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Precision in Promoting Physical Activity and Exercise With the Overarching Goal of Moving More

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ABSTRACT

Physical inactivity is strongly associated with an unfavorable health profile, increasing an individual's risk for developing cardiovascular disease. Initiating a regular exercise routine contributes to improvements in cardiorespiratory fitness, body composition, resting blood pressure, blood glucose, and circulating lipoproteins. However, the extent to which positive changes occur come with significant inter-individual variability within intervention groups; non-responders and responders have been commonly identified across populations, highlighting that not all exercise regimens are universally effective in all individuals and should therefore not be treated as a "one-size fits all" prescription. Recent studies have therefore emphasized reporting the quantity of participants favorably and meaningfully "responding" to varying amounts and intensities of exercise, thereby presenting the opportunity to view exercise prescription in the context of precision medicine. This review will address the impact of varying amounts and intensities of physical activity and exercise, highlighting their impact on key health metrics.

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Physical activity (PA) broadly encompasses all physical movement performed above the resting state and may include purposeful (i.e., aerobic/resistance exercise), occupational, household, active transportation, and/or recreation. Sedentary time and physical inactivity have been directly associated with low cardiorespiratory fitness (CRF), hypertension, diabetes, hyperlipidemia, and premature death. The degree to which health benefits are acquired depend on the frequency, intensity, time, or more comprehensively, the volume of PA performed[1,2]. The expansive literature documenting the health benefits achieved through PA has empirically demonstrated that greater volumes of activity contribute to a progressively higher degree of protection from premature cardiovascular disease (CVD), certain types of cancers, metabolic disorders, obesity, dementia, and morbidity.[3] Accordingly,

Abbreviations and Acronyms: BMI, Body Mass Index; BP, Blood pressure; CRF, Cardiorespiratory Fitness; CVD, Cardiovascular Disease; DBP, Diastolic Blood Pressure; HAHI, High-Amount, High-Intensity; HALI, High-Amount, Low-Intensity; HDL, High Density Lipoprotien; LALI, Low-Amount, Low-Intensity; LAMI, Low-Amount, Moderate-Intensity; LDL, Low Density Lipoprotien; NCDs, Noncommunicable diseases; PA, Physical Activity; SBP, Systolic Blood Pressure; STRIDDE, Studies of a targeted risk reduction intervention through defined exercise; TG, Triglycerides; VLDL, Very Low Density Lipoprotien; VO_2, Oxygen Consumption.

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adopting a physically active lifestyle to combat the development of noncommunicable diseases (NCDs) has been a key strategy promoted by health organizations.[4–9]

Trials that investigate the effects PA in improving common CVD risk factors, CRF, and other markers of health and wellbeing, consistently show favorable *group* changes in a health marker of interest (i.e., mean improvement in a cohort receiving a PA intervention).[10] These reported mean improvements, while often statistically significant and clinically important, may lead to the incorrect assumption that the application of evidence based exercise regimens to combat CVD risk factors will result in similar improvements in one or more health outcomes of interest in all individuals receiving the intervention. However, pivotal findings from the HEalth, Risk factors, exercise Training And GEnetics (HERITAGE) study convincingly highlight inter-individual responses to similar exercise volumes. Notably, CRF responses ranged from 0 to 50% after participating in a 20 week exercise intervention[11]. Familial traits were determined to influence CRF levels by 50% and changes to a PA intervention by roughly 25%. However, only when examining individual responses to PA interventions was it clear that not all individuals responded to a similar degree; some with no response at all. Corroborations of these findings in recent investigations[12] shed light on the need to gain a greater understanding of individual responses to various amounts and intensities of exercise in order to enhance the ability to prescribe PA and exercise in the context of precision medicine (i.e., take an individualized approach).[13]

With respect to traditional CVD risk factors (i.e., body weight/composition, hypertension, elevated blood glucose, hyperlipidemia), regular PA and exercise has been shown to favorably modify each to a variable degree, leading to conflicting reports of change in response to similar interventions. Moreover, an individual's genetic phenotype significantly contributes to variability in the response to exercise training.[14] Recent interventions have advanced our understanding of inter-individual responses to exercise, providing evidence of a greater potential to apply exercise prescriptions as a form of precision medicine.[12,15–19] This review will highlight key investigations assessing the responses of commonly assessed CVD risk factors to varying amounts and intensities of exercise.

The volume of PA necessary to enhance CRF

CRF is widely recognized as a robust prognostic measure for the future development of NCDs[20] and has been endorsed by the American Heart Association as a metric that should be treated as a vital sign.[14] Increasing PA and exercise levels from low to nationally recommended volumes[8] is known to contribute to increases in CRF in the context of significant numeric mean improvements at the group level.[21] Higher volumes of activity compared to the recommended levels (i.e., 150 min of moderate intensity or 75 min of vigorous intensity exercise per week), whether accomplished through a longer exercise duration and/or intensity, has generally resulted in greater improvements in CRF.[22] There has also been considerable interest in elucidating the independent effects of intensity on CRF responses by matching caloric expenditure between intervention groups. Early work revealed that healthy sedentary middle-aged men randomized to perform 12 weeks of vigorous intensity (i.e., 63–81% of maximal aerobic capacity, 350 kcal per session) exercise 5 days per week experienced greater increases in CRF (15%) compared to men randomized to the control, moderate intensity (42–60% of maximal aerobic capacity, 350 kcal per session) exercise program (8% increase in CRF). In recent years, sprint interval training that incorporates short bouts (30–60 s) of supermaximal intensity (>100% of maximal aerobic capacity) exercise have elicited similar[23] if not greater[24,25] increases in CRF compared to moderate, continuous aerobic exercise training. Yet, the inter-individual variability of CRF responses to a training method (i.e., moderate vs. high intensity) obscures the expected outcomes at the individual level and may therefore impair a practitioner's ability to provide precise PA and exercise training recommendations to elicit the desired, optimal increase in CRF.

A point of focus in recent investigations has been to extend analyses beyond the group level and explore the individual responses to varying amounts and intensities of structured aerobic exercise training. A strategy to quantify individual responses within groups is to determine the number of "non-responders" and "responders". This technique has notably been applied by Ross and colleagues[12] in which sedentary, middle-aged, men and women were randomized to 5 days per week of either: 1) low-amount, low-intensity (LALI, ~30 min at 50% maximal aerobic capacity, 180 and 300 kcal/session for women and men, respectively); 2) high-amount, low-intensity (HALI, ~60 min at 50% maximal aerobic capacity, 360 and 600 kcal/session for women and men, respectively); or 3) high-amount, high-intensity (HAHI, ~40 min at 75% maximal aerobic capacity, 360 and 600 kcal/session for men and women, respectively) exercise training for 24 weeks. The classification of a "non-responder" was given to those that did not increase CRF above the technical error[26] associated with measuring CRF (i.e., 0.204 L/min). Of the participants randomized to the LALI, 38.5% (15 of 39) did not experience meaningful improvements in CRF, while the percentage of non-responders in the HALI was reduced to 17.6% (9 of 51). Of note, all individuals performing a HAHI exercise training over the 24 weeks experienced significant improvements in CRF with no participant classified as a non-responder. These findings provide compelling evidence that when exercise training is performed in high amounts and intensities, the likelihood of participating individuals meaningfully increasing their CRF is greater. It is also important to note that there was a considerable range of responses in CRF within the HAHI group (0.25 to 1.34 L/min), once again demonstrating inter-individual variability in the response to exercise training. At this time it is unclear if there are characteristics that can predict one's response to HAHI or for any other training volume for that matter. This is an area of investigation that requires much more attention in order to improve the precision of exercise prescription and subsequent outcomes.

Body composition responses to varying volumes and intensities of exercise and PA

The prevalence of overweight and obesity in the United States has steadily increased and now affects nearly three fourths of adults.[27,28] This major CVD risk factor independently increases risk of developing hypertension, dyslipidemia, diabetes, and metabolic syndrome.[29] Body composition that favors a large volume of adipose tissue, particularly central visceral fat deposition, increases the likelihood of sobering health consequences[30,31]. PA and exercise training interventions that result in an increase in CRF in obese individuals dramatically reduces risk of developing CVD and protects against premature mortality.[32,33] Moreover, the combination of increased CRF and reduced weight provides further protective effects against poor health outcomes.[34] Both exercise/PA and diet are key synergistic strategies to achieve and sustain weight loss over the long term. Below we will focus on the effects of PA and exercise training on weight reduction and body composition modification.

The "studies of a targeted risk reduction intervention through defined exercise" (STRRIDE) was the first prospective trial to study the effects of varying volumes of exercise training on body weight, body composition (skinfold measurements of the triceps, suprailiac, abdominal, and thigh) and measures of central obesity (abdominal and suprailiac skinfolds, minimal waist and abdominal circumferences).[35] Participants were randomized to either an activity control group; HAHI (calorically equivalent to ~20 miles of jogging per week at 65–80% peak oxygen consumption (VO_2)); LAHI (equivalent to ~12 miles of jogging per week at 65–80% peak VO_2); or LA moderate intensity (LAMI, ~12 miles of jogging at 40–55% of peak VO_2). Participants following the HAHI training regimen were found to lose the greatest amount

of overall body weight (−2.9 ± 2.8 kg) and fat mass (−4.8 ± 3.0 kg) compared to the control and LAHI groups. Both LAHI (−0.6 ± 2.0 and −2.5 ± 3.4 kg, respectively) and LAMI (−0.9 ± 1.8 kg and −2.0 ± 2.6 kg, respectively) experienced similar, significant decreases in body and fat mass compared to control participants (1.0 ± 2.1 kg and 0.4 ± 3.0 kg, respectively). Abdominal (horizontal at the umbilicus), waist (smallest horizontal circumference above the umbilicus and below the xiphoid process), and hip (horizontal, at maximal protrusion of gluteus maximus) circumferences significantly decreased in the activity groups compared to control. Among the differing intensity groups, however, only those performing HAHI had significantly greater decreases in hip circumference compared to HALI and LAMI groups, suggesting that any activity level contributes to favorable reductions in abdominal, waist, and hip circumferences (surrogate measures of obesity), but longer durations at higher intensities of exercise may be necessary to experience greater decreases in hip circumference. Hammond and colleagues[15] reported similar decreases in waist circumference and body weight loss in response to a 24 week intervention of comparable exercise training workloads. Any amount and intensity of exercise training contributed to decreases in waist circumference [LALI, adjusted mean difference, −4.7 cm, 95% confidence interval (CI) −6.4 to −3.0; HALI, −5.3 cm (95% CI, −7.0 to −3.6); HAHI, −5.8 cm (95% CI, −7.6 to −4.0)] compared to the control group, but did not differ among exercise groups, which also remained true for weight loss [LALI, −4.0 kg, (95% CI, −5.7 to −2.3); HALI −5.1 kg (95% CI, −6.7 to −3.4); and HAHI −5.2 kg (95% CI, −7.0 to −3.4)]. The percentage of participants that were considered to have a clinically meaningful change (>2 kg) in body weight was highest in the HAHI group (68.4%), followed by the HALI (66.1%) and LALI (49.9%) groups, whereas the HALI (69.8%) had the highest proportion of participants with a clinically meaningful change (>2 cm) in waist circumference, followed by the HAHI (60.5%) and LALI (50%) groups. However, examination of individual responses of waist circumference and body weight to the respective volumes of activity demonstrated considerable inter-individual variability within groups, without consistent predictors of the individual response. This is not entirely surprising considering the various behavioral and physiologic factors that have been identified to influence weight regulation. Compensatory mechanisms in response to increased activity have been proposed to influence energy balance through decreases in non-exercise activity, basal metabolic rate, thermic effect of feeding, reproductive function and other components of energy expenditure.[36] Future efforts examining potential compensatory changes to behavior or physiology in response to varying amounts and intensities of exercise should implement sensitive measures of total daily energy expenditure.

Circumferential measures representing body composition are quick and cost effective markers that can be acquired in any setting while providing a clinically meaningful predictor of future mortality.[37] The addition of imaging techniques to quantify the volume of adipose tissue in specific compartments have increased our understanding of the effects of exercise and its relation to decreasing adiposity. Similar to favorable reductions in WC and body weight discussed above, LALI, HALI, and HAHI training volumes have contributed to greater, significant decreases in total adipose tissue compared to sedentary control groups (−3.5 ± 0.9 kg, −4.5 ± 0.9 kg, −5.4 ± 0.9 kg, respectively).[16] However, the amount and/or intensity of exercise does not appear to significantly impact the degree to which total adipose, visceral and abdominal subcutaneous adipose tissue is lost when dietary patterns are kept constant. Considering the significant health risks associated with elevated adipose tissue, performing low to high amounts at either low or high intensities seem to facilitate the loss of total adipose tissue. Furthermore, in Cowan et al.'s study[16], performing exercise training at the various amounts and intensities previously discussed, total skeletal muscle mass was preserved and did not change compared to the control group. However, both HALI and HAHI led to significant reductions in upper body skeletal muscle mass compared to the control group. Adding a resistance exercise regimen to a high volume aerobic exercise training program may prevent the loss of muscle mass while optimizing loss of adipose tissue.[38]

Considering exercise training alone with assumed maintenance of caloric intake and non-structured physical activity, exercising at any amount and intensity appears to confer significant reductions in body weight, circumference and adipose tissue. This is clinically relevant information to be considered by practitioners when recommending weight loss strategies, allowing for flexibility in prescribing an exercise program and general PA recommendations for weight loss. However, there is still much that needs to be elucidated in regards to identifying personal characteristics that influence weight loss in response to exercise training in order to enhance the level of precision for weight loss via exercise prescription.

Impact of exercise training and PA on blood pressure (BP)

Among the numerous health benefits of becoming physically active, a notable benefit is the blood pressure lowering effects.[39–43] While the degree to which resting systolic and diastolic BP (SBP and DBP) decreases remains wide[39–44], the most pronounced decreases (6–8 mm Hg and 5–6 mm Hg reductions in SBP and DBP, respectively) appear to be in individuals with a higher resting BP.[45] However, even minimal changes in resting BP (i.e., 3–5 mm Hg in SBP and 2–4 mm Hg in DBP), can translate into as much as 7% to 10% reductions in stroke and ischemic CVD events.[46] There is still much variability in the BP lowering effects of PA and exercise training among the studies that have investigated the role of varying amounts and intensity of exercise, with some demonstrating no improvement in BP at increasing volumes. Church and colleagues randomized women with elevated BP to perform moderate intensity exercise (50% of maximal aerobic capacity) at 50%, 100% or 150% of the exercise volume of the national PA recommendations,[8] finding no effect on lowering SBP or DBP compared to participants in the control group over a 6 month period.[47] In contrast, a recent meta-analysis[48] of studies that examined the effects of high intensity interval training compared to moderate intensity continuous training in older adults with pre- or established hypertension demonstrated equivalent SBP (−6.3 mm Hg vs. 5.8 mm Hg, respectively) and DBP (−3.8 vs. −3.5 mm Hg, respectively) lowering effects with both training methods. To our knowledge, there has not yet been an investigation on the effects of differing amounts and intensities of exercise training on BP in the context of identifying “responders” and “non-responders” within the cohort. Taking this approach may provide greater clarity on the BP lowering effects of exercise training and enhance a practitioner's ability to provide individualized exercise prescriptions with the aim of lowering BP.

Effects of PA on glucose and glucose handling

Increasing trends in the incidence and prevalence of diabetes in recent years has contributed to premature CVD and mortality. Glycemic dysregulation, although complex, is largely attributed to chronic physical inactivity and poor dietary habits. It is clear that initiation of a structured exercise regimen in prediabetic individuals can increase insulin sensitivity to the same degree, as initiating pharmacologic treatment alone; exercise training may in fact be superior to pharmacologic treatment.[49] Moreover, maintaining regular PA throughout life protects against the development of diabetes.[50] Recent evidence may also suggest that HAHI as well as HALI exercise training may result in more favorable adaptations in glucose and insulin responses to a two hour oral glucose tolerance test.[18] Participants randomized to perform 24 weeks of HAHI experienced significant decreases in two hour glucose compared to the control group, while insulin area under the curve was significantly lower for both HALI and HAHI groups. Similar to trends described in body composition changes, there were variable improvements within each group; neither exercise duration nor intensity were clearly associated with their observations. Certainly, these findings

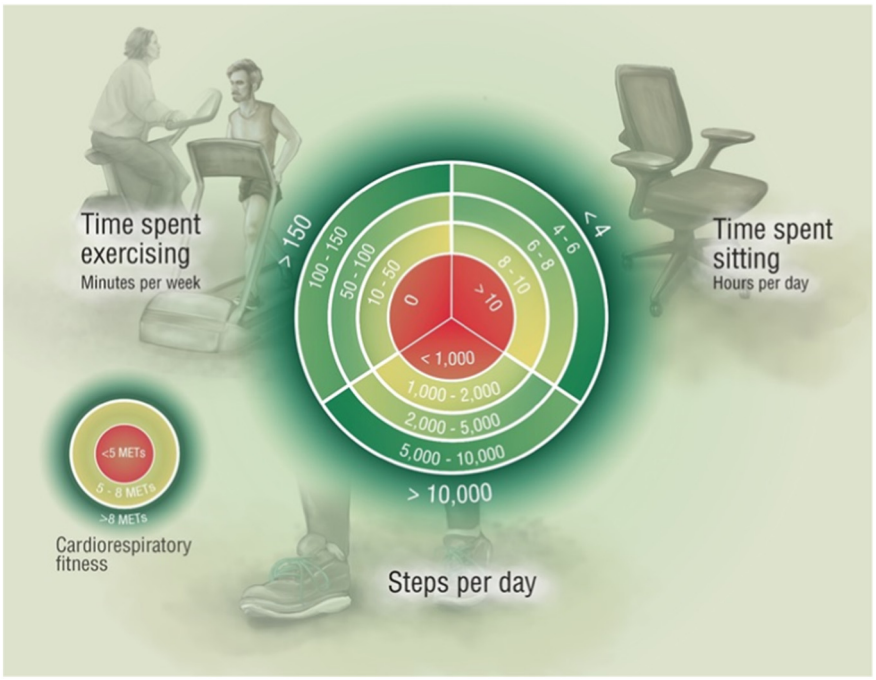

Fig 1. A newly proposed model for assessing and tracking movement.
Reprinted with Permission: Arena R, McNeil A, Street S, et al. Let Us Talk About Moving: Reframing the Exercise and Physical Activity Discussion. Curr Probl Cardiol. 2018;43(4):154–179.

would suggest that performing exercise at HAHI elicits a clinically favorable response. Recently, a re-examination of these data included the day-to-day variability that occurs with glucose and insulin levels.[17] The day-to-day variation in glucose and insulin levels were derived from the variation that was experienced by the control group from baseline and 24 week measures. Two hour glucose and insulin area under the curve "nonresponse" thresholds were determined to be within ±2.2 mmol/L and ±940.2 pmol/L, respectively, and ± 38.9 pmol/L for fasting insulin. Applying these thresholds revealed that regardless of exercise group (LALI, HALI, or HAHI), a high number of 2-hour glucose nonresponders existed (98.0%, 86.8%, 94.2%, respectively) and did not differ from the number of nonresponders in the control group (86.7%). These trends were similar when examining changes in insulin area under the curve (88.0%. 75.7%, 75.0%, and 80.0%, respectively $p > 0.05$) as well as fasting insulin (88.2%, 84.2%, 84.6%, and 93.9%, respectively, $p > 0.05$).

Impact of PA on lipoprotein levels

Regular PA and exercise training favorably alters circulating plasma levels of high-density lipoproteins (HDLs) and triglycerides (TG). Aerobic exercise training at moderate to vigorous intensities have been associated with increasing HDL by roughly 4%, with minimal changes in low density lipoproteins (LDLs), roughly a 2% decrease in total cholesterol, and 11% decrease in TG.[51] A deeper look into the influence of various particle size, density, composition, and function have assisted in enhancing detection of individuals at risk for developing CVD.[52] A meta-analysis of studies quantifying the effects of aerobic exercise training on particle size demonstrated increases in concentrations of large HDL, LDL, and mean LDL size, while decreasing the concentration of large very LDL (VLDL), small LDL, medium HDL, and mean VLDL size, independent of age, sex, race, and body mass index (BMI).[19] However, due to wide variations in exercise intensity among the studies included, identifying the effects of exercise intensity on particle size change was not possible. Data from STRRIDE also demonstrated the favorable effects of HAHI exercise training in increasing HDL, large HDL particles, and HDL particle size. These changes were preserved after 5 and 15 days of detraining.[53] Participants of the LAMI group also experienced the maintenance of increased HDL size at 5 and 15 days of detraining. Further, HDL cholesterol's most recognized characteristic is its role in facilitating the reverse transport of cholesterol from foam cells back to the liver. The capacity of HDL to transport cholesterol in this manner is inversely related to the development of CVD.[54–56] Data from the STRRIDE and "examination of mechanisms of exercise-induced weight compensation" studies investigated the ability for exercise training to improve cholesterol efflux capacity.[57] Across the 6 different exercise interventions, changes in cholesterol efflux capacity was shown to only occur when exercise intensities were performed at a high amount and intensity.

Overarching considerations for practitioners: getting individuals to move more

The overall risk reductions in future CVD and mortality achieved by any volume and/or intensity of PA and exercise training are noteworthy reasons to promote participation in any form of movement.[58,59] Moreover, minimizing sitting or screen time appears to have independent health benefits. Recently, Arena et al.[58] proposed a new paradigm for clinicians to consider when assessing movement patterns and counselling their patients on moving more, which is illustrated in Fig 1. In this model, decreased sitting time as well as increased steps/day and exercise training are all important independent components of a movement plan. In addition, when assessed and current data is available, an individual's CRF should always be included as part of the prognostic health assessment. When all three components of movement are integrated into an individual's daily life toward optimal levels the health benefits are compounded, as well as potential improvements in CRF. Adoption of the proposed paradigm by clinicians allows for a more individualized approach to prescribing a movement plan. Due to the various barriers associated with becoming active in previously inactive individuals, the initial focus of practitioners prescribing exercise should be to encourage sitting less and adopting of reasonable volumes of general PA and exercise training for the individual, while promoting a gradual progression toward meeting the PA guidelines.[3,60] Although there are still many

areas of investigation needed to determine the effects of varying amounts and intensities of exercise on individual responses to exercise, it is becoming clear that precision medicine, as it relates to PA, can be applied to improve CRF. Performing regular exercise at HAHI in previously sedentary individuals increases the likelihood of clinically meaningful increases in CRF compared to HALI and LALI exercise prescriptions. Exercise prescriptions that aim to reduce body weight and composition may not be greatly impacted by the amount or intensity of exercise. However, time efficient exercise programs performed at higher intensities to match similar caloric expenditures of longer, moderated exercise can result in similar reductions in body composition.[18] Similarly, neither exercise amount nor intensity appears to significantly impact the degree to which SBP, DBP, and insulin sensitivity change as long as weekly exercise meets PA guidelines. Lastly, while most PA volumes that at least reach recommended PA levels favorably improve blood lipid profiles, higher amounts and intensities of exercise seem to be necessary to improve the highly prognostic measures of the HDL cholesterol carrying capacity.

Conclusions

PA and exercise training are powerful behaviors that alters an individual's health trajectory to promote long term physical independence, quality of life and reduced risk of developing NCDs and premature morbidity/mortality. Future studies are still needed to fully understand the long term effects of varying amounts and intensities of PA and exercise training and whether there is an upper limit to the benefits that one can achieve. Furthermore, it is clear that inter-individual responses of health markers to exercise training exist, with limited understanding of characteristics that help identify non-responders and responders. Identifying these predictors will greatly enhance a clinician's ability to prescribe PA and exercise training in a more individualized and effective manner, embracing the tenants of precision medicine.

Statement of conflict of interest

There is no conflict of interest of any of the listed authors.

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