Using response variation to develop more effective, personalized behavioral medicine?: evidence from the Resist Diabetes study

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Abstract

Health behavior interventions have achieved some notable outcomes through generally higher dose interventions with intensive initial phases and long-term, faded contact maintenance phases with attention to mean changes and adherence rates. Interventions may be improved by shifting attention to the very large response variation that is typical for such protocols as exercise with non-, low, moderate, and high responders and even those who show adverse responses. Data from the Resist Diabetes study, which included adults ($N=159$, ages 50–69 years) with prediabetes who were overweight or obese ($BMI\ 25\text{--}39.9\text{ kg/m}^2$) and previously inactive, are presented. The data show a typical pattern of wide variation for changes on a 2-h oral glucose tolerance test (OGTT), defined by blood glucose concentration measured after 2 h following ingestion of 75 g of glucose, lean body mass, fat mass, strength, and blood pressure to the same resistance training protocol within a highly supervised phase and where adherence was high. A personalized behavioral medicine approach could focus on such individual patterns of response variation to tailor and alter additional intervention components, the staging of maintenance interventions, and then determining how to most effectively, and systematically, translate this adaptive intervention approach into practice to potentially achieve more optimal clinical outcomes.

Keywords

Response variation, Personalized behavioral medicine, Clinical outcomes, Health behavior interventions, Tailoring

USUAL HEALTH BEHAVIOR CHANGE INTERVENTION APPROACH

Over the last several decades, most health behavior interventions [1], with a few exceptions [2], have followed a similar pattern [1]. Typically, there is an intensive, high-dose part of an intervention lasting several months (or more [3, 4]) where individually or in groups, or both, people receive considerable attention and support and gain knowledge and self-regulation skills, to change one or multiple behav-

Implications

Policy: Health behavior, lifestyle change programs are essential for reducing the costs and burdens of preventable diseases, but more optimal clinical outcomes may be achieved with personalized behavioral medicine programs that are designed for tailoring based on individual response patterns.

Research: Research within personalized behavioral medicine can focus on how to design health behavior interventions with tailoring and adaptation based on individual response patterns and then translating this new adaptive intervention approach into practice.

Practice: The wide variation in response to most treatment protocols such as exercise with non-, low, moderate, and high responders and even those who experience an adverse response is a key to more personalized behavioral medicine and can be a focus when designing initiation and maintenance phases of interventions requiring alteration and tailoring of adaptive interventions based on individual response to achieve optimal clinical outcomes.

iors. During the intensive part of the intervention, adherence is generally very high and mean clinical outcomes, e.g., weight loss, body composition change, minutes of physical activity per day, or increases in cardiorespiratory fitness and strength, are encouraging, and if sustained, would equate to meaningful disease risk reduction [3, 4]. After the intensive part of the intervention, there is a maintenance phase lasting months or even years [1, 3, 4]. In this phase, personal contact is gradually reduced and other intervention components such as problem solving [1] may be emphasized through some continued personal or other (print, internet, phone apps) interactions. Longer term, theory-based maintenance programs generally reduce

Fig 1 | Frequency distributions of changes in 2-h OGTT from the Resist Diabetes study

relapse, but there often is some erosion of both adherence and overall outcomes during maintenance [1]. The focus throughout is on mean change on key outcomes measures and adherence rates. The overall approach has produced some notable interventions with high public health value such as the Diabetes Prevention Program and the companion Look Ahead program [3, 4]. We propose, however, the approach could be altered (adjusted or modified) and instead of doing “well,” we could do “much better” as far as producing clinical outcomes.

RESPONSE VARIATION

The key alteration in the overall approach is relatively simple. What once was considered “noise” in the outcomes now becomes the focus of a new approach, *personalized behavioral medicine*. The focus is on “response variation,” well-known, but not often appreciated, for example, to an exercise stimulus [5–9]. That is, for any specific exercise stimulus or protocol and with the provision that adherence is high, there is a very wide variation in responsiveness, i.e., “non- and low responders,” “moderate and

high responders,” or “low and high sensitivity” to the stimulus [10]. This has been shown in an amalgamation of different exercise studies [11]. For example, in response to the same resistance training protocol, strength increases can vary from no change in strength to more than doubling strength [7]. What’s more, and of particular concern, is that (1) high responsiveness to one stimulus, e.g., resistance training, on one outcome measure such as strength, may not be associated with responsiveness to the stimulus for another health-related outcome measure such as blood pressure [10]; and (2) about 6–8 % of people exposed to the stimulus will show an *adverse* response [11]. That is, on the appropriate measure for an intervention such as cardiorespiratory fitness for aerobic training, a segment of people actually will show reduced fitness [11]. A caveat is that there are not yet standard definitions for categories of responsiveness.

EXAMPLE

The example and data for response variation are from our Resist Diabetes study [12, 13], with adults

Fig 2 | Frequency distributions of changes in strength (3-RM, chest press) from the Resist Diabetes study

Fig 3 | Frequency distributions of changes in lean body mass from the Resist Diabetes study

($N=159$) 50–69 years old, who are prediabetic [3], have a BMI 25–39.9 kg/m², were previously inactive, and had no additional health concerns (e.g., uncontrolled hypertension) or diseases or musculoskeletal problems. The study was approved by the Institutional Review Board at Virginia Tech., and all participants provided informed consent for all assessment and intervention components of the study. The major aim of the study is to assess the long-term effects of brief resistance training fitting national guidelines (ACSM [14]) to improve glucose metabolism. In the study, there is an intensive 3-month phase where study participants train in a lab/gym, one-on-one with a trainer twice per week. The training unfolds in a social cognitive theory (SCT [15])-based intervention using mastery experiences through trainer modeling, guidance, feedback, and support. In this way, study participants learn to use good form, how to safely exert a high level of effort on each exercise, an essential part of the stimulus [16], and how to progress over time. During the 3-month intensive phase, adherence (attending sessions) was high (91 %). At the end of the phase, there is post-assessment and then participants are ran-

domly assigned, stratified by gender and strength gain, to one of two conditions where participants train on their own in an approved but self-selected community facility: (1) an SCT-based, higher dose 6-month maintenance phase. This featured an extended transition phase to the community facility, then faded personal, nontraining contact and personalized web-based interactions focused on self-regulation procedures (planning, scheduling, tracking, reporting workouts, receiving feedback; problem solving); or (2) standard maintenance involving an abbreviated transition phase, more minimal personal contact and web interactivity, and didactic instruction on self-regulation procedures. Additional details for recruitment, assessment, training, and intervention are available elsewhere [12].

At posttest, there were significant, positive changes (all $p < .01$) on 2-h OGTT, strength (chest press, leg press, 3-RM testing), lean body mass and body fat assessed by dual energy X-ray absorptiometry (DXA), and blood pressure, but no significant ($p < .05$) associations between changes on any pairs of these outcome measures except for changes in chest press and leg press, which were significantly corre-

Fig 4 | Frequency distributions of changes in fat mass from the Resist Diabetes study

Fig 5 | Frequency distributions of changes in systolic blood pressure from the Resist Diabetes study

lated ($r=.263$; $p<.01$). As noted, and as is typical, after posttest, *regardless* of outcomes on a major primary outcome measure, participants were randomly assigned (though stratified by gender and strength gain) to one of two maintenance conditions.

Figures 1, 2, 3, 4, and 5 are histograms showing the frequency distribution of outcomes (change from pretest to posttest) for each of these measures. The very wide response variation on each measure is not unusual, but rather, as noted, typical. It is not attributable to differential adherence which across participants was high. Thus, participants cannot be “blamed” if they were not responsive, because they were adherent and followed the protocol with a trainer. What can be seen for each measure is that there are some very high responders (e.g., gaining ~8.5 kg of lean body mass as assessed by DXA), more usual, modest responders, but clearly for each measure, some participants had no or a negative response. We do not believe a negative response can be described as an adverse response in the absence of an adjustment for measurement error [11]. Some

good responders on one measure were poor responders on other measures. Interestingly, as shown in Fig. 6 and noted above, there was only a low, significant correlation ($r=.263$; $p<.01$) between changes in strength on the chest press and on the leg press, suggesting some specificity of strength by muscle group and not an overall trait. In addition, and detailed elsewhere [17], there were minimal changes across participants during this phase in nutrition or physical activity.

CHANGING THE APPROACH

We emphasize again that our data showing a large variation of response on each outcome measure with little or no association between measures are typical rather than unusual [8]. The 3-month phase with high adherence also is enough time to show an individual’s enduring pattern of responses to a specific stimulus [16]. That is, the early pattern of response is unlikely to be markedly altered without

Fig 6 | The scatter plot shows the distributions for the changes in chest press (3-RM) and leg press (3-RM), which were similar and significantly ($p<.01$) correlated ($r=.263$) but with only 6.7 % of variance accounting for a common “change in strength”

changing the dose of the stimulus (frequency and volume of training). However, there is no overwhelming evidence that a change in dose of conventional resistance training would lead to meaningful differences [16], and the cost may be lower adherence and the inability to recover from training [16]. There are, however, some recent experiments with quite different resistance training stimuli, though still consistent with the size principle of motor unit recruitment [18], that *may* enable non- or low responders to conventional training for glucose metabolism to produce a more positive response [19].

A relevant question that can be asked is: After posttest, should only those participants who showed clinical improvement and were no longer prediabetic be assigned to transition and maintenance? Following guidelines from personalized medicine [10], adaptive interventions [20], and stepped care [21], and what we now can call *personalized behavioral medicine*, other questions can be asked. After posttest, should non- or low responders to resistance training for glycemic control be assigned to a different empirically supported intervention such as dietary change and/or weight loss [3, 4] and then assessed at the end of that intervention for prediabetes status? Should such individuals, however, continue to resistance train given other benefits such as increases in strength and lean body mass? And, perhaps, in the interests of furthering the field, should some participants be assigned to a different exercise stimulus such as interval training? Interval training has produced favorable outcomes for glucose metabolism [22] but is in need of further investigations. After one of these interventions, those people who are no longer prediabetic would then move to transition and maintenance and those remaining prediabetic can then try an additional empirically supported intervention [20].

The overall approach also requires a decision algorithm based on a range of individual outcomes. For example, what would be the next intervention for people who show good responsiveness for 2-h OGTT but now have moved from a normal range in systolic blood pressure to prehypertension or, for that matter, hypertension? Which risk factor is more important than the other? Based on an adverse blood pressure response, should this segment of people cease that particular exercise or continue the specific exercise which is providing some beneficial effects and add another intervention for blood pressure reduction such as the Dietary Approach to Stop Hypertension (DASH) nutrition plan [23]?

The sharp attention to individual clinical outcomes, and not only overall mean outcomes, can reveal non- or low responders to a protocol and adapt the intervention in subsequent components to improve clinical outcomes for more people. The pressing need for lifestyle changes to reduce the costs and burdens of disease risk and premature death [24] amplifies the

need for effective, theory-based [15] behavioral intervention and maintenance approaches [25]. While perhaps underappreciated, the alteration of interventions based on individual responsiveness, a critical aspect of these endeavors, is part of our traditions, for example, in behavior therapy and applied behavior analysis [26]. Using this tradition and stepped care [21], the fields of, adaptive interventions [19], and tailoring and personalization [27] can be integrated into personalized behavioral medicine to produce more beneficial clinical phenotypic outcomes. This is especially the case when it is realized that there likely is a similar wide variation in response to behavioral elements of an intervention such as, for example, how feedback is provided. And, it is clearly possible to provide feedback in different forms with theoretical fidelity [15, 27], for different preferred targets (e.g., specific performance), in real or delayed time, and through different preferred mediums (immediate, visual feedback on a smart phone; delayed print feedback via hard copy).

Wide response variation across measures also points toward another intervention approach, though one not without its costs and problems, and one that also needs tailoring. This approach involves empirically supported multiple behavioral interventions. Given the multiple stimuli appropriate for different conditions and diseases, these interventions may lead to more favorable distributions across key clinical outcome measures [25]. This hypothesis, however, remains one that needs to be tested.

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1. Middleton KM, Patidar SM, Perri MG. The impact of extended care on the long-term maintenance of weight loss: a systematic review and meta-analysis. *Obes Rev*. 2012; 13: 509-517.
2. Kiernan M, Brown SD, Schoffman DE, et al. Promoting healthy weight with "stability skills first": a randomized trial. *J Consult Clin Psychol*. 2013; 81(2): 336-346.
3. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *NEJM*. 2002; 345: 393-403.
4. AHEAD The Look Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *NEJM*. 2013; 369: 145-154.
5. Bouchard C. Individual differences in the response to regular exercise. *Int J Obes Relat Metab Disord*. 1995; 19(4): S5-S8.
6. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Scie Sports Ex*. 2001; 33(6): S446-S451. discussion S452-3.
7. 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: 964-972.
8. Bouchard C, An P, Rice T, et al. Familial aggregation of 'VO2 max response to exercise training: results from the HERITAGE Family Study. *J Appl Physiol*. 1999; 87: 1003-1008.
9. Bouchard C, Rankinen T, Timmons JA. Genomics and genetics in the biology of adaptation to exercise. *Compr Physiol*. 2011; 1(3): 1603-1648. doi:10.1002/cphy.c100059.
10. Buford TW, Roberts MD, Church TS. Toward exercise as personalized medicine. *Sports Med*. 2013; 43: 157-165.
11. 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.
12. Marinik EL, Kelleher S, Savla JT, Winett RA, Davy BM. The Resist Diabetes trial: rationale, design, and methods of a hybrid efficacy/effectiveness intervention trial for resistance training

- maintenance to improve glucose homeostasis in older prediabetic adults. *Contemp Clin Trials*. 2014; 37: 19-42.
13. Eikenberg JD, Savla J, Marinik EL., Pownall J, Baugh ME, Flack KD et al. Prediabetes phenotype influences improvements in glycemia with resistance training. Paper presented at the annual meeting of The Obesity Society, 2013, Atlanta, GA.
14. ACSM's Guidelines for Exercise Testing and Prescription. Ninth edition. Philadelphia. Lippincott, Williams & Wilkins. 2013.
15. Bandura A. Health promotion by social cognitive means. *Health Educ Behav*. 2004; 31: 143-164.
16. Phillips SM, Winett RA. Uncomplicated resistance training and health-related outcomes: evidence for a public health mandate. *Curr Sports Med Rep*. 2010; 9: 208-213.
17. Halliday TM, Clark AG, Marinik EL, Baugh ME, Flack KD, Savla J et al. Spontaneous dietary intake modification in response to resistance training: findings from the Resist-Diabetes Study. Presented at the meeting of the American College of Sports Medicine, 2013, Indianapolis, IN.
18. Carpinelli RN. The size principle and a critical analysis of the unsubstantiated heavier-is-better recommendation for resistance training. *J Ex Sci Fitness*. 2008; 6: 67-85.
19. Van Roie E, Delecluse C, Coudyzer W, Boonen S, Bautman I. Strength training at high versus low external resistance in older adults: effects on muscle volume, muscle strength, and force/velocity characteristics. *Exp Gerontol*. 2013; 48: 1351-1361. doi:10.1016/j.exger.2013.08.010.
20. Shani IN, Qian M, Almirall D, et al. Experimental design and primary data analysis methods for comparing adaptive interventions. *Psychol Methods*. 2012; 17: 457-477.
21. Jakicic JM, Tate DF, Lang W, et al. Effect of a stepped-care intervention approach on weight loss in adults: a randomized clinical trial. *JAMA*. 2012; 307: 2617-2626.
22. Tjønnå AE, Leinan IM, Bartnes AT, et al. Low- and high-volume of aerobic interval training improves maximal oxygen uptake to the same extent over a 10-week period in healthy men. *PLoS One*. 2013; 8: e65382.
23. U.S. Department of Health and Human Services, NIH, NHLBI. Your guide to lowering your blood pressure with DASH: DASH (Dietary Approaches to Stop Hypertension) eating plan—lower your blood pressure. NIH publication no. 06-4082, NHLBI/NIH, Bethesda; 2006.
24. Goodarz, D., Ding, E.L., Mozaffarian D, Taylor B., Rehm J., Murray, CJL et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic factors. *PLOS Med*. 2009; 6 (4): (4/28/09)
25. Winett RA, Davy BM, Marinik E, et al. (online first). Developing a new treatment paradigm for disease prevention and healthy aging. *Transl Behav Med*.
26. Kazdin AE. Behavior Modification in Applied Settings. 6th ed. Belmont, CA: Wadsworth; 2001.
27. Williams DM, Papandonatos GD, Jennings EG, et al. Does tailoring on additional theoretical constructs enhance the efficacy of a print-based physical activity promotion intervention? *Health Psychology*. 2011; 30: 432-441. doi:10.1037/a0023084.
27. Williams DM, Papandonatos GD, Jennings EG, et al. Does tailoring on additional theoretical constructs enhance the efficacy of a print-based physical activity promotion intervention? *Health Psychology*. 2011; 30: 432-441. doi:10.1037/a0023084.