Title: Exercise Response Efficiency – A novel way to enhance population health?

Running Head: Exercise Response Efficiency

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Abstract

Rates of obesity and its related co-morbidities have increased substantially over the last thirty years, with approximately 35% of all US adults now classified as obese. Whilst the causes of obesity are both complex and multifactorial, one contributor is a reduction in leisure time physical activity, with no concurrent reduction in energy intake. Physical activity interventions have been demonstrated to promote fat loss, and yet more than 50% of US adults undertake no leisure time physical activity at all, with a lack of time and enjoyment often cited as the main drivers of rising inactivity levels. Furthermore, recent evidence has demonstrated that a sub-group of individuals may experience no improvement in a given fitness or health-related measure following a specific training programme, suggesting that there may be optimal exercise types for different groups of individuals. In this paper, we introduce the concept of exercise response efficiency, whereby individuals are matched to the training type from which they are most likely to derive the greatest improvements for the least time commitment. We propose that a more precise targeting of exercise interventions is likely to drive more rapid improvements in health, thereby promoting exercise adherence and enjoyment, whilst simultaneously reducing obesity and mortality risks. Such an innovation would, we suggest, confer important public health benefits.

1. Authors Note

At the end of this paper, you'll notice that there is a conflict of interest disclosure. The purposes of such a disclosure are to make the reader aware of any potential conflicts of interests relevant to the content of this article. One of the authors of this article (CP) is a former employee of DNAFit Life Sciences, a genetic testing company selling direct-to-consumer genetic tests. Whilst he received no payment or direction to prepare this article from DNAFit, with the article resulting from his doctoral studies, he realises that, given the subject matter, it is important to make the reader aware of this conflict from the outset. The second author (JK) is CPs academic supervisor. He has no conflict of interest relevant to this article to declare, and has thoroughly vetted the arguments contained within.

2. Introduction

Obesity, the condition of excess body fat [1], has become increasingly prevalent over the last thirty years [2,3]. Between 1980 and 2008, mean Body Mass Index (BMI) increased globally by 0.4 kg/m^2, resulting in 1.47 billion adults being categorized as overweight (BMI $\geq$ 25 kg/m^2), and 503 million adults classified as obese (BMI $\geq$ 30 kg/m^2) [2]. These increases were most pronounced in Western countries, with the US—where 35% of all adults are classed as obese—leading the way, closely followed by the UK and Australia [2,3]. Obesity is recognized as a leading cause of a number of co-morbidities, including cardiovascular disease, type-II diabetes, dyslipidemia, and cancer [4,5]. As such, increasing obesity rates represent a significant global healthcare burden [6,7], with the costs associated with treating obesity and its related diseases forecast to increase by up to $66 billion per year in the US and £2 billion per year in the UK by 2030 [7]. As a result, considerable effort is being expended by public health bodies in the quest to better prevent and treat obesity [4,6].

So far, however, these efforts have done little to arrest the increasing obesity rates. In part, this is due to the complex, multifactorial nature of obesity; whilst tempting to believe that obesity is merely a relative overconsumption of energy, the reasons underpinning this can be varied and multi-faceted. These include increased sugar intake, increased portion sizes, alteration of gut microbiota, and genetic predispositions, along with societal, cultural, and environmental influences [8-10]. Recent research has further demonstrated the complex nature of obesity, with aspects such as exposure to environmental toxicants, such as bisphenol-A, shown to modify obesity risk [11], alongside the effects of early-life nutrition [12]. However, a commonly cited reason for the recent explosion in obesity rates is that of a lack of physical activity (PA) [13,14]. In the US, the rise in obesity occurred alongside a significant reduction in leisure time PA, with no change in caloric intake [15], suggesting that a lack of PA is potentially a major driver of climbing obesity rates, at least in the US, where just under 50% of adults report no leisure time PA [15]. Furthermore, recent reports suggest that almost no obese adults meet the currently recommended activity guidelines [16]. Additionally, increasing PA drives caloric expenditure and promotes fat loss [17-19], suggesting that PA could be important in the prevention and treatment of obesity and its related co-morbidities.

Alongside the inverse association between PA and obesity, PA also reduces the risk of a number of other chronic diseases, including cancer [20] and cardiovascular disease [21], and has demonstrated efficacy as a treatment for type-II diabetes [22]. As a result, physical exercise has been termed a "polypill" [23-26], with wide-ranging health benefits; indeed, the positive health benefits of exercise can be greater than comparative drug treatment, particularly with regards to cardiovascular disease [24,26].

Accordingly, it's clear that PA has important, wide-ranging health promoting aspects, serving to reduce the risk of both chronic disease and obesity [13,14], and acting as a treatment for these issues [27]; as a result, exercise can be thought of as a beneficial and cost-effective medicine [28]. Nevertheless, adult rates of PA are low, having declined over the past thirty years [15] in correlation with large increases in obesity and other chronic disease rates. As such, there a plausible relationship between the demonstrated reduction in PA and the increase in obesity seen globally. Free-living adults seem aware of this, with many stating their motivations for partaking in PA stem from their desire to enhance weight management and reduce age-related decline [29]. And yet, despite this awareness, many adults do not take part in any PA at all, with many more failing to meet the recommended guidelines [15,30]. Again, the reasons for this are multi-faceted, but include a lack of confidence [29], time pressures [31,32], and a lack of enjoyment [33]. All of these factors appear to contribute to poor uptake of, and adherence to, exercise training programmes, thereby contributing to an increased incidence of obesity and chronic disease. Enhancing exercise adherence is, therefore, a potentially important aspect of improving population health.

With a view to offsetting some of the barriers to exercise adherence, here we propose the concept of *exercise response efficiency*, whereby individuals are matched to the exercise modalities most likely to deliver the greatest improvements in fitness in the shortest amount of time. From this perspective, exercise response efficiency can be described as the appropriate matching of individuals to exercise modalities to which they are most likely to positively respond. We believe exploring the concept of exercise response efficiency is important, and may provide a viable tactic capable of positively contributing to the ongoing fight against obesity and rising chronic disease rates.

3. Exercise – Good for everyone, all of the time?

There are many different forms of exercise. Regardless of modality, however, exercise can be conceptualized as existing along a continuum, ranging from lower intensity, longer duration exercise at one end, to higher intensity, shorter duration at the other [34]. These divergent exercise stimuli have demonstrated wide-ranging health promoting effects, including reductions in adipose tissue, enhancement of glucose metabolism, reductions in blood pressure, and increases in bone mineral density [34]. Increasingly, short but highly intense exercise efforts are being demonstrated to promote health and weight-management [35,36], although such high-intensity exercise may—but not always—reduce enjoyment and hence adherence [33,37].

Given the wide-ranging and well-established health benefits of exercise, it is tempting to believe that exercise is good for everyone, all of the time, and that there is a reasonably standard, predictable adaptive response to such exercise. However, recent research has called into question some of these long-held beliefs. There is now a wide body of evidence suggesting there is inter-individual variation in response to any given exercise training programme. For example, in the seminal HERITAGE Family Study, which explored inter-individual variation in response to a 20-week aerobic training programme, training-induced changes in VO_{2max} ranged from a decline of approximately 100 mL O_2/min to an increase of over 1000 ml O_2/min [39]. Interestingly, whilst the majority of subjects demonstrated a reduction in heart rate (HR) response to a given workload following the training programme, approximately 100 individuals (~14% of subjects) demonstrated an increase in HR response, suggesting a reduction in physical fitness. Furthermore, when analyzing pooled data from six different training interventions, Bouchard and colleagues [39] reported that, following exercise, 8% of subjects had an adverse change in fasting insulin, 12% an adverse change in systolic blood pressure, 10% an increase in triglycerides, and 13% a reduction in high density lipoprotein – all undesired responses that potentially serve to increase the risk of disease. Finally, and of specific interest in the fight against obesity, there is a well-established variation in the amount of energy expended during exercise [40,41], and the subsequent effect of exercise on appetite [42].

Individuals demonstrating an increase in risk factors following exercise have been termed *adverse responders*, whilst those demonstrating no measurable improvement in a measured fitness variable have been termed *non-responders*. Recently, a number of researchers have explored the use of such terms skeptically [43-47], suggesting that this heterogeneity in response may be (at least partly) due to measurement error and random daily variation, and may not be clinically relevant. In a recent review [48], we suggested that global non-responders to exercise—i.e. individuals demonstrating no beneficial response to exercise—likely do not exist. Nevertheless, when it comes to changes in disease-associated measures, such as cardiorespiratory fitness and fasting insulin, it seems clear that not all exercise exerts the same beneficial effects for all.

4. The causes of exercise response heterogeneity

The drivers of this inter-individual exercise responsivity are wide and varied. Exercise response is most often determined by comparing the pre- and post-intervention scores on a given measure. Inherent within any measurement, however, are technical error and random within-subject variation; both of which are said to represent "false" inter-individual variation [43]. Conversely, drivers of "true"—that is, real—inter-individual variation can best be categorized as either genetic, environmental, or epigenetic in origin [49]. As an example of the impact of a genetic factor, a single nucleotide polymorphism (SNP) within *ACTN3* has been demonstrated to affect the adaptive response to resistance training in elderly subjects [50]. An example of an environmental influence on exercise adaptation is that of stress; individuals who have experienced elevated levels of life stress may exhibit a reduced adaptation to training stimuli [51]. Finally, exemplifying epigenetic modifications and translational control mechanisms, microRNAs may modulate the adaptive response to exercise [52], either by making specific points within DNA more accessible to translation, or exerting control over messenger RNA through either inhibiting translation or causing degradation before translation occurs [53].

5. A lack of exercise response is both modality and measurement specific

The existence of non- or low-responders to exercise is potentially problematic, as it suggests that a sub-group of people may gain little or no benefit from exercise training. However, it appears that such a low response to exercise is both modality and measurement specific [48], thereby suggesting that changing exercise training type, intensity, volume, or duration, and/or introducing additional measurements, may serve to reduce the rate of exercise non-response.

A limited number of studies have explored exercise response across more than one exercise modality. Hautala and colleagues [54] had 73 participants undertake separate endurance and resistance training programmes in a randomized cross-over design, and determined improvements in peak oxygen uptake (VO_{2peak}) following both interventions. There were individual variations in VO_{2peak} improvements following both aerobic (range -5 to +22%) and resistance (range -8 to +16%) training, illustrating that some subjects demonstrated no improvements following a particular training type. However, subjects with the lowest VO_{2peak} improvements following aerobic training exhibited a greater improvement in this measure following resistance training.

Furthermore, when increasing the number of measurements taken, exercise non-response appears to disappear. Karavirta and colleagues [55] illustrated that, whilst a small number of subjects demonstrated a negative training response in terms of VO_{2peak} or maximum voluntary contraction following a combined aerobic and strength training programme, no subject exhibited a negative response to both. Similarly, Bonafiglia and colleagues [56] subjected individuals to both endurance and sprint interval training, determining improvements in VO_{2peak}, lactate threshold, and heart rate following training. Whilst some subjects exhibited non-response to one of these measures, very few (5% following endurance training, 24% following sprint interval training, and 0% from both training modalities combined) were non-responders across all three.

6. Exercise response efficiency

Given the research discussed previously, it is apparent that not everyone demonstrates favorable adaptations to every exercise modality, all of the time. Given the clear disease prevention, control, and treatment benefits of exercise, such a finding is potentially problematic, illustrating, as it does, that not everyone obtains the same benefits from the recommended exercise guidelines, and that we clearly don't all gain the same reductions in, nor protection from, disease risk factors. Instead, it would perhaps be of greater benefit to match individuals to the type of training from which they are most likely to reap beneficial adaptations. At present, such an approach typically occurs through trial and error; an individual undertakes a training intervention—often lasting weeks or months—and then discovers whether they have improved or not. If they have, they may continue the intervention; if they haven't, they can try a different exercise modality. However, such an approach is costly in terms of time; given that one of the cited reasons for a lack of exercise adherence are time pressures [31,32], such an approach may not be viable. Additionally, many people who do not currently meet exercise guidelines are anxious and unconfident regarding exercise [29]; failure to demonstrate improvements may further reduce individual confidence, and reduce enjoyment, limiting the potential of that person to undertake exercise in the future.

Recent evidence suggests that exercise non- or low-response can be abated through increases in training volume, intensity, or duration [48]; however, in high-risk populations, increasing exercise intensity may be poorly tolerated and unpalatable [57], whilst increased volumes and durations are unlikely to be successful due to a perceived lack of available time to exercise [31,32]. Instead, by matching individuals to the exercise type in which they demonstrate the greatest adaptive potential, it might be possible to:

1) Reduce disease risk factors in a shorter period of time. This is especially important given the lack of time—real or perceived—often cited as a reason for non-adherence to exercise guidelines. If we can drive larger improvements in shorter time-frames through targeted training, this would be hugely beneficial to many people.
2) Promote greater adherence to exercise. Research from the nutrigenetics field demonstrates that, when individuals are placed on a personalized dietary intervention, they are more likely to adhere to that intervention for a greater period of time [58] – we see no reason why that would not be the case with exercise. Additionally, by increasing the improvements gained from exercise, the fulfilment and enjoyment experienced by the individual is likely to be increased – further promoting long-term exercise adherence.

7. How can we match individuals to their optimal training type?

The ability to match individuals to the training type most likely to yield the greatest improvements in specific outcomes is, at present, hugely under-explored. In part, this is because it remains to be fully elucidated which variables may predict the most effective training type. From an obesity standpoint, recent work by Leonska-Duniec and colleagues [58-62] has explored the impact of a number of SNPs on changes in fat mass and improvements in aerobic fitness in a group of untrained female subjects. Following a 12-week aerobic training programme, only 75% of subjects lost fat mass, and, notably, subjects with a greater number of obesity-risk alleles tended to lose less fat following training [58]. Other obesity SNPs, such as *LEP* and *LEPR*, which encode for leptin and its receptor, modified the improvements in glucose and LDL cholesterol levels following this same training intervention [62], results which replicated findings from HERITAGE [63]. Similar results have been reported by Klimentidis and colleagues [64], who found that the possession of a greater number of obesity-risk alleles was associated with smaller reductions in fat mass following resistance training. However, at present, whilst we understand that a variety of SNPs, such as *ACTN3* [65] and the obesity related SNPs discussed previously [62,64], impact the adaptive, fat loss, and health biomarker response to training, at present very few studies have attempted to utilise this information to inform training programme design. Furthermore, the relationship between genetic variants and body composition and/or obesity is also potentially affected by measurement characteristics, with Bordoni and colleagues [66], for example, reporting that hydration status modified the relationship between *ACE* genotype and body composition, making accurate quantification of the effects of these SNPs difficult.

Jones and colleagues [67] utilised a 15 SNP total genotype score to classify subjects as those expected to more favorably respond to high-volume, moderate-intensity resistance training, and those expected to more favorably respond to low-volume, high-intensity resistance training. The subjects were then randomized to receive either "matched" (i.e. training matched to their genotype score) or "mismatched" training over an eight-week resistance training intervention. Those in the matched training group experienced significantly greater improvements in a test of power and a test of endurance compared to those in the mismatched group. Furthermore, 83% of high responders to the training intervention were from the matched group, whilst 82% of low- and non-responders were from the mismatched training group. Recently, Pickering and colleagues [68] utilised a 5 SNP genetic test to predict the magnitude of improvements in Yo-Yo test score—a measure of aerobic capacity—in a group of youth soccer players. Subjects possessing a greater number of SNPs thought to be associated with larger improvements in aerobic capacity did indeed demonstrate such improvements, whilst those predicted to demonstrate smaller improvements did so. These findings suggest that genetic information may hold promise in matching individuals to the training type most likely to instigate the greatest adaptive response.

Similar results have been reported in relation to aerobic training. Timmons and colleagues [69] discovered a specific molecular signature, comprised of 29 RNAs expressed within muscle prior to a training intervention, which predicted the improvements in VO_{2max} demonstrated following that training intervention. Similarly, Davidsen et al. [52] uncovered four miRNAs that were differentially expressed between low and high responders following a twelve-week resistance training programme, adding further to the promise of the matching of individuals to their most responsive training type in the future.

At present, tentative research suggests that a combination of genetic and miRNA markers at baseline may be able to predict the magnitude of training response to a given intervention [52,68,69]. This raises the potential for those individuals expected to demonstrate a lower response to a specific intervention to undertake a separate intervention—one in which they are expected to demonstrate a larger improvement, and hence derive increased health benefits. Early research suggests that genetic information may assist in the matching of optimal training type to each individual [67], although substantially more research is required to confirm and expand on these early promising findings.

8. Conclusion

In this paper, we introduced the concept of exercise response efficiency, speculating that, by matching individuals to the type of training they are most likely to see the greatest improvements from, we can increase the protective effects of exercise against disease and promote long term exercise adherence. Such an outcome, we propose, represents a time-efficient method to maximise the health of at-risk populations, offsetting the risks associated with an increasingly sedentary lifestyle. Early research suggests that genotype-matched training [60] can enhance training adaptations, and that a number of biomarkers, including methylation [70], miRNA [52; 70] and genetics [67,68], may enhance prediction of the magnitude of training response prior to an intervention taking place, thereby allowing for the early individualization of training prescription.

Clearly, this suggestion requires more substantial investigation before it can be integrated into disease control and treatment plans, with the early positive findings requiring replication. Similarly, further studies are needed to explore the efficacy of such an approach on training-induced outcomes and adherence in at-risk populations, with it being unclear as to whether such an intervention enhances health above the standardized guidelines. There is also evidence that perceived "negative" genetic information may harm dietary and exercise outcomes [71]. Additionally, the cost of genetic and miRNA testing may make such an approach cost-prohibitive, at least in the short-term, to publicly funded health bodies, or lower socio-economic status individuals wishing to pursue such an approach privately. However, any such initial cost may be offset by the potential positive ramifications to multiple dimensions of public health.

Consequently, we believe that this approach may prove hugely valuable, especially to at-risk populations, in the near future. Given the wide-ranging and well-established health benefits of exercise on obesity and disease risk and treatment, yet the current poor uptake of exercise programmes, this approach may serve to both increase exercise adherence and outcomes. As PA rates decline, and the number of individuals with obesity and chronic disease increases, this approach represents a potentially impactful, yet largely unconsidered and under-investigated, tool to combat these global health threats. Given the increasing numbers of individuals with obesity and chronic disease across the globe, along with declining PA rates, such an approach represents a potentially useful tool to attack such issues.

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Conflicts of Interest

Craig Pickering is a former employee of DNAFit LifeSciences, a genetic testing company. He received no financial incentives for the preparation of this manuscript, which was prepared as part of his doctoral studies. John Kiely declares that he has no conflict of interest relevant to the content of this article.

Author Contributions

CP conceived of the idea for this manuscript, and authored the first draft. JK provided substantial edits and rewriting. Both authors approve the final version of the manuscript.

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