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

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3 **Running Head:** Exercise Response Efficiency

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60 **Exercise Response Efficiency – A novel way to enhance population health?**
61

62 **Abstract**
63

64 Rates of obesity and its related co-morbidities have increased substantially over the last thirty years,
65 with approximately 35% of all US adults now classified as obese. Whilst the causes of obesity are both complex
66 and multifactorial, one contributor is a reduction in leisure time physical activity, with no concurrent reduction
67 in energy intake. Physical activity interventions have been demonstrated to promote fat loss, and yet more than
68 50% of US adults undertake no leisure time physical activity at all, with a lack of time and enjoyment often
69 cited as the main drivers of rising inactivity levels. Furthermore, recent evidence has demonstrated that a sub-
70 group of individuals may experience no improvement in a given fitness or health-related measure following a
71 specific training programme, suggesting that there may be optimal exercise types for different groups of
72 individuals. In this paper, we introduce the concept of exercise response efficiency, whereby individuals are
73 matched to the training type from which they are most likely to derive the greatest improvements for the least
74 time commitment. We propose that a more precise targeting of exercise interventions is likely to drive more
75 rapid improvements in health, thereby promoting exercise adherence and enjoyment, whilst simultaneously
76 reducing obesity and mortality risks. Such an innovation would, we suggest, confer important public health
77 benefits.
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119 **1. Authors Note**

120
121 At the end of this paper, you'll notice that there is a conflict of interest disclosure. The purposes of
122 such a disclosure are to make the reader aware of any potential conflicts of interests relevant to the content of
123 this article. One of the authors of this article (CP) is a former employee of DNAFit Life Sciences, a genetic
124 testing company selling direct-to-consumer genetic tests. Whilst he received no payment or direction to prepare
125 this article from DNAFit, with the article resulting from his doctoral studies, he realises that, given the subject
126 matter, it is important to make the reader aware of this conflict from the outset. The second author (JK) is CPs
127 academic supervisor. He has no conflict of interest relevant to this article to declare, and has thoroughly vetted
128 the arguments contained within.

129
130 **2. Introduction**

131
132 Obesity, the condition of excess body fat [1], has become increasingly prevalent over the last thirty
133 years [2,3]. Between 1980 and 2008, mean Body Mass Index (BMI) increased globally by 0.4 kg/m², resulting
134 in 1.47 billion adults being categorized as overweight (BMI ≥ 25 kg/m²), and 503 million adults classified as
135 obese (BMI ≥ 30 kg/m²) [2]. These increases were most pronounced in Western countries, with the US—where
136 35% of all adults are classed as obese—leading the way, closely followed by the UK and Australia [2,3].
137 Obesity is recognized as a leading cause of a number of co-morbidities, including cardiovascular disease, type-II
138 diabetes, dyslipidemia, and cancer [4,5]. As such, increasing obesity rates represent a significant global
139 healthcare burden [6,7], with the costs associated with treating obesity and its related diseases forecast to
140 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,
141 considerable effort is being expended by public health bodies in the quest to better prevent and treat obesity
142 [4,6].

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144 So far, however, these efforts have done little to arrest the increasing obesity rates. In part, this is due
145 to the complex, multifactorial nature of obesity; whilst tempting to believe that obesity is merely a relative
146 overconsumption of energy, the reasons underpinning this can be varied and multi-faceted. These include
147 increased sugar intake, increased portion sizes, alteration of gut microbiota, and genetic predispositions, along
148 with societal, cultural, and environmental influences [8-10]. Recent research has further demonstrated the
149 complex nature of obesity, with aspects such as exposure to environmental toxicants, such as bisphenol-A,
150 shown to modify obesity risk [11], alongside the effects of early-life nutrition [12]. However, a commonly cited
151 reason for the recent explosion in obesity rates is that of a lack of physical activity (PA) [13,14]. In the US, the
152 rise in obesity occurred alongside a significant reduction in leisure time PA, with no change in caloric intake
153 [15], suggesting that a lack of PA is potentially a major driver of climbing obesity rates, at least in the US,
154 where just under 50% of adults report no leisure time PA [15]. Furthermore, recent reports suggest that almost
155 no obese adults meet the currently recommended activity guidelines [16]. Additionally, increasing PA drives
156 caloric expenditure and promotes fat loss [17-19], suggesting that PA could be important in the prevention and
157 treatment of obesity and its related co-morbidities.

158
159 Alongside the inverse association between PA and obesity, PA also reduces the risk of a number of
160 other chronic diseases, including cancer [20] and cardiovascular disease [21], and has demonstrated efficacy as
161 a treatment for type-II diabetes [22]. As a result, physical exercise has been termed a “polypill” [23-26], with
162 wide-ranging health benefits; indeed, the positive health benefits of exercise can be greater than comparative
163 drug treatment, particularly with regards to cardiovascular disease [24,26].

164
165 Accordingly, it's clear that PA has important, wide-ranging health promoting aspects, serving to reduce
166 the risk of both chronic disease and obesity [13,14], and acting as a treatment for these issues [27]; as a result,
167 exercise can be thought of as a beneficial and cost-effective medicine [28]. Nevertheless, adult rates of PA are
168 low, having declined over the past thirty years [15] in correlation with large increases in obesity and other
169 chronic disease rates. As such, there a plausible relationship between the demonstrated reduction in PA and the
170 increase in obesity seen globally. Free-living adults seem aware of this, with many stating their motivations for
171 partaking in PA stem from their desire to enhance weight management and reduce age-related decline [29]. And
172 yet, despite this awareness, many adults do not take part in any PA at all, with many more failing to meet the
173 recommended guidelines [15,30]. Again, the reasons for this are multi-faceted, but include a lack of confidence
174 [29], time pressures [31,32], and a lack of enjoyment [33]. All of these factors appear to contribute to poor
175 uptake of, and adherence to, exercise training programmes, thereby contributing to an increased incidence of
176 obesity and chronic disease. Enhancing exercise adherence is, therefore, a potentially important aspect of
177 improving population health.

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

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

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

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

212 Individuals demonstrating an increase in risk factors following exercise have been termed *adverse*
213 *responders*, whilst those demonstrating no measurable improvement in a measured fitness variable have been
214 termed *non-responders*. Recently, a number of researchers have explored the use of such terms skeptically [43-
215 47], suggesting that this heterogeneity in response may be (at least partly) due to measurement error and random
216 daily variation, and may not be clinically relevant. In a recent review [48], we suggested that global non-
217 responders to exercise—i.e. individuals demonstrating no beneficial response to exercise—likely do not exist.
218 Nevertheless, when it comes to changes in disease-associated measures, such as cardiorespiratory fitness and
219 fasting insulin, it seems clear that not all exercise exerts the same beneficial effects for all.

223 4. The causes of exercise response heterogeneity

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

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

239
240 The existence of non- or low-responders to exercise is potentially problematic, as it suggests that a sub-
241 group of people may gain little or no benefit from exercise training. However, it appears that such a low
242 response to exercise is both modality and measurement specific [48], thereby suggesting that changing exercise
243 training type, intensity, volume, or duration, and/or introducing additional measurements, may serve to reduce
244 the rate of exercise non-response.

245
246 A limited number of studies have explored exercise response across more than one exercise modality.
247 Hautala and colleagues [54] had 73 participants undertake separate endurance and resistance training
248 programmes in a randomized cross-over design, and determined improvements in peak oxygen uptake (VO_{2peak})
249 following both interventions. There were individual variations in VO_{2peak} improvements following both aerobic
250 (range -5 to +22%) and resistance (range -8 to +16%) training, illustrating that some subjects demonstrated no
251 improvements following a particular training type. However, subjects with the lowest VO_{2peak} improvements
252 following aerobic training exhibited a greater improvement in this measure following resistance training.

253
254 Furthermore, when increasing the number of measurements taken, exercise non-response appears to
255 disappear. Karavirta and colleagues [55] illustrated that, whilst a small number of subjects demonstrated a
256 negative training response in terms of VO_{2peak} or maximum voluntary contraction following a combined aerobic
257 and strength training programme, no subject exhibited a negative response to both. Similarly, Bonafiglia and
258 colleagues [56] subjected individuals to both endurance and sprint interval training, determining improvements
259 in VO_{2peak} , lactate threshold, and heart rate following training. Whilst some subjects exhibited non-response to
260 one of these measures, very few (5% following endurance training, 24% following sprint interval training, and
261 0% from both training modalities combined) were non-responders across all three.

262 263 **6. Exercise response efficiency**

264
265 Given the research discussed previously, it is apparent that not everyone demonstrates favorable
266 adaptations to every exercise modality, all of the time. Given the clear disease prevention, control, and treatment
267 benefits of exercise, such a finding is potentially problematic, illustrating, as it does, that not everyone obtains
268 the same benefits from the recommended exercise guidelines, and that we clearly don't all gain the same
269 reductions in, nor protection from, disease risk factors. Instead, it would perhaps be of greater benefit to match
270 individuals to the type of training from which they are most likely to reap beneficial adaptations. At present,
271 such an approach typically occurs through trial and error; an individual undertakes a training intervention—
272 often lasting weeks or months—and then discovers whether they have improved or not. If they have, they may
273 continue the intervention; if they haven't, they can try a different exercise modality. However, such an approach
274 is costly in terms of time; given that one of the cited reasons for a lack of exercise adherence are time pressures
275 [31,32], such an approach may not be viable. Additionally, many people who do not currently meet exercise
276 guidelines are anxious and unconfident regarding exercise [29]; failure to demonstrate improvements may
277 further reduce individual confidence, and reduce enjoyment, limiting the potential of that person to undertake
278 exercise in the future.

279
280 Recent evidence suggests that exercise non- or low-response can be abated through increases in
281 training volume, intensity, or duration [48]; however, in high-risk populations, increasing exercise intensity may
282 be poorly tolerated and unpalatable [57], whilst increased volumes and durations are unlikely to be successful
283 due to a perceived lack of available time to exercise [31,32]. Instead, by matching individuals to the exercise
284 type in which they demonstrate the greatest adaptive potential, it might be possible to:

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

295 296 **7. How can we match individuals to their optimal training type?**

297

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

316
317 Jones and colleagues [67] utilised a 15 SNP total genotype score to classify subjects as those expected
318 to more favorably respond to high-volume, moderate-intensity resistance training, and those expected to more
319 favorably respond to low-volume, high-intensity resistance training. The subjects were then randomized to
320 receive either “matched” (i.e. training matched to their genotype score) or “mismatched” training over an eight-
321 week resistance training intervention. Those in the matched training group experienced significantly greater
322 improvements in a test of power and a test of endurance compared to those in the mismatched group.
323 Furthermore, 83% of high responders to the training intervention were from the matched group, whilst 82% of
324 low- and non-responders were from the mismatched training group. Recently, Pickering and colleagues [68]
325 utilised a 5 SNP genetic test to predict the magnitude of improvements in Yo-Yo test score—a measure of
326 aerobic capacity—in a group of youth soccer players. Subjects possessing a greater number of SNPs thought to
327 be associated with larger improvements in aerobic capacity did indeed demonstrate such improvements, whilst
328 those predicted to demonstrate smaller improvements did so. These findings suggest that genetic information
329 may hold promise in matching individuals to the training type most likely to instigate the greatest adaptive
330 response.

331
332 Similar results have been reported in relation to aerobic training. Timmons and colleagues [69]
333 discovered a specific molecular signature, comprised of 29 RNAs expressed within muscle prior to a training
334 intervention, which predicted the improvements in VO_{2max} demonstrated following that training intervention.
335 Similarly, Davidsen et al. [52] uncovered four miRNAs that were differentially expressed between low and high
336 responders following a twelve-week resistance training programme, adding further to the promise of the
337 matching of individuals to their most responsive training type in the future.

338
339 At present, tentative research suggests that a combination of genetic and miRNA markers at baseline
340 may be able to predict the magnitude of training response to a given intervention [52,68,69]. This raises the
341 potential for those individuals expected to demonstrate a lower response to a specific intervention to undertake a
342 separate intervention—one in which they are expected to demonstrate a larger improvement, and hence derive
343 increased health benefits. Early research suggests that genetic information may assist in the matching of optimal
344 training type to each individual [67], although substantially more research is required to confirm and expand on
345 these early promising findings.

346 8. Conclusion

347
348
349 In this paper, we introduced the concept of exercise response efficiency, speculating that, by matching
350 individuals to the type of training they are most likely to see the greatest improvements from, we can increase
351 the protective effects of exercise against disease and promote long term exercise adherence. Such an outcome,
352 we propose, represents a time-efficient method to maximise the health of at-risk populations, offsetting the risks
353 associated with an increasingly sedentary lifestyle. Early research suggests that genotype-matched training [60]
354 can enhance training adaptations, and that a number of biomarkers, including methylation [70], miRNA [52; 70]
355 and genetics [67,68], may enhance prediction of the magnitude of training response prior to an intervention
356 taking place, thereby allowing for the early individualization of training prescription.

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

367
368 Consequently, we believe that this approach may prove hugely valuable, especially to at-risk
369 populations, in the near future. Given the wide-ranging and well-established health benefits of exercise on
370 obesity and disease risk and treatment, yet the current poor uptake of exercise programmes, this approach may
371 serve to both increase exercise adherence and outcomes. As PA rates decline, and the number of individuals
372 with obesity and chronic disease increases, this approach represents a potentially impactful, yet largely
373 unconsidered and under-investigated, tool to combat these global health threats. Given the increasing numbers
374 of individuals with obesity and chronic disease across the globe, along with declining PA rates, such an
375 approach represents a potentially useful tool to attack such issues.

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380 Conflicts of Interest

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

385 **Author Contributions**

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

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