Published in final edited form as:
*Sports Med*. 2013 March ; 43(3): 157–165. doi:10.1007/s40279-013-0018-0.

# Toward Exercise as Personalized Medicine

**Thomas W. Buford**,
Department of Aging and Geriatric Research, College of Medicine, University of Florida, PO Box 112610, Gainesville, FL 32611, USA, Department of Applied Physiology and Kinesiology, College of Health & Human Performance, University of Florida, Gainesville, FL, USA

**Michael D. Roberts**, and
Department of Biomedical Sciences, College of Veterinary Medicine, University of Missouri, Columbia, MO, USA

**Timothy S. Church**
Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, USA

Thomas W. Buford: tbuford@ufl.edu

## Abstract

The early 21st century has witnessed a steady push by scientists, industry leaders, and government officials to make medicine more personalized. To date, the concept of personalized medicine has referred largely to the field of pharmacogenomics. In contrast, relatively few data exist regarding the application of preventive strategies such as physical exercise in the context of personalized medicine. Within this review, we highlight the extant literature and propose five strategies for scientists that may propel the exercise and sports science fields toward this global goal. Notably, these approaches are in addition to methods to maintain adherence to training – a well-known factor in determining exercise responsiveness. Briefly, these strategies include (1) evaluating participant responses to training at the individual as well as group level; (2) identifying sources of variability in responsiveness to training; (3) optimizing exercise dosing strategies to maximize benefits while minimizing barriers to participation; (4) evaluating the efficacy of multimodal interventions for relevant population subgroups; and (5) increasing the clinical relevance of study populations and outcomes in exercise trials. We look forward to seeing these strategies considered in trials of preventive health interventions such as exercise. Extensive future research in this area is needed for the vision of exercise as a personalized form of medicine to become a reality.

## 1 Introduction

Hippocrates (460–377 BC), widely recognized as the father of modern medicine, is credited with remarking that “if we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health.” He is perhaps the first individual to document that physical exercise is a critical component of medicine, a view now shared by scientific and regulatory bodies including the WHO, American College of Sports Medicine, American Heart Association, and US Department of Health and Human Services [1–4]. Accordingly, the importance of exercise and other forms of physical activity has become increasingly recognized as an essential component of an



Correspondence to: Thomas W. Buford, tbuford@ufl.edu.

The authors have no conflicts of interest to disclose.

individual's overall health. So, with extensive research supporting the universal prescription of exercise and physical activity, questions exist regarding future research in this area.

Certainly, research focused on public dissemination remains an important field. Despite the overwhelming evidence regarding the health benefits of exercise and physical activity, only 35% of US adults even report engaging in regular physical activity [5]. More concerning are objective measurements indicating that only 5% of US adults obtain the recommended 30 min/day of physical activity [6]. Furthermore, these data indicate that less than half of children aged 6–11 years and only 8% of adolescents achieve this goal [6]. Thus, implementation studies designed to identify effective methods of increasing engagement and adherence are a high priority. However, scientists concentrating on earlier stages of translation must also think proactively to prevent stagnation and continue advancing the field.

This opportunity may lie in the area of personalized medicine. The early 21st century has witnessed a steady push by scientists, industry leaders and government officials to make medicine more personalized [7–9]. While personalized medicine is intended to include preventive as well as therapeutic interventions, the majority of research to date has focused on the study of pharmacogenomics. Yet despite the breadth of utility of exercise and that the concept of heterogeneity in exercise responsiveness was proposed nearly three decades ago [10], information remains relatively limited regarding the individualized health responses to regular exercise. Therefore, we review here the extant literature and propose potential research strategies to increase individualization and, consequently, efficacy of exercise prescriptions.

## 2 Research Strategies to Increase Individualization of Exercise Prescription

### 2.1 Look Beyond the Group Mean

In 2001, Bouchard and Rankinen [11] wrote that the "number of publications dealing with physical inactivity and activity and their effects on one or several risk factors, health outcomes, or mortality is already impressive and is growing. However, it is fair to say that the vast majority of the published studies have emphasized main effects and group differences while paying little attention, if any, to individual differences…. It needs to be recognized that contributions documented at the level of a group may not fully apply to each member of that group." Indeed, even well controlled studies using homogenous populations have demonstrated significant heterogeneity training responses. For instance, changes in maximal oxygen consumption ($VO_{2max}$) vary greatly (e.g. 0–100%) in response to standardized aerobic training [12, 13]. Likewise, significant variation exists in individual responsiveness to resistance training. Hubal et al. [14] reported that 1-repetition maximum (1RM) strength of the elbow flexors increased between 0 % and 250 % following 12 weeks of training. Similarly, Bamman et al. [15] utilized K-means clustering to categorize participants as either extreme, moderate, or low responders to a resistance training regimen. These authors demonstrated that, despite similar adherence to a 16 week resistance training programme, mean changes in muscle fibre size among response clusters varied from 0 % to 60 %.

Certainly, an evaluation of the mean change in each of these variables indicates a strong, positive impact of exercise training. However, closer evaluation reveals the need for improved strategies for many individuals. Such disparities in training responsiveness are likely very common; however, they are rarely reported. Future trials would be strengthened by supplementing the group data in study publications with individual participant responses. For example, Church et al. recently reported changes in body mass among 411 overweight or obese women who participated in the Dose-Response to Exercise in postmenopausal

Women (DREW) study [16]. In addition to the mean changes in body mass by intervention group, these authors displayed the change in body mass for each study participant (Figure 1). Such depictions efficiently provide important information regarding the variability in participant responses for a given study outcome.

Proper consideration of such variability is critical to establish clinical meaningfulness as clinicians and scientists often assume that if the mean effect of an intervention is less that that traditionally considered minimally important, then the intervention has no effect [17]. However, the intervention may in fact be beneficial for many individuals. For example, walking speed is a clinically important performance characteristic among older adults and prior studies have identified 0.05 m/s as a minimally important improvement following an intervention [18, 19]. Hypothetically, if a particular intervention given to 100 older adults resulted in a mean improvement of 0.04 m/s, it might be considered to be clinically ineffective. However, consider the situation in which 40 of the participants improved their walking speed by 0.10 m/s while walking speed was unchanged in the remaining 60 (Figure 2). While this scenario would indeed result in a mean improvement of only 0.04 m/s, it would have a tremendous positive impact on a significant proportion of individuals. While this is certainly an extreme and possibly unrealistic example, it highlights the potential for mean improvement to be misleading if examined in isolation. Indeed, evaluation of the individual participant data might reveal much more information than simply looking at the group-level data.

### 2.2 Identify Sources of Variability in Exercise Responsiveness

The preceding example also highlights the fact that some individuals may have a non-existent or negative response to an intervention that is beneficial to other group members. Recently, some investigators have explored such variability in exercise responsiveness by categorizing individuals as either ‘responders’ or ‘non-responders’ to an exercise training programme based on change in a given outcome measure. Indeed, further understanding of the heterogeneity in exercise responsiveness –that is ‘kinesio-dynamics’ – is an important goal, although challenges certainly exist. One challenge may be the responder/non-responder concept itself as these designations may be misleading as, for any given physiological construct, responses to exercise are likely not binary but rather graded in nature [20]. As such, Booth and Laye [21] recently suggested that one of the major challenges for exercise scientists in coming years will be how to address the wide interindividual variability in the change of a given physiological adaptation to an identical exercise intervention. Given this typically graded nature of adaptation, these authors claim that meeting this challenge will require a shift to alternate terminology such as ‘high and low sensitivity’. However, even this designation may need further consideration as recent evidence has even identified a portion of individuals who experience adverse metabolic responses to exercise [22]. Still, these are important concepts given that the observation of exercise-derived changes in any physiological construct likely depends on multiple factors including the chosen outcomes, study population and exercise stimulus (e.g. mode, frequency, duration, etc.).

Multiple sources of variability create another challenge in identifying personalized training regimens. Interindividual differences in genetics, disease, lifestyle and daily environment are all potential modulators of exercise responsiveness. Although numerous individual studies are available that support this concept, no systematic approach has synthesized these data to produce a consistent literature base for any given trait or response variable. For instance, in recent years, investigators have become keenly interested in genetic contributions to exercise responsiveness to exercise. Indeed, numerous studies have investigated the association of individual candidate genes with various physiological responses to exercise. However, to the authors’ knowledge only two studies to date – the HERITAGE family study

[23, 54] and the FAMuSS (functional single nucleotide polymorphisms associated with muscle size and strength) study [24] – have been conducted with the express purpose of broadly and comprehensively addressing the causes of heterogeneity in responsiveness to exercise training. Certainly, the relative paucity of firm conclusions from genetic studies is due in part to the massive expense of conducting chronic studies with sample sizes large enough to detect genome-wide significance. However, even candidate gene studies have been limited by dramatic interstudy variation in study populations and outcomes. These studies are also limited by the fact that they are largely unable to evaluate the multitude of interactions that may occur between involved genes and their protein products [25]. Such limitations have, to date, impeded the synthesis of data regarding the effects of various phenotypic characteristics. Dedicated research programmes investigating consistent study populations and response outcomes are warranted to provide a more complete literature in this area.

An additional strategy for accurately identifying response variability will be to consider a wide range of study outcomes. As mentioned previously, some authors have suggested that some individuals are non-responsive to various training interventions. Without deeper inspection, the aforementioned evidence suggesting that some individuals exhibit no changes in aerobic capacity or muscle growth in response to training appears to validate this suggestion. However, one must consider that while exercise interventions may produce a cohort of non-responders for a certain measured variable, other physiological variables in the non-respondent group may be improved. For instance, the ‘non-responders’ reported in Bamman et al. [15] who did not achieve muscle hypertrophy, may still have exhibited an increase in lower-body strength. Similarly, Bouchard and Rankinen [11] measured other study outcomes beyond increases in $VO_{2max}$ including changes in high-density lipoprotein cholesterol as well as systolic blood pressure and heart rate responses to submaximal exercise. While results were not reported as such, it is likely that some who did not exhibit increases in $VO_{2max}$ experienced improvements in other measured outcomes. These are merely two examples that highlight a fundamental point regarding exercise training: for a standard training programme all individuals will not obtain equal benefits with respect to a single outcome measure, but, all individuals will almost assuredly obtain some health benefit. Accordingly, exercise appears to be far more beneficial to one’s health than is typically observed by the measurement of traditional risk factors alone [26]. Therefore, a wide range of response outcomes is critical for evaluating the full efficacy of the intervention on participant health.

### 2.3 Investigate Exercise Dosing

Design of studies to investigate exercising dosing is another important approach to developing tailored exercise strategies. In this regard, those who have low sensitivity to a generalized exercise prescription may simply need a greater exercise stimulus (i.e. volume, intensity, etc.). To investigate this possibility, the STRRIDE (Studies of Targeted Risk Reduction Interventions through Defined Exercise) study examined the broad-spectrum efficacy of an eight-month exercise programme. STRRIDE include the following three study groups: (1) high volume of vigorous-intensity exercise equivalent to 32 km of jogging per week; (2) low volume of vigorous-intensity exercise equivalent to 32 km of jogging per week; and (3) low volume of moderate-intensity exercise equivalent to 32 km of walking per week. Notably, the high-volume/vigorous-intensity group experienced the greatest increase in lean body mass while demonstrating the greatest losses in bodyweight and fat mass over the 8-month intervention [27]. Furthermore, this same group experienced the greatest increase in absolute $VO_{2max}$ (~16%), compared to the low-volume/vigorous-intensity (~10%) groups and low-volume/moderate-intensity (~6%) groups [28]. Finally, STRRIDE

investigators also reported dose-dependent improvements in insulin sensitivity [29], visceral adiposity [30] and blood lipids [31].

STRRIDE and similar studies have firmly established that exercise has dose-dependent effects on various health outcomes [16, 20, 27, 29–33]. However, studies are also needed to determine the effects of varying doses of exercise in low-sensitivity individuals. For example, Sisson et al. provided a strong example of such a study in their recent analysis of the DREW study [20]. These authors' aimed to detect predictors of $VO_{2max}$ non-responsiveness following cardiorespiratory endurance training. Using logistic regression, the authors concluded that women who were younger, less fit and exercised more had greater odds of improving their fitness with training. Notably, the authors concluded that the most important finding of this study was that greater volumes of exercise were associated with a lower probability of being a non-responder.

In addition to studies investigating the efficacy of differing doses of exercise, future studies are needed to identify low-sensitivity individuals among varied populations and in response to varied training regimens. Once these individuals are identified, subsequent investigations can evaluate the efficacy of altering the frequency, volume, mode and/or intensity of training among these individuals (Figure 3). For example, Bickel et al. [32] reported that following a 16-week resistance training programme that induced muscle hypertrophy, a reduction to one-ninth of the original training dose was sufficient to maintain muscle mass in young adults. However, even one-third of the original dose was insufficient to maintain hypertrophy gains in older adults. These data clearly demonstrate that age is an important factor influencing the dose-responsiveness to resistance training with respect to myofibre size. It should, however, be noted that muscle strength was largely maintained by older adults, even among those receiving the lowest exercise dose. This finding reiterates the need to consider a wide range of outcomes to accurately reflect the full utility of a particular training regimen.

### 2.4 Identify Multimodal Interventions

Potential strategies to enhance the efficacy of exercise also include the use of adjuvant therapies. In recent years, authors have highlighted the potential synergism of exercise with other pharmacological and non-pharmacological therapies [21, 34]. According to Kitzman, research studies that seek to isolate the effects of an exercise training intervention are likely to underestimate the full range of potential benefits of training [34]. Others have also proposed that exercise may be used to stimulate certain adaptations to pharmaceuticals that may not be observed in response to the drug alone [21]. For example, an oral peroxisome proliferator-activated receptor delta agonist was shown to improve exercise tolerance in mice only when combined with exercise [35]. Similarly, angiotensin converting enzyme (ACE) inhibitors appear to potentiate exercise-mediated improvements in physical performance among aged rats and humans [36–38]. Furthermore, Huffman et al. [39] reported that overweight and dyslipidaemic women taking hormone replacement therapy (HRT) had greater improvements in insulin sensitivity following aerobic training than women not using HRT. These and similar findings suggest that the investigation of multimodal therapies is certainly promising and should be considered an essential step in moving the field forward.

To this end, future research is needed to determine if other commonly used medications (HMG-CoA reductase inhibitors [statins] may be prime candidates) have pleiotropic effects when combined with exercise. Such findings could have strong implications not only for the improvement of exercise outcomes, but also for the cost/benefit ratio of medication prescription and usage. Evaluation of such interactions may occur in trials specifically designed to evaluate the additive effect of the adjuvant to exercise responsiveness or

secondarily in large-scale trials evaluating the efficacy of a relevant medication on specific health outcomes. In the latter example, exercise scientists should encourage investigators to include some assessment of physical activity, preferably using objective measures (e.g. accelerometers or pedometers), to provide some ability to assess interactions between medication usage and physical activity levels.

Once identified, these multimodal therapies may indeed be capable of enhancing the efficacy of exercise for low-sensitivity individuals. However, benefits such as reduced time needed for training may also be possible for high-sensitivity individuals. This point is quite significant given that perceived time constraint is a primary barrier to exercise participation [40]. Such targeted interventions are likely to combine a nutritional or pharmaceutical therapy with chronic exercise training. For example, recent randomized controlled trials have demonstrated that dietary restriction significantly enhances the effects of exercise on the physical function of obese and overweight older adults [41–44]. Notably, these interventions were tailored specifically for obese older adults as dietary restriction is contraindicated for non-obese seniors [45]. This multimodal intervention is a prime example of how the efficacy of exercise was optimized by considering the phenotypical and environmental uniqueness of this group as well as the targeted outcome.

Numerous other potential adjuvant therapies exist that may be useful for enhancing the efficacy of exercise among most individuals or particular subpopulations. To date, studies exist that have investigated the effects of interventions that utilize nutritional, pharmacological, neurocognitive, mechanical or environmental strategies to optimize the beneficial effects of exercise. Briefly, potential interventions that have been investigated to date include dietary restriction, high-protein diets, testosterone and/or dehydroepiandrostenodione supplementation, ACE inhibitors, blood-flow restricted exercise, split-belt or harnessed treadmill training, eccentrically biased resistance training, home- and community-based exercise, and use of exercise tasks that mimic daily activities. Although an exhaustive discussion of the literature related to each of these interventions is beyond the scope of this work, each therapy has, to date, been proposed as a potentially efficacious adjuvant to exercise for some population of individuals. Future data will indicate just how useful these interventions are for persons of differing genetic, phenotypical and environmental backgrounds.

### 2.5 Increase Clinical Relevance

The aforementioned strategies are critical for the development of personalized exercise regimens. However, additional steps will be needed to implement and disseminate these strategies once identified. One such important step will be to increase the clinical relevance of investigations through the use of clinically relevant populations and outcomes. In recent years, demand has increased for clinical research to produce direct evidence of clinical effectiveness due, in large part, to increasing expenditures and high rates of inappropriate care [46, 47]. Physicians and other health professional are influential sources of health information, evidenced by recent study demonstrating increases in patient physical activity participation and fitness following physician counselling [48].

Sadly, however, in 2010, only one of every three doctors even advised their patients to engage in exercise or physical activity [49]. Almost assuredly, far fewer took an active counselling role in prescribing exercise. Although speculative, exercise prescription by healthcare professionals may be increased by a greater accumulation of studies, which indicate beneficial effects of exercise on patient populations and outcomes that are within their scope of practice. Many exercise training studies are designed to evaluate the physiological effects of a given paradigm among the healthiest segment of the population. While these studies are certainly informative, a more significant public health benefit will be

provided by evaluating the paradigm in those most likely to obtain clinically meaningful benefits.

Accordingly, exercise scientists may be wise to consider the principles of practical clinical trials [47] in designing studies. Adherence to these principles includes (1) selecting clinically-relevant interventions to compare; (2) a diverse study population; (3) recruiting from heterogenous population settings; and (4) collecting data on a broad range of health outcomes. While exercise studies may not be able to incorporate all aspects unless they are phase III trials, these principles provide important concepts for improving the clinical relevance of conducted studies. For example, Church et al. [50] compared the efficacy of aerobic training, resistance training or a combination of the two, on haemoglobin A1c ($HBA_{1c}$) levels in persons with type 2 diabetes mellitus. This study demonstrated that only the combination of the two modalities was successful at improving $HBA_{1c}$ levels. By evaluating clinically relevant interventions and outcomes, studies such as this have important implications for clinical practice. In our opinion, this approach is important for our future ability to tailor exercise prescriptions to individual patients.

## 3 Future Perspectives

To date, personalized medicine has been primarily concerned with understanding heterogeneity in drug responsiveness. However, in our opinion, it is time to begin considering preventive medicine strategies such as exercise within a broader scope of personalized care [51]. Just as medical decision making should not made without considering an individual's physical condition and personal history, so should it be for prescribing exercise training. However, we certainly recognize that several challenges exist in making this goal a reality.

Primary among these is the ability to stimulate participation in exercise training programmes. As noted in the introduction, our collective ability to stimulate participation in traditional programmes has been poor to say the least. In our opinion, the personalization of exercise prescription has potential to improve this level of participation in several ways. First and foremost, an enhanced engagement of physicians may increase patients' awareness of the seriousness of inactivity. The promotion of physical activity by Government agencies and educational movements such as the 'Exercise is Medicine' campaign by the American College of Sports Medicine have provided an important start to raising awareness of the importance of exercise. However, we must go further to promote more than just a general awareness of the benefits of exercise, as the lack of physical activity continues to be a primary contributor to the development of metabolic disorders and premature death [52]. To this end, Joyner [53] recently called for deconditioning to be recognized as a medical diagnosis. He claims that the use of inactivity as a medical diagnosis may be needed to stimulate physician familiarity with the principles and full benefits of exercise training. From a scientific perspective, we believe that the principles proposed in the present work will first need to be widely incorporated by scientists for such a change in medical practice to occur.

In our view, another primary benefit of these research strategies will be the identification of tailored exercise strategies for targeted outcomes and specific population groups. Primary barriers to exercise often include perceived time constraints or lack of desired results. Future research related to the personalized aspects of training responsiveness has the potential to not only enhance the efficacy of training but to also minimize the required time commitment. Theoretically, time-efficient training programmes could be developed that target specific physiological outcomes or that promote overall health for target populations. To achieve this objective, however, more information is needed regarding the source of

heterogeneity in responses to exercise. Rather than viewing heterogeneity as a nuisance, we, as scientists, should view it as an opportunity to understand how to better target these interventions. Such knowledge will assist in identifying potentially efficacious adjuvants for particular groups. Furthermore, a broader physiological understanding of factors influencing exercise responsiveness will inform the conduct of clinical trials designed to test these strategies on clinically relevant outcomes. Reflexively, these trials can support further biological understanding and clinical relevance by considering study results from the participant as well as group perspective.

In summary, we provided here suggestions for enhancing the collective ability of scientists to interpret findings of exercise training studies in the context of personalized medicine. Undoubtedly, however, this framework is merely a small step toward making personalized exercise prescriptions a reality. We hope that exercise scientists will take these suggestions and build upon them in their future research. Certainly, enhanced dialogue and idea exchange is needed for exercise to become an accepted component of personalized care. We anticipate and look forward to the continued development of this area in coming years.

## Acknowledgments

Thomas Buford's work on this project was partially supported by the University of Florida Older Americans Independence Center (NIH 1P30AG028740) and Clinical and Translational Science Institute (NIH KL2TR000065). The remaining authors did not receive funding that directly contributed to this project.

## References

1. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007; 39(8):1435–45. [PubMed: 17762378]
2. DHHS. [Accessed 25 Jun 2012] 2008 physical activity guidelines for Americans [online]. http://www.health.gov/paguidelines/pdf/paguide.pdf
3. Office of the Surgeon General, U.S. Department of Health and Human Services. [Accessed 25 Jun 2012] The surgeon general's call to action plan to prevent and decrease overweight and obesity. 2001. [online]. http://www.surgeongeneral.gov/library/calls/obesity/CalltoAction.pdf.pdf
4. World Health Organization. Global recommendations on physical activity for health. Geneva: WHO Press; 2010.
5. Pleis, JR.; Ward, BW.; Lucas, JW. [Accessed 25 Jun 2012] Summary health statistics for U.S. adults: national health interview survey, 2009. National Center for Health Statistics. 2010. Report No.: 10 [online]. http://www.cdc.gov/nchs/data/series/sr_10/sr10_249.pdf
6. Troiano RP, Berrigan D, Dodd KW, et al. Physical activity in the united states measured by accelerometer. Med Sci Sports Exerc. 2008; 40(1):181–8. [PubMed: 18091006]
7. Ginsburg GS, Willard HF. Genomic and personalized medicine: foundations and applications. Transl Res. 2009; 154(6):277–87. [PubMed: 19931193]
8. Obama, B. [Accessed 25 Jun 2012] Genomics and personalized medicine act of 2007 [online]. http://olpa.od.nih.gov/legislation/110/pendinglegislation/genomics_personalized.asp
9. Institute of Medicine. Initial national priorities for comparative effectiveness research. Washington, DC: The National Academies Press; 2009.
10. Bouchard, C. Human adaptability may have a genetic basis. In: Landry, F., editor. Health risk estimation, risk reduction, and health promotion. Ottawa: Canadian Public Health Association; 1983. p. 463-76.
11. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. Med Sci Sports Exerc. 2001; 33(6 Suppl):S446–51. discussion S452–3. [PubMed: 11427769]
12. Bouchard C. Individual differences in the response to regular exercise. Int J Obes Relat Metab Disord. 1995; 19(Suppl 4):S5–8. [PubMed: 8581095]

13. Kohrt WM, Malley MT, Coggan AR, et al. Effects of gender, age, and fitness level on response of $VO_2$max to training in 60–71 yr olds. J Appl Physiol. 1991; 71(5):2004–11. [PubMed: 1761503]
14. Hubal MJ, Gordish-Dressman H, Thompson PD, et al. Variability in muscle size and strength gain after unilateral resistance training. Med Sci Sports Exerc. 2005; 37(6):964–72. [PubMed: 15947721]
15. Bamman MM, Petrella JK, Kim JS, et al. Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. J Appl Physiol. 2007; 102(6):2232–9. [PubMed: 17395765]
16. Church TS, Martin CK, Thompson AM, et al. Changes in weight, waist circumference and compensatory responses with different doses of exercise among sedentary, overweight postmenopausal women. PLoS One. 2009; 4(2):e4515. [PubMed: 19223984]
17. Guyatt GH, Juniper EF, Walter SD, et al. Interpreting treatment effects in randomised trials. BMJ. 1998; 316(7132):690–3. [PubMed: 9522799]
18. Perera S, Mody SH, Woodman RC, et al. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc. 2006; 54(5):743–9. [PubMed: 16696738]
19. Kwon S, Perera S, Pahor M, et al. What is a meaningful change in physical performance? Findings from a clinical trial in older adults (the LIFE-P study). J Nutr Health Aging. 2009; 13(6):538–44. [PubMed: 19536422]
20. Sisson SB, Katzmarzyk PT, Earnest CP, et al. Volume of exercise and fitness nonresponse in sedentary, postmenopausal women. Med Sci Sports Exerc. 2009; 41(3):539–45. [PubMed: 19204597]
21. Booth FW, Laye MJ. The future: genes, physical activity and health. Acta Physiol (Oxf). 2010; 199(4):549–56. [PubMed: 20345416]
22. 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(5):e37887. [PubMed: 22666405]
23. Bouchard C, Leon AS, Rao DC, et al. The HERITAGE family study: aims, design, and measurement protocol. Med Sci Sports Exerc. 1995; 27(5):721–9. [PubMed: 7674877]
24. Thompson PD, Moyna N, Seip R, et al. Functional polymorphisms associated with human muscle size and strength. Med Sci Sports Exerc. 2004; 36(7):1132–9. [PubMed: 15235316]
25. Noble D. Differential and integral views of genetics in computational systems biology. Interface Focus. 2011; 1(1):7–15. [PubMed: 22419970]
26. Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. J Physiol. 2009; 587(Pt 23):5551–8. [PubMed: 19736305]
27. Slentz CA, Duscha BD, Johnson JL, et al. Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE: a randomized controlled study. Arch Intern Med. 2004; 164(1):31–9. [PubMed: 14718319]
28. Duscha BD, Slentz CA, Johnson JL, et al. Effects of exercise training amount and intensity on peak oxygen consumption in middle-age men and women at risk for cardiovascular disease. Chest. 2005; 128(4):2788–93. [PubMed: 16236956]
29. Houmard JA, Tanner CJ, Slentz CA. Effect of the volume and intensity of exercise training on insulin sensitivity. J Appl Physiol. 2004; 96(1):101–6. [PubMed: 12972442]
30. Slentz CA, Aiken LB, Houmard JA, et al. Inactivity, exercise, and visceral fat. STRRIDE: a randomized, controlled study of exercise intensity and amount. J Appl Physiol. 2005; 99(4):1613–8. [PubMed: 16002776]
31. Slentz CA, Houmard JA, Johnson JL, et al. Inactivity, exercise training and detraining, and plasma lipoproteins. STRRIDE: a randomized, controlled study of exercise intensity and amount. J Appl Physiol. 2007; 103(2):432–42. [PubMed: 17395756]
32. Bickel CS, Cross JM, Bamman MM. Exercise dosing to retain resistance training adaptations in young and older adults. Med Sci Sports Exerc. 2011; 43(7):1177–87. [PubMed: 21131862]
33. Kesaniemi YK, Danforth E Jr, Jensen MD, et al. Dose-response issues concerning physical activity and health: an evidence-based symposium. Med Sci Sports Exerc. 2001; 33(6 Suppl):S351–8. [PubMed: 11427759]

34. Kitzman DW. Exercise training in heart failure with preserved ejection fraction: beyond proof-of-concept. J Am Coll Cardiol. 2011; 58(17):1792–4. [PubMed: 21996392]
35. Narkar VA, Downes M, Yu RT, et al. AMPK and PPARdelta agonists are exercise mimetics. Cell. 2008; 134(3):405–15. [PubMed: 18674809]
36. Habouzit E, Richard H, Sanchez H, et al. Decreased muscle ACE activity enhances functional response to endurance training in rats, without change in muscle oxidative capacity or contractile phenotype. J Appl Physiol. 2009; 107(1):346–53. [PubMed: 19407247]
37. Carter CS, Marzetti E, Leeuwenburgh C, et al. Usefulness of preclinical models for assessing the efficacy of late-life interventions for sarcopenia. J Gerontol A Biol Sci Med Sci. 2012; 67(1):17–27. [PubMed: 21636833]
38. Buford TW, Manini TM, Hsu FC, et al. Angiotensin-converting enzyme inhibitor use by older adults is associated with greater functional responses to exercise. J Am Geriatr Soc. 2012; 60(7): 1244–52. [PubMed: 22726232]
39. Huffman KM, Slentz CA, Johnson JL, et al. Impact of hormone replacement therapy on exercise training-induced improvements in insulin action in sedentary overweight adults. Metabolism. 2008; 57(7):888–95. [PubMed: 18555828]
40. Sherwood NE, Jeffery RW. The behavioral determinants of exercise: implications for physical activity interventions. Annu Rev Nutr. 2000; 20:21–44. [PubMed: 10940325]
41. Villareal DT, Chode S, Parimi N, et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med. 2011; 364(13):1218–29. [PubMed: 21449785]
42. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the arthritis, diet, and activity promotion trial. Arthritis Rheum. 2004; 50(5):1501–10. [PubMed: 15146420]
43. Anton SD, Manini TM, Milsom VA, et al. Effects of a weight loss plus exercise program on physical function in overweight, older women: a randomized controlled trial. Clin Interv Aging. 2011; 6:141–9. [PubMed: 21753869]
44. Rejeski WJ, Brubaker PH, Goff DC Jr, et al. Translating weight loss and physical activity programs into the community to preserve mobility in older, obese adults in poor cardiovascular health. Arch Intern Med. 2011; 171(10):880–6. [PubMed: 21263080]
45. Miller SL, Wolfe RR. The danger of weight loss in the elderly. J Nutr Health Aging. 2008; 12(7): 487–91. [PubMed: 18615231]
46. Lauer MS, Collins FS. Using science to improve the nation's health system: NIH's commitment to comparative effectiveness research. JAMA. 2010; 303(21):2182–3. [PubMed: 20516419]
47. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. JAMA. 2003; 290(12):1624–32. [PubMed: 14506122]
48. Petrella RJ, Lattanzio CN, Shapiro S, et al. Improving aerobic fitness in older adults: effects of a physician-based exercise counseling and prescription program. Can Fam Physician. 2010; 56(5):e191–200. [PubMed: 20463260]
49. Barnes, PM.; Schoenborn, CA. [Accessed 25 Jun 2012] Trends in adults receiving a recommendation for exercise or other physical activity from a physician or other health professional. 2012. Report No.: 86 [online]. http://www.cdc.gov/nchs/data/databriefs/db86.pdf
50. Church TS, Blair SN, Cocreham S, Johannsen N, Johnson W, Kramer K, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2010; 304(20):2253–62. [PubMed: 21098771]
51. Buford TW, Pahor M. Making preventive medicine more personalized: implications for exercise-related research. Prev Med. 2012; 55:34–6. [PubMed: 22588227]
52. Thyfault JP, Booth FW. Lack of regular physical exercise or too much inactivity. Curr Opin Clin Nutr Metab Care. 2011; 14(4):374–8. [PubMed: 21519238]
53. Joyner MJ. Standing up for exercise: should deconditioning be medicalized? J Physiol. 2012; 590(Pt 15):3413–4. [PubMed: 22855052]
54. 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(6):1487–96. [PubMed: 20133430]

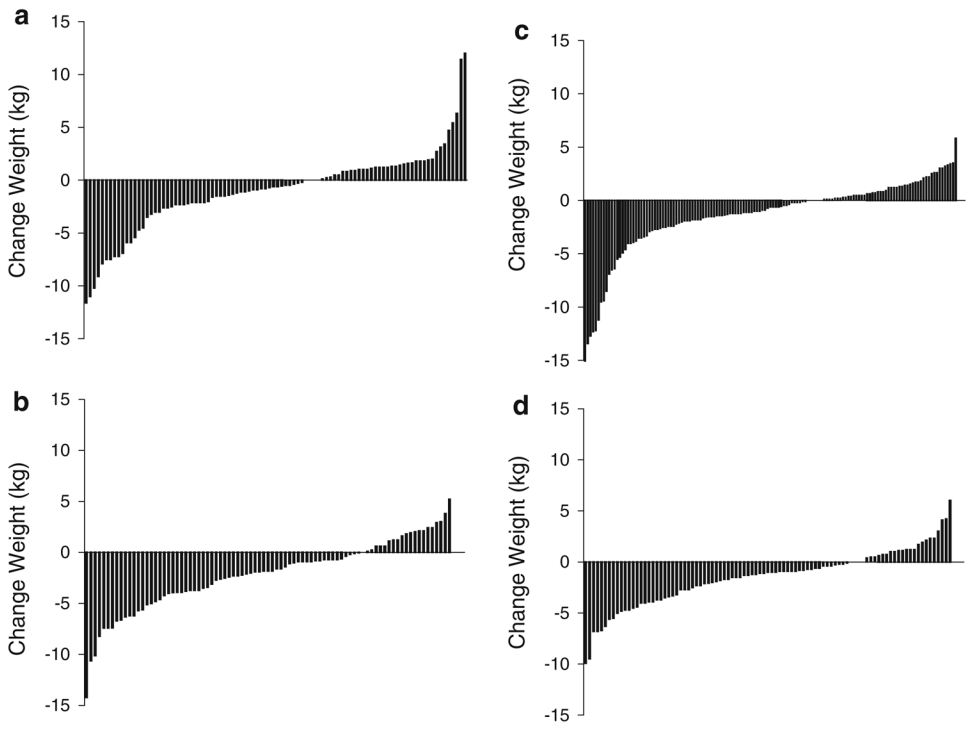


**Fig. 1.**

Demonstration of the feasibility of providing individual participant training responses in study publications. Sections indicate the change in bodyweight of individual study participants (solid bars) in (**a**) a non-exercise control group and in response to three exercise dosing strategies; (**b**) 8 KKW; (**c**) 4 KKW; and (**d**) 12 KKW. These data highlight the interindividual variability of participant responses to a standard training programme. Reproduced from Church et al. [16], under the Open-Access Creative Commons Attribution License. *KKW* kilocalories per week

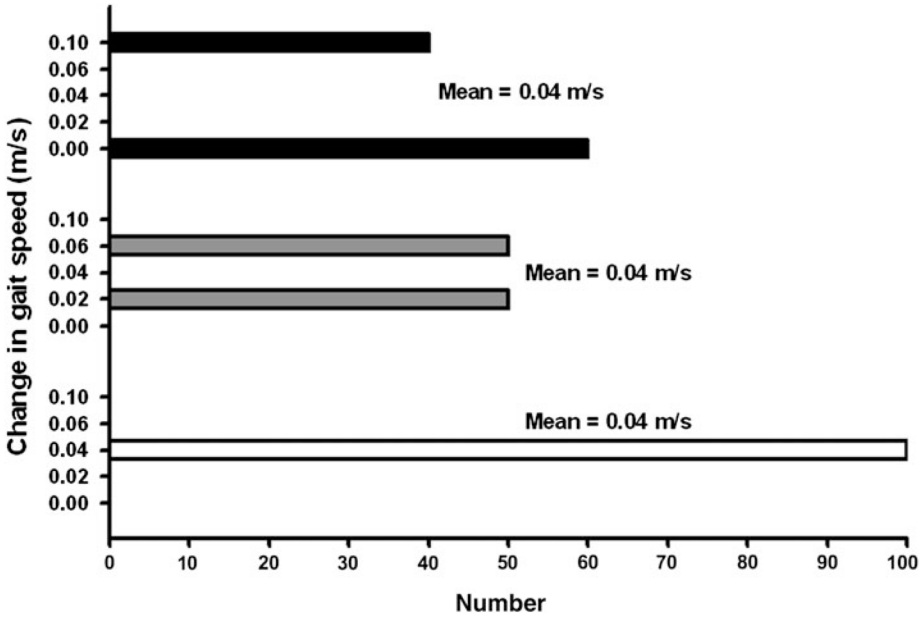


**Fig. 2.**

Hypothetical scenario depicting the differential impact of three supposed interventions on a given outcome despite identical changes in the group mean. The figure depicts a scenario in which 100 older adults are given an intervention to improve usual-paced gait speed. The x-axis depicts the number of individuals with a specific change in gait speed (y-axis) in response to each intervention. This extreme example highlights how simply evaluating the mean response of a group can be misleading with respect to the clinical utility of a given intervention. *N* number

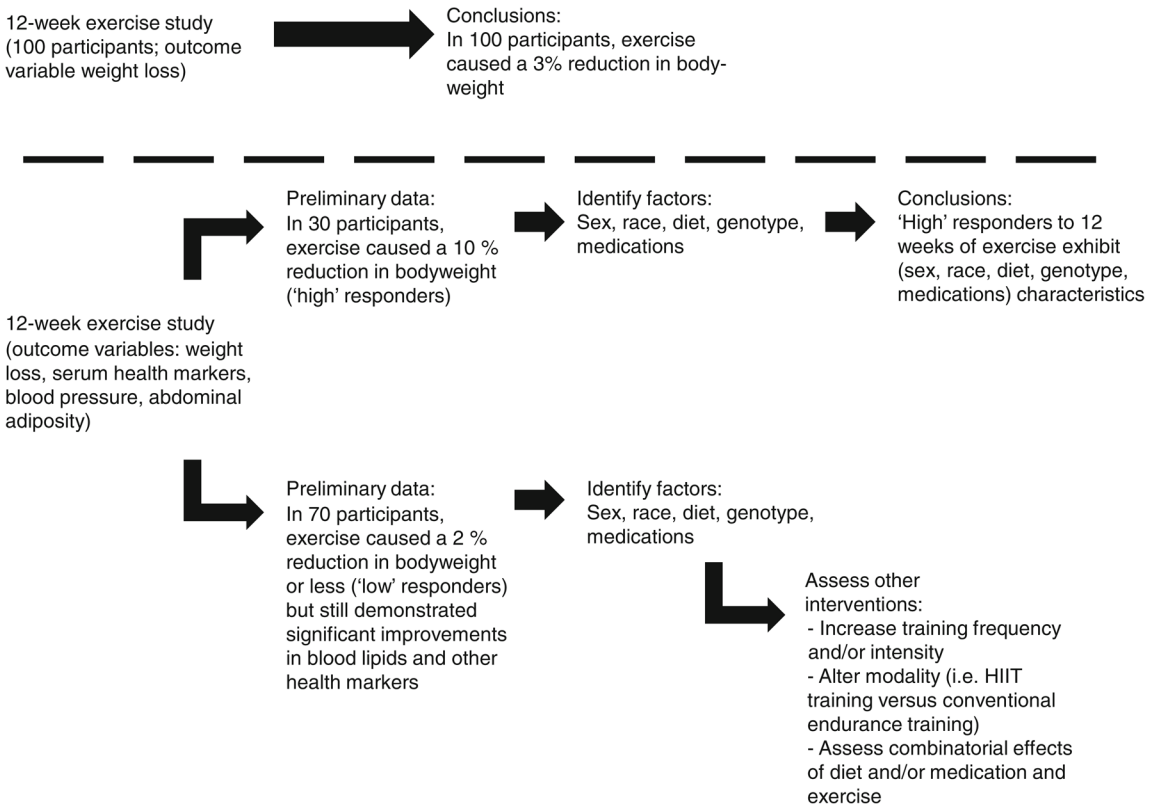


**Fig. 3.**

Conceptual study design framework for investigations designed to evaluate heterogeneity in responsiveness to exercise and identify potential alternative interventions for low-sensitivity individuals. The hypothetical scenario above the dotted line depicts a 'standard' study design in which the efficacy of an exercise intervention on a specific health outcome is evaluated by comparing the mean change in the outcome between groups. The framework below the dotted line depicts a scenario in which the exercise study evaluates multiple health outcomes at the participant level. This approach allows investigators to identify subgroups of individuals who are either 'high or low sensitivity' and provides the framework for follow-up studies to improve efficacy among low-sensitivity individuals. *HIIT* high-intensity interval training