315–24.
85. Miller GE. Psychological stress and antibody response to influenza vaccination: when is the critical period for stress, and how does it get inside the body? Psychosom Med. 2004;66:215–23.
86. Kiviniemi AM, Hautala AJ, Kinnunen H, et al. Endurance training guided individually by daily heart rate variability measurements. Eur J Appl Physiol. 2007;101:743–51.
87. Kiviniemi AM, Hautala AJ, Kinnunen H, et al. Daily exercise prescription on the basis of HR variability among men and women. Med Sci Sports Exerc. 2010;42:1355–63.
88. Capostagno B, Lambert MI, Lamberts RP. Standardized vs. customized high-intensity training: effects on cycling performance. Int J Sports Physiol Perform. 2014;9:292–301.
89. Buchheit M. Monitoring training status with HR measures: do all roads lead to Rome? Front Physiol. 2014;5:73.
90. Plews DJ, Laursen PB, Stanley J, et al. Training adaptation and heart rate variability in elite endurance athletes: opening the door to effective monitoring. Sports Med. 2013;43:773–81.
91. Daanen HAM, Lamberts RP, Kallen VL, et al. A systematic review on heart-rate recovery to monitor changes in training status in athletes. Int J Sports Physiol Perform. 2012;7:251–60.
92. Hawley JA, Tipton KD, Millard-Stafford ML. Promoting training adaptations through nutritional interventions. J Sports Sci. 2006;24:709–21.
93. Hawley JA, Burke LM, Phillips SM, et al. Nutritional modulation of training-induced skeletal muscle adaptations. J Appl Physiol. 2011;110:834–45.
94. Civitarese AE, Hesselink MKC, Russell AP, et al. Glucose ingestion during exercise blunts exercise-induced gene expression of skeletal muscle fat oxidative genes. Am J Physiol Endocrinol Metab. 2005;289:E1023–9.
95. Harber MP, Konopka AR, Jemiolo B, et al. Muscle protein synthesis and gene expression during recovery from aerobic exercise in the fasted and fed states. Am J Physiol Regul Integr Comp Physiol. 2010;299:R1254–62.
96. Hopkins WG, Hawley JA, Burke LM. Design and analysis of research on sport performance enhancement. Med Sci Sports Exerc. 1999;31:472–85.
97. Hopkins WG, Schabort EJ, Hawley JA. Reliability of power in physical performance tests. Sports Med. 2001;31:211–34.
98. Paton CD, Hopkins WG, Vollebregt L. Little effect of caffeine ingestion on repeated sprints in team-sport athletes. Med Sci Sports Exerc. 2001;33:822–5.
99. Pyne DB, Hopkins WG, Batterham AM, et al. Characterising the individual performance responses to mild illness in international swimmers. Br J Sports Med. 2005;39:752–6.
100. Saunders PU, Pyne DB, Telford RD, et al. Reliability and variability of running economy in elite distance runners. Med Sci Sports Exerc. 2004;36:1972–6.
101. Robertson EY, Saunders PU, Pyne DB, et al. Reproducibility of performance changes to simulated live high/train low altitude. Med Sci Sports Exerc. 2010;42:394–401.
102. Al Haddad H, Laursen PB, Ahmaidi S, et al. Influence of cold water face immersion on post-exercise parasympathetic reactivation. Eur J Appl Physiol. 2010;108:599–606.
103. Saxena A, Minton D, Lee D, et al. Protective role of resting heart rate on all-cause and cardiovascular disease mortality. Mayo Clin Proc. 2013;88:1420–6.
104. Bouchard C, Blair SN, Church TS, et al. Adverse metabolic response to regular exercise: is it a rare or common occurrence? PLoS ONE. 2012;7:e37887.