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Biological / Genetic Regulation of Physical Activity Level: Consensus from GenBioPAC

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ABSTRACT:

PURPOSE: Physical activity unquestionably maintains and improves health; however, physical activity levels globally are low and not rising despite all the resources devoted to this goal. Attention in both the research literature and the public policy domain has focused on social-behavioral factors; however, a growing body of literature suggests that biological determinants play a significant role in regulating physical activity levels. For instance, physical activity level, measured in various manners, has a genetic component in both humans and non-human animal models. This consensus paper, developed as a result of an ACSM-sponsored round table, provides a brief review of the theoretical concepts and existing literature that supports a significant role of genetic and other biological factors in the regulation of physical activity. CONCLUSION: Future research on physical activity regulation should incorporate genetics and other biological determinants of physical activity instead of a sole reliance on social and other environmental determinants.

Introduction:

Physical activity promotes health and quality of life, and prevents premature death, with supporting literature reviewed in a number of different places (1, 2). Conversely, physical inactivity is a root cause of several chronic health conditions, is a major risk factor for obesity and diabetes, and has been reported to be the second leading actual cause of death in the U.S. (3). Physical activity is considered an effective means of maintaining body weight, a necessary part of any effort to increase or decrease an individual's weight in a stable manner (4–6), a significant environmental modifier of weight (7), and an effective treatment option for some aspects of mental health, such as depression (8, 9). In spite of the strong evidence favoring physical activity as an effective and cost-effective component of both preventive medicine and therapy, general activity levels in the United States are low, with studies using direct activity measurements suggesting that less than 5% of adults over 20 years of age engage in at least 30 minutes of moderate intensity physical activity daily (10). This trend is not limited to the United States, but also has been reported as a worldwide health issue with the World Health Organization naming physical inactivity as the fourth leading risk factor for global mortality (11). Moreover, community-based attempts to promote physical activity have had mixed success (e.g. 12, 13).

Beyond the direct health effects and the reduction in quality of life suffered by those that are not active, physical inactivity imposes significant costs on health care systems. Using admittedly conservative estimates, with consideration of only the impact on the top five non-communicable diseases globally and ignoring mental health, Ding et al. (14) estimated that physical inactivity costs $67.5 billion yearly in health care expenditures and productivity losses. Other estimates have generated an even higher financial burden based on different models. For example, Chenoweth and Leutzinger reported that the estimated nationwide costs of risk factors due to physical inactivity were approximately $507 billion per year in the United States alone (15). No matter what model is used, the effect of physical inactivity on just health economics is profound. In fact, given the overall economic impact in conjunction with the impact on health, public health authorities worldwide have launched interventions aimed at increasing physical activity during work/school time, during transportation to work and school, and in leisure time (1, 11, 16, 17).

In spite of this wide and deep literature showing the health and economic benefits of physical activity, the widely disseminated Physical Activity Guidelines (1), and the large amount of information and programs available to the public, in general, overall activity statistics have not improved significantly over the past 50 years. As noted earlier, the most recent large-scale accelerometer database available suggests that only a small minority of U.S. citizens meet physical activity guidelines, with less than 5% of adults, less than 8% of adolescents, and less than 58% of children being classified as "active" (10). These national accelerometer-based numbers are markedly lower than more subjective historic data (Fig. 1) of the estimated activity levels from the Behavioral Risk Factor Surveillance System (BRFSS, 18). The volatility of the more subjective estimates is illustrated by the fluctuations in percentage of adults reportedly engaging in activity from the 2000 to the 2001 BRFSS survey, particularly by the striking rise in physical activity engagement that was largely attributable to a change in the survey questions that were asked regarding physical activity. However, regardless of the metric used, be it the objective measures or the more subjective estimates, it is clear that a significant portion of the global population does not accumulate enough physical activity on a weekly basis to avoid elevated risk, let alone confer health benefits (11).

Why is it that, in spite of the recognition of the critical role of physical activity in health over the past 50 years, the number of physically active individuals has not significantly increased? Some have cited technological encroachment or other lifestyle changes as primary factors for the persistently depressed activity levels. The worldwide decrease in the number of occupations requiring physical labor is also part of the explanation (19, 20). Further, a large literature indicates potential social and environmental factors that inhibit physical activity level, but this has been – at best – ambiguous and non-consistent as to which factors are important (19).

Given that all human behavioral traits are usually determined by both environmental/social and biological factors, it is alarming that the vast majority of the literature on physical activity (e.g. 19, 21) has excluded biological factors as potential determinants of physical activity levels in humans. However, even a brief and targeted literature review as included in this paper shows conclusively that physical activity level is strongly influenced by biological mechanisms. The hypothesis that biological mechanisms regulated physical activity level was supported by an early review in this journal (22) and with the advances in genomics and genetics since that time, the foundational science supporting the contention that biological determinants regulate physical activity level has only grown stronger. Thus, the purpose of this consensus paper is to provide a brief review of the literature that supports the concept that biological, including genetic and genomic, factors are important determinants and regulators of physical activity level. This brief review is offered to motivate further research aimed at understanding rates of physical activity participation by incorporating biology and genetics in research paradigms.

Evidence of Biological Regulation of Physical Activity:

In this review, we take the broadest view of 'physical activity' – namely, we define physical activity as any locomotion or movement that is the result of skeletal muscle contraction (23). A broad definition of physical activity is important in the present context as it needs to be applicable to both human and animal models, and should allow for the incorporation of spontaneous physical activity (e.g. "fidgeting"), non-exercise activity thermogenesis, as well as both leisure-time recreational activity and occupational activity. Further, and probably most importantly, we treat physical activity as the *dependent variable*, where the measured amount of physical activity or the energy expenditure caused by physical activity is being investigated, as opposed to the common consideration of physical activity as an *independent variable or mediator of change,* where activity is manipulated to determine its impact on health or other traits. This implies that the focus is on genes, pathways, systems, tissues, organs, and organ systems influencing physical activity levels.

Some of the earliest suggestions that physical activity levels could be influenced by biological factors were in multiple studies in the 1920s and early 1930s, primarily from Richter and his colleagues (e.g. 24, 25), which showed that an unknown internal biological substance associated with reproduction altered running-wheel activity of rats. The 'substance' suggested was later identified as the sex hormones, testosterone and estrogen, and a rich body of work shows clearly that sex hormones can influence activity (e.g. 26). Further, even before DNA was identified, Rundquist (27) in 1933 made the earliest suggestion that heritability influenced physical activity level. Rundquist (27), after selectively breeding rats for 12 generations on the basis of daily activity in rotating-drum cages, noted “It is, then, quite safe to ascribe the major role in the production of the individual differences in this activity to inheritance.” Confirmatory data for this conclusion has become overwhelming in the past 80 years, with at least 45 studies in adult human and mature rodent models showing that individual variation in physical activity is, to an important extent, influenced by genetic variation (28–72).

The relative contribution of the genetic variance to the total variance for a trait in a given population at a certain time is called the "heritability" of the trait and is typically expressed as a percentage. In all models considered, the estimated heritability of physical activity in adults ranges from approximately 20% (67) to 90% (60). These estimates vary based on the activity criterion used, the study design and type of heritability statistics used, the species studied, the gene pool of the study population, age and sex of the organism, and the environmental conditions. Additionally, in the human studies that have been able to parse out the differing sources of variability (e.g. 58, 60–62, 67–69), the role of environmental influences that are experienced similarly by family members (collectively known as ‘common’ environmental factors) has generally been zero, with only one study (67) indicating a small common environmental influence on activity level (≈12%). Thus, the available literature clearly shows that the primary determinants of physical activity are genetic factors and environmental factors that are unique to an individual (i.e. independent of other family members’ characteristics), which can consist of the individual’s socio-demographic characteristics, personal life history, and social settings, but could also subsume the effects of chance, normal day-to-day variability, and measurement error, depending on the study. For the interested reader, a thorough discussion of the phenotypic variance and its genetic and environmental components and subcomponents can be found in standard genetics textbooks.

Figure 2 provides a conceptual model of the biological determinants of physical activity, divided into three main components (brain, cardiorespiratory system, muscle), all of which can interact. All three components can have a substantial genetic basis, but are also influenced by various factors in the external environment. Importantly, this model of multi-faceted regulation includes both central (brain) and peripheral (cardiorespiratory, muscle) control components. A pre-set, brain-located “activity-stat” was earlier hypothesized (22) and it was proposed that it would not only serve as a pre-programmed activity-level controller, but also receive signals from various other factors that may themselves be partly genetically regulated, such as sex hormone levels, dietary habits, and exposure to toxicants. The activity-stat was seen as part of a much larger motivational regulatory system that integrates reward and punishment cues related to ongoing or recently completed physical activity, arising from afferent somato-visceral feedback in cardiorespiratory and muscle (fatigue) sources. In humans, motivational states are further modulated by trait-dependent individual differences in the drive to be active related to personality, social support or the many social-environmental opposing or enabling factors for physical activity. The science has evolved since an activity-stat was part of the discussion on the regulation of physical activity level, and the concept is hard to justify today (e.g. 73). It is now better appreciated that the regulation of behavioral traits is influenced by complex multifactorial and redundant genetic, epigenetic, and other biological systems, with each component characterized by small effect sizes.

This conceptual holistic model of the control of physical activity in which genetic and other biological factors play a key role is supported by a variety of literature. The use of the conceptual model in Figure 2 is critical in further studying, understanding, and altering physical activity, as well as driving future research directions (Fig. 3). The existing literature, while having several gaps, is robust enough to conclude that investigators studying physical activity - as well as policy makers pondering relevant policies - must consider all factors in their deliberations and not just focus on social-environmental aspects.

Biology of Regulation of Physical Activity Level and Future Research Directions:

Even though a significant amount of evidence in both humans and rodents shows that daily physical activity level is genetically controlled to a significant extent, the specific mechanisms involved are still incompletely delineated. Efforts to identify from where in the genome this regulation arises have used genome-wide association studies (GWAS), positional cloning approaches, and other –omics technologies in both humans and rodents. These efforts, including the use of large-scale twin studies (68, 69, 74) and both inbred (e.g. 64, 66) and selectively-bred animal models (e.g. 23, 70, 75–77), have been fruitful in identifying promising quantitative trait loci (i.e. chromosomal locations) associated with physical activity level. Further, it has been suggested using cross-sectional designs in humans (e.g. 69) and longitudinal designs in rodents (71) that the genetic influence on activity level varies by age, increasing toward the end of puberty and waning as the individual reaches later ages. Additionally, a few rodent studies have documented genetic dominance (e.g. 78) and epistasis (79, 80), as well as pleiotropic interactions (81) in regards to physical activity level. There have been successes in determining the genetic underpinnings of some muscle traits in mice selectively bred for high activity (e.g. the mini-muscle phenotype, 82, 83) as well as providing expression quantitative trait loci (QTL) results from these mice (76, 84). These studies have resulted in initial summary genomic maps of quantitative trait loci associated with activity, as well as suggested candidate genes involved in regulating physical activity (85), with limited data from congenic animals supporting some of these genetic associations (e.g. 86, 87). However, as noted (85) most potential candidate genes still lack rigorous validation, which is a widespread issue when working to move candidate genes from the 'associative' to 'causative' category in regards to any phenotype (88). Further, although some authors have discussed translation of rodent results into humans (85), the only study that has attempted to translate between mouse and human data in the same study (89) suffered from critical design issues (e.g. incorrect translation of low-active mouse QTL onto high-active humans; rejecting objective measures of human activity in favor of subjective measures) that limited interpretation of the results. Given the amount of both human and rodent data available, more translational efforts need to be conducted.

Besides using traditional genetic approaches to illuminate the genetic component of activity level, some investigators have taken a hypothesis-driven approach targeting specific factors that may influence daily activity in one or more of the areas shown in Figures 2 and 3. Given the ability to interrogate a wide-variety of tissues, the large majority of this work has been in animal models, the human translatability of which has been discussed in several venues (e.g. 23, 90). For example, research in the biological regulation of physical activity level has focused on several specific areas depicted in the conceptual model as defined in Figure 2:

- The central reward center of the brain (primarily structures in the striatum) as a major site of physical activity regulation;

- The peripheral cardiovascular and musculoskeletal capabilities associated with high and low-activity profiles in animal models;
- Genomic and other biological factors, such as sex and other hormones, and illness and disease, which may cause changes in inflammatory signals and metabolite levels that participate in the regulation of daily physical activity level;
- Environmental factors such as diet and the presence of environmental toxicants that may augment/inhibit physical activity level regulatory mechanisms; and
- Social-environmental factors that may influence activity.

Research focused on central mechanisms regulating physical activity level has provided evidence of altered dopaminergic (91, 92) as well as differential endocannabinoid activity (93–95) in the brains of highly active animals. Garland's group in particular has worked to elucidate the neural control of high levels of voluntary exercise in selectively bred lines of mice (e.g. 23, 76, 84, 92). More recently Booth's group has employed a selectively bred rat model to investigate the neural control of low vs. high voluntary exercise on wheels (e.g. 96). Additionally, early efforts have been presented at describing the central transcriptomic (97, 98) and proteomic signatures of high- and/or low-active animals (99), along with efforts to produce transient gene silencing to investigate neural candidate genes in whole animals (100).

Common sense and various lines of research indicate that even if an animal has a high neural drive to be physically active (e.g. arising from the nucleus accumbens), without the physiological capability for extended activity, it will not be able to be highly active (e.g. 23, 84). As such, a variety of studies have suggested the importance of heritable peripheral components – primarily in the skeletal muscle – in the determination of activity level. Tsao and coworkers' intriguing data showed that mice with overexpressed glucose transporter 4 (Glut4/*Slc2a4*) also exhibited a four-fold increase in voluntary wheel running (101). The authors suggested that augmented substrate availability caused this increase in activity, implying that daily activity could be regulated by substrate-delivery mechanisms in the muscle. Presuming the genetic manipulation primarily affected ability for endurance exercise, this finding implies that the wild-type mice had an excess central "drive" to be physically active, or that this drive was increased by the genetic manipulation. Additionally, Meek et al. (102) showed that mice bred for high voluntary exercise on wheels and that had reached a plateau in their breeding-induced activity levels, increased wheel-running activity when fed a high-fat, high-sucrose diet. Again, however, it is possible that this diet affected motivation for, or reward received from, wheel running, rather than just exercise ability (102). Further, Pistilli, et al. (103) showed that knocking out IL-15Rα, which influences substrate usage particularly in fast-twitch fibers, increased daily wheel running, while O'Neill, et al. (104) noted that knocking out AMPK ß1ß2 decreased wheel running. As noted earlier, work from Garland's group with the mini-muscle phenotype in their selectively-bred high active animals (78, 82, 83) has revealed a recessive allele that results in a 50% reduction in the mass of the triceps surae muscle complex and of total hindlimb muscle mass with a doubling of the mass-specific aerobic capacity and an altered fiber type composition and contractile performance, along with an increase in size of the animal's heart ventricles, liver, and spleen. As with central mechanisms, initial work has been published regarding differing skeletal muscle proteomes of high- and low-active animals (105), with preliminary work considering the effect of transient gene silencing on some of the proteins overexpressed in highly active animals (100).

The idea that both peripheral and central mechanisms contribute to the regulation of physical activity level (Fig. 2) has been reinforced by literature on the determinants of voluntary exercise behavior in humans (106). Instrumental conditioning – which has been defined as operant conditioning that pairs a response with a reinforcement (107) - plays a key role in many voluntary behaviors, and exercise seems no exception. When people engage in regular exercise activities, they are exposed to a combination of acute (during the exercise bout and shortly after) affective effects, which are in part experienced as pleasant and in part as unpleasant (108). The net balance of these effects determines whether the activity will be experienced as punishing or rewarding, respectively, and this balance will strongly contribute to the adoption and maintenance of regular exercise behavior, or the failure to do so. Previous studies showed a robust association between a more favorable affective response (i.e. relating to moods, feelings, and attitudes) during exercise and the intention to engage in voluntary exercise (109, 110) as well as greater actual participation in (voluntary) moderate to vigorous exercise (111–115).

Various potential modulators of the affective response have been shown to influence regular exercise behavior in humans, including personality and self-regulation. Regular exercisers score lower on neuroticism and higher on extraversion, conscientiousness, and sensation seeking (116–119), 'brain' traits known to be under substantial genetic control (120). Neuroticism may increase the fear of embarrassment or injury, which are often cited as perceived barriers to exercise. Introverts, with a high intrinsic arousal level, might be easily over-stimulated and less attracted to exercise activities, particularly in socially rich contexts. Self-regulation, or the related concepts of self-motivation and conscientiousness are well-known correlates of regular exercise behavior program (121–123). This is not surprising, as the ability to endure the temporary discomforts of exercise in view of a future reward (e.g. physical fitness, losing weight, winning the game) or a long-term goal (health, ability to attract romantic partners) is a core characteristic of self-regulation. Perhaps less well known is that self-regulation is itself a heritable trait (124) as are motives for activity (125). Self-regulation should therefore be considered as part of the biological network that regulates the level of physical activity.

Exercise ability can also modulate the affective response to exercise in humans. Being good at exercise and performing better than others will lead to feelings of competence, whereas lower levels of performance might lead to disappointment or shame. Perceptions of differences in exercise ability may strongly contribute to the affective response to exercise. These perceptions will largely but not perfectly, reflect actual exercise ability. The latter may be influenced by skills specific to a sport, but a number of general fitness characteristics, including strength and endurance, are strong predictors of performance across a variety of sports and exercise activities (126). These general fitness characteristics are known to be highly heritable, and this applies to individual differences encountered in cross-sectional samples (127, 128) as well as in the response to a fixed training regime (129). In the latter case, being a good responder to regular exercise for a relevant biological trait (e.g. exercise capacity) is likely to augment rather than diminish the interest in remaining physically active. One could hypothesize that the opposite would be true for a poor responder to the same exercise regimen.

The heritable influence on exercise ability might be especially relevant for self-chosen levels of exercise behavior during late adolescence, when the influence of role models in health behaviors is large (130). Likewise, the association of extraversion and sensation seeking with exercise behavior might be particularly prominent in adolescence, when many exercise activities are performed in teams with friends and peers. This may explain the relatively high levels of heritability that are noted for exercise behavior in mid- and late-adolescence (131).

In addition to work on both central- and peripheral-genetically influenced physical activity regulatory mechanisms, a large and deep, though somewhat dated, pool of literature addresses the effects of sex hormones on physical activity. This body of literature, as noted earlier, reaches back to the mid-1920s, but showed resurgence in the early 2000s. Seminal work by Roy and Wade (132) suggested that estrogen was the primary driver of physical activity, primarily through aromatase mechanisms. However, more recent direct testing of that hypothesis with both reversible and non-reversible aromatase inhibitors, as well as modern methods of exogenous hormone supplementation, have suggested that testosterone may actually be primary in the sex hormone effects on physical activity (133, 134). Although sex hormones have a significant effect on physical activity, it remains an open question whether their regulation of physical activity arises from genetic mechanisms (e.g. some variation in the androgen receptor gene) or whether the sex hormone effect is a modifier of other, more basic genetically controlled regulatory pathways (e.g. effect on dopaminergic signaling pathways). Also unclear is the extent to which sex differences in physical activity in rodents and humans are caused by physiological differences invoked by differences in hormone production (e.g. more testosterone, more muscle mass, different activity choice) or by direct regulation of activity due to the differences in their hormonal milieu (e.g. 134).

Lastly, modification of genetic regulation of activity by unique-to-the-individual environmental factors – either through epigenetic mechanisms or direct inhibition/augmentation of the genetic mechanisms of control – is still a relatively unexplored area. Results from the late 1800s suggested that diet could affect physical activity level (135) and it is well known and accepted that certain experimental paradigms that moderately reduce caloric intake will reliably increase physical activity in rodents and non-human primates (136–138) and probably humans (139, 140). Interestingly, altering dietary composition in selectively bred, highly active mice markedly increases activity (102, 141), while feeding a high fat, high sugar diet in inbred mice resulted in large reductions in daily activity in both sexes (142). It is currently unclear if these diet-induced alterations in activity are moderated through hormonal alterations (e.g. ghrelin/leptin or sex hormone changes, 143–145), through a direct effect on central neurotransmitters (e.g. serotonin pathways, 146), or simply due to alterations in substrate availability for activity (102). Additionally, early-life exposure to unique environmental toxicants, such as a common plasticizer (BBP), may inhibit lifelong activity in offspring through alterations in sex hormone levels or other biological mechanisms when their mothers are exposed to physiologically relevant doses during pregnancy (147). Also, it has been suggested that maternal diet (148) or exercise in and of itself may affect the activity level of the offspring (149, 150).

In summary, a large and growing body of literature examines the various areas of potential biological control of physical activity level in both humans and other animals. This literature provides the foundation for the recommended research flow as outlined in Figure 3; this research flow is predicated on the results from previous studies of both human and rodent models, as well as on existing results based on genetic methods and environmental inputs. Current consensus recommends that future research in the biological control of physical activity concentrate on three areas: central neural mechanisms providing the ‘drive to be active’ (motivation); peripheral mechanisms that provide the ‘capability to be active’ (capability); and integrative and mediating biological mechanisms and factors that inhibit or augment the central and peripheral mechanisms (e.g. aspects of endocrine function, 151). This level of research will provide a further foundation for future basic investigations that can be translated into both human and animal studies, with the ultimate goal of developing physical activity-based trials aimed at investigating specific activity regulators.

In conclusion, it is well established that physical activity is healthy behavior, but worldwide levels of physical activity remain low in spite of the increased emphasis and knowledge available to the general population. The preponderance of literature in sports medicine and exercise science has treated physical activity regulation as a largely non-biological construct and this perspective is reflected in the main intervention approaches to increase daily physical activity. Such interventions focus on goal setting, social support, and behavioral reinforcement through self-reward, structured problem solving, and relapse prevention. Although these social-behavioral approaches make good sense, an undisputed body of empirical data also reveals that biological determinants play an important role in the regulation of daily physical activity in both humans and other animals. They do so by influencing brain circuitry related to some of the core elements in the social-behavioral models, including personality, affect regulation and reward processing, or by influencing cardiorespiratory and muscle capacity to regularly engage in physical activity, which we expect to be closely tied to physical self-efficacy, another core element in social-behavioral models of physical activity. The existence of individual differences in physical activity behavior is undeniable, as is the fact that biological/genetic mechanisms are largely responsible for those differences. Choosing not to investigate these mechanisms would be irresponsible and would hinder the science or understanding the causes of this critical health issue. Thus, future research needs to focus on investigating and identifying these biological pathways participating in the regulation of physical activity level, how they are affected by genetic variants, early-life experiences, epigenetic events, biological intermediates and environmental factors, such as diet and toxicant exposures, and how they impact our attempts to intervene on physical activity level. In keeping with the acknowledged importance of the interplay of nature and nurture in many other behavioral traits, it is the consensus of this authorship group that future research on physical activity regulation should prominently include the identification of the biological determinants of physical activity instead of a sole reliance on the social/environmental determinants.

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Citations:

1. United States Department of Health and Human Services. 2008 Physical Activity Guidelines for Americans. Washington DC: United States Department of Health and Human Services; 2008.
2. United States Department of Health and Human Services. Physical activity and health: A report of the Surgeon General. 1996.
3. Mokdad AH, Marks JS, Stroup DF and Gerberding JL. Actual causes of death in the United States, 2000. JAMA. 2004; 291(10):1238-45.
4. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW and Smith BK. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc. 2009; 41 (2):459-71.
5. Haskell WL, Lee IM, Pate RR *et al.* Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc. 2007; 39(8):1423-34.
6. Lyznicki JM, Young DC, Riggs JA and Davis RM. Obesity: Assessment and management in primary care. Am Fam Physician. 2001; 63(11):2185-96.
7. Bouchard C. Gene-environment interactions in the etiology of obesity: Defining the fundamentals. Obesity (Silver Spring). 2008; 16 Suppl 3:S5-S10.
8. Radovic S, Gordon MS and Melvin GA. Should we recommend exercise to adolescents with depressive symptoms? A meta-analysis. J Paediatr Child Health. 2017; 53(3):214-20.
9. Schuch FB, Vancampfort D, Richards J, Rosenbaum S, Ward PB and Stubbs B. Exercise as a treatment for depression: A meta-analysis adjusting for publication bias. J Psychiatr Res. 2016; 77:42-51.

10. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T and Mcdowell M. Physical activity in the United States measured by accelerometer. Med. Sci. Sports Exerc. 2008; 40(1):181-8.

11. World Health Organization. Global Recommendations on Physical Activity for Health. Switzerland: World Health Organization; 2010.

12. Bock C, Jarczok MN and Litaker D. Community-based efforts to promote physical activity: A systematic review of interventions considering mode of delivery, study quality and population subgroups. J Sci Med Sport. 2014; 17(3):276-82.

13. Everson-Hock ES, Johnson M, Jones R, Woods HB, Goyder E, Payne N and Chilcott J. Community-based dietary and physical activity interventions in low socioeconomic groups in the UK: A mixed methods systematic review. Prev Med. 2013; 56(5):265-72.

14. Ding D, Lawson KD, Kolbe-Alexander TL *et al.* The economic burden of physical inactivity: A global analysis of major non-communicable diseases. Lancet. 2016; 388(10051):1311-24.

15. Chenoweth D and Leutzinger J. The economic cost of physical inactivity and excess weight in American adults. J Phys Act Health. 2006; 3:148-63.

16. Brown WJ, Bauman AE, Bull FC and Burton NW. Development of evidence-based physical activity recommendations for adults (18-64 years). Australian Government Department of Health; 2012.

17. European Union Member State Sport Ministers. EU physical activity guidelines: Recommended policy actions in support of health-enhancing physical activity. EU Working group “Sports and Health”. 2008.

18. Centers for Disease Control and Prevention. BRFSS prevalence & trends data. Online.

2015; accessed May 08, 2017.

19. Brownson RC, Boehmer TK and Luke DA. Declining rates of physical activity in the United States: What are the contributors. Annu Rev Public Health. 2005; 26:421-43.

20. Church TS, Thomas DM, Tudor-Locke C *et al.* Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. PLoS One. 2011; 6(5):e19657.

21. Hasson RE, Brown DR, Dorn J *et al.* Achieving equity in physical activity participation: ACSM experience and next steps. Med Sci Sports Exerc. 2017; 49(4):848-58.

22. Rowland TW. The biological basis of physical activity. Med Sci Sports Exerc. 1998; 30(3):392-299.

23. Garland Jr. T, Schutz H, Chappell MA *et al.* The biological control of voluntary exercise, spontaneous physical activity and daily energy expenditure in relation to obesity: Human and rodent perspectives. J Exp Biol. 2011; 214(Pt 2):206-29.

24. Richter CP. Animal behavior and internal drives. Q Rev Biol. 1927; 2(3):307-43.

25. Richter CP and Wislocki GB. Activity studies on castrated male and female rate with testicular grafts, in correlation with histological of the grafts. Am J Physiol. 1928; 86(3):651-60.

26. Bowen RS, Turner MJ and Lightfoot JT. Sex hormone effects on physical activity levels: Why doesn’t Jane run as much as Dick? Sports Med. 2011; 41(1):73-86.

27. Rundquist EA. Inheritance of spontaneous activity in rats. J Comp Psych. 1933; 16 (3):415-38.

28. Heller RF, O’Connell DL, Roberts DC, Allen JR, Knapp JC, Steele PL and Silove D. Lifestyle factors in monozygotic and dizygotic twins. Genet Epidemiol. 1988; 5:311-21.

29. De Moor MH, Stubbe JH, Boomsma DI and De Geus EJ. Exercise participation and self-

rated health: Do common genes explain the association. Eur J Epidemiol. 2007; 22(1):27-32.

30. Seabra AF, Mendonça DM, Göring HH, Thomis MA and Maia JA. Genetic and environmental factors in familial clustering in physical activity. Eur J Epidemiol. 2008; 23(3):205-11.

31. Aaltonen S, Ortega-Alonso A, Kujala UM and Kaprio J. A longitudinal study on genetic and environmental influences on leisure time physical activity in the Finnish twin cohort. Twin Res Hum Genet. 2010; 13(5):475-81.

32. Aaltonen S, Ortega-Alonso A, Kujala UM and Kaprio J. Genetic and environmental influences on longitudinal changes in leisure-time physical activity from adolescence to young adulthood. Twin Res Hum Genet. 2013; 16(2):535-43.

33. De Chaves RN, Baxter-Jones A, Santos D *et al.* Clustering of body composition, blood pressure and physical activity in Portuguese families. Ann Hum Biol. 2014; 41(2):159-67.

34. De Moor MH, Posthuma D, Hottenga JJ, Willemsen G, Boomsma DI and De Geus EJ. Genome-wide linkage scan for exercise participation in Dutch sibling pairs. Eur J Hum Genet. 2007; 15(12):1252-9.

35. De Moor MH, Willemsen G, Rebollo-Mesa I, Stubbe JH, De Geus EJ and Boomsma DI. Exercise participation in adolescents and their parents: Evidence for genetic and generation specific environmental effects. Behav Genet. 2011; 41(2):211-22.

36. Den Hoed M, Brage S, Zhao JH *et al.* Heritability of objectively assessed daily physical activity and sedentary behavior. Am J Clin Nutr. 2013; 98(5):1317-25.

37. Diego VP, De Chaves RN, Blangero J *et al.* Sex-specific genetic effects in physical activity: Results from a quantitative genetic analysis. BMC Med Genet. 2015; 16:58.

38. Duncan GE, Goldberg J, Noonan C, Moudon AV, Hurvitz P and Buchwald D. Unique environmental effects on physical activity participation: A twin study. PLoS One. 2008; 3(4):e2019.

39. Gielen M, Westerterp-Plantenga MS, Bouwman FG *et al.* Heritability and genetic etiology of habitual physical activity: A twin study with objective measures. Genes Nutr. 2014; 9(4):415.

40. Horimoto AR, Giolo SR, Oliveira CM *et al.* Heritability of physical activity traits in Brazilian families: The Baependi Heart Study. BMC Med Genet. 2011; 12:155.

41. Huppertz C, Bartels M, Jansen IE, Boomsma DI, Willemsen G, De Moor MH and De Geus EJ. A twin-sibling study on the relationship between exercise attitudes and exercise behavior. Behav Genet. 2014; 44(1):45-55.

42. Mitchell BD, Rainwater DL, Hsueh WC, Kennedy AJ, Stern MP and Maccluer JW. Familial aggregation of nutrient intake and physical activity: Results from the San Antonio Family Heart Study. Ann Epidemiol. 2003; 13(2):128-35.

43. Mustelin L, Latvala A, Pietiläinen KH *et al.* Associations between sports participation, cardiorespiratory fitness, and adiposity in young adult twins. J Appl Physiol (1985). 2011; 110(3):681-6.

44. Mustelin L, Joutsi J, Latvala A, Pietiläinen KH, Rissanen A and Kaprio J. Genetic influences on physical activity in young adults: A twin study. Med Sci Sports Exerc. 2012; 44(7):1293-301.

45. Perusse L, Leblanc C and Bouchard C. Familial resemblance in lifestyle components: Results from the Canada Fitness Survey. Can J Public Health. 1988; 79(3):201-5.

46. Seabra AF, Mendonça DM, Göring HH, Thomis MA and Maia JA. Genetic influences of

sports participation in Portuguese families. Eur J Sport Sci. 2014; 14(5):510-7.

47. Simonen RL, Perusse L, Rankinen T, Rice T, Rao DC and Bouchard C. Familial aggregation of physical activity levels in the Quebec Family Study. Med Sci Sports Exerc. 2002; 34(7):1137-42.

48. Spinath FM, Wolf H, Angleitner A, Borkenau P and Riemann R. Genetic and environmental influences on objectively assessed activity in adults. Pers Individ Dif. 2002; 33:633-45.

49. Vink JM, Boomsma DI, Medland SE *et al.* Variance components models for physical activity with age as modifier: A comparative twin study in seven countries. Twin Res Hum Genet. 2011; 14(1):25-34.

50. Simonen R, Levälahti E, Kaprio J, Videman T and Battié MC. Multivariate genetic analysis of lifetime exercise and environmental factors. Med Sci Sports Exerc. 2004; 36(9):1559-66.

51. Eriksson M, Rasmussen F and Tynelius P. Genetic factors in physical activity and the equal environment assumption-- the Swedish Young Male Twins Study. Behav Genet. 2006; 36(2):238-47.

52. Carlsson S, Andersson T, Lichtenstein P and Michaelsson K. Genetic effects on physical activity: Results from the Swedish Twin Registry. Med Sci Sports Exerc. 2006; 38(8):1396-401.

53. McCaffery JM, Papandonatos GD, Bond DS, Lyons MJ and Wing RR. Gene x environment interaction of vigorous exercise and body mass index among male Vietnam-era twins. Am J Clin Nutr. 2009; 89(4):1011-8.

54. Aarnio M, Winter T, Kujala UM and Kaprio J. Familial aggregation of leisure-time physical activity -- a three generation study. Int J Sports Med. 1997; 18(7):549-56.

55. Maia JA, Thomis M and Beunen G. Genetic factors in physical activity levels: A twin study. Am J Prev Med. 2002; 23(2 Suppl):87-91.
56. Frederiksen H and Christensen K. The influence of genetic factors on physical functioning and exercise in second half of life. Scand J Med Sci Sports. 2003; 13(1):9-18.
57. De Geus EJ, Boomsma DI and Snieder H. Genetic correlation of exercise with heart rate and respiratory sinus arrhythmia. Med Sci Sports Exerc. 2003; 35(8):1287-95.
58. Boomsma DI, Van Den Bree MB, Orlebeke JF and Molenaar PC. Resemblances of parents and twins in sports participation and heart rate. Behav Genet. 1989; 19(1):123-41.
59. Festing MFW. Wheel activity in 26 strains of mouse. Lab Anim. 1977; 11:257-8.
60. Joosen AM, Gielen M, Vlietinck R and Westerterp KR. Genetic analysis of physical activity in twins. Am J Clin Nutr. 2005; 82(6):1253-9.
61. Kaprio JM, Koskenvuo M and Sarna S. Progress in clinical and biological research. Twin research 3: Epidemiological and clinical studies. editors Gedda L, Parisi P and Nance WE, New York: Alan R Liss; 1981. Cigarette smoking, use of alcohol and leisure-time activity among same-sexed adult male twins; p. 37-46.
62. Lauderdale DS, Fabsitz R, Meyer JM, Sholinsky P, Ramakrishnan V and Goldberg J. Familial determinants of moderate and intense physical activity: A twin study. Med Sci Sports Exerc. 1997; 29(8):1062-8.
63. Lerman I, Harrison BC, Freeman K, Hewett TE, Allen DL, Robbins J and Leinwand LA. Genetic variability in forced and voluntary endurance exercise performance in seven inbred mouse strains. J Appl Physiol. 2002; 92:2245-55.
64. Lightfoot JT, Leamy LJ, Pomp D *et al.* Strain screen and haplotype association mapping of wheel running in inbred mouse strains. J Appl Physiol. 2010; 109:623-34.

65. Lightfoot JT, Turner MJ, Daves M, Vordermark A and Kleeberger SR. Genetic influence on daily wheel running activity level. Physiol Genomics. 2004; 19:270-6.

66. Lightfoot JT, Turner MJ, Pomp D, Kleeberger SR and Leamy LJ. Quantitative trait loci (QTL) for physical activity traits in mice. Physiol Genomics. 2008; 32:401-8.

67. Perusse L, Tremblay A, Leblanc C and Bouchard C. Genetic and environmental influences on level of habitual physical activity and exercise participation. Am J Epidemiol. 1989; 129:1012-22.

68. Stubbe JH, Boomsma DI, Vink JM *et al.* Genetic influences on exercise participation in 37,051 twin pairs from seven countries. PLoS ONE. 2006; 1:e22.

69. Stubbe JH, Boomsma DI and De Geus EJC. Sports participation during adolescence: A shift from environmental to genetic factors. Med Sci Sports Exerc. 2005; 37(4):563-70.

70. Swallow JG, Carter PA and Garland Jr T. Artificial selection for increased wheel-running behavior in house mice. Behav Genet. 1998; 28(3):227-37.

71. Turner MJ, Kleeberger SR and Lightfoot JT. Influence of genetic background on daily running-wheel activity differs with aging. Physiol Genomics. 2005; 19:270-6.

72. Dunnington EA, White JM and Vinson WE. Selection for serum cholesterol, voluntary physical activity, 56-day body weight and feed intake in randombred mice. I. Direct responses. Can J Genet Cytol. 1981; 23(3):533-44.

73. Gomersall SR, Rowlands AV, English C, Maher C and Olds TS. The activitystat hypothesis: The concept, the evidence and the methodologies. Sports Med. 2013; 43(2):135-49.

74. De Moor MH, Liu YJ, Boomsma DI *et al.* Genome-wide association study of exercise behavior in Dutch and American adults. Med Sci Sports Exerc. 2009; 41(10):1887-95.

75. Garland Jr. T and Kelly SA. Phenotypic plasticity and experimental evolution. J Exp Biol. 2006; 209:2344-61.

76. Kelly SA, Nehrenberg DL, Hua K, Garland Jr T and Pomp D. Quantitative genomics of voluntary exercise in mice: Transcriptional analysis and mapping of expression QTL in muscle. Physiol Genomics. 2014; 46(16):593-601.

77. Xu S and Garland Jr. T. A mixed model approach to genome-wide association studies for selection signatures, with application to mice bred for voluntary exercise behavior. Genetics. 2017; 207:785-99.

78. Nehrenberg DL, Wang S, Hannon RM, Garland Jr T and Pomp D. QTL underlying voluntary exercise in mice: Interactions with the "mini muscle" locus and sex. J Hered. 2010; 101 (1):42-53.

79. Leamy LJ, Pomp D and Lightfoot JT. An epistatic genetic basis for physical activity traits in mice. Journal of Heredity. 2008; 99(6):639-46.

80. Leamy LJ, Pomp D and Lightfoot JT. Epistatic interactions of genes influence within-individual variation of physical activity traits in mice. Genetica. 2011; 139(6):813-21.

81. Leamy LJ, Pomp D and Lightfoot JT. Genetic variation in the pleiotropic association between physical activity and body weight in mice. Genet Sel Evol. 2009; 41:41-53.

82. Garland Jr. T, Morgan MT, Swallow JG, Rhodes JS, Girard I, Belter JG and Carter PA. Evolution of a small-muscle polymorphism in lines of house mice selected for high activity levels. Evolution. 2002; 56(6):1267-75.

83. Hartmann J, Garland Jr. T, Hannon RM, Kelly SA, Munoz G and Pomp D. Fine mapping of "mini-muscle," a recessive mutation causing reduced hindlimb muscle mass in mice. J Hered. 2008; 99(6):679-87.

84. Kelly SA, Nehrenberg DL, Hua K, Garland Jr T, and Pomp D. Functional genomic architecture of predisposition to voluntary exercise in mice: Expression QTL in the brain. Genetics. 2012; 191(2):643-54.

85. Lightfoot JT. Exercise Genomics. editors Pescatello LS and Roth SM, New York, New York: Humana Press; 2011. Can you be born a couch potato? The genomic regulation of physical activity; p. 45-72.

86. Yang HS, Vitaterna MH, Laposky AD, Shimomura K and Turek FW. Genetic analysis of daily physical activity using a mouse chromosome substitution strain. Physiol Genomics. 2009; 39(1):47-55.

87. Yang HS, Shimomura K, Vitaterna MH and Turek FW. High-resolution mapping of a novel genetic locus regulating voluntary physical activity in mice. Genes Brain Behav. 2012; 11(1):113-24.

88. Flint J and Mackay TF. Genetic architecture of quantitative traits in mice, flies, and humans. Genome Res. 2009; 19(5):723-33.

89. Kostrzewa E, Brandys MK, Van Lith HA and Kas MJ. A candidate syntenic genetic locus is associated with voluntary exercise levels in mice and humans. Behav Brain Res. 2014.

90. Eikelboom R. Human parallel to voluntary wheel running: Exercise. Anim Behav. 1999; 57:F11-2.

91. Knab AM, Bowen RS, Hamilton AT and Lightfoot J. Pharmacological manipulation of the dopaminergic system affects wheel-running activity in differentially active mice. J Biol Regul Homeost Agents. 2012; 26(1):119-29.

92. Rhodes JS, Gammie SC and Garland Jr T. Neurobiology of mice selected for high voluntary wheel-running activity. Integr Comp Biol. 2005; 45(3):438-55.

93. Dubreucq S, Durand A, Matias I *et al.* Ventral tegmental area cannabinoid type-1 receptors control voluntary exercise performance. Biol Psychiatry. 2012; 73(9): 895-903.

94. Keeney BK, Meek TH, Middleton KM, Holness LF and Garland Jr. T. Sex differences in cannabinoid receptor-1 (CB1) pharmacology in mice selectively bred for high voluntary wheel-running behavior. Pharmacol Biochem Behav. 2012; 101(4):528-37.

95. Thompson Z, Argueta D, Garland Jr. T and DiPatrizio N. Circulating levels of endocannabinoids respond acutely to voluntary exercise, are altered in mice selectively bred for high voluntary wheel running, and differ between the sexes. Physiol Behav. 2017; 170:141-50.

96. Roberts MD, Toedebusch RG, Wells KD *et al.* Nucleus accumbens neuronal maturation differences in young rats bred for low versus high voluntary running behaviour. J Physiol. 2014; 592(Pt 10):2119-35.

97. Caetano-Anollés K, Rhodes JS, Garland Jr T, Perez SD, Hernandez AG, Southey BR and Rodriguez-Zas SL. Cerebellum transcriptome of mice bred for high voluntary activity offers insights into locomotor control and reward-dependent behaviors. PLoS One. 2016; 11:e0167095.

98. Saul MC, Majdak P, Perez S, Reilly M, Garland Jr T and Rhodes JS. High motivation for exercise is associated with altered chromatin regulators of monoamine receptor gene expression in the striatum of selectively bred mice. Genes Brain Behav. 2017; 16(3):328-41.

99. Ferguson DP, Dangott LJ, Vellers HL, Schmitt EE and Lightfoot JT. Differential protein expression in the nucleus accumbens of high and low active mice. Behav Brain Res. 2015; 291:283-8.

100. Ferguson DP, Schmitt EE and Lightfoot JT. Vivo-morpholinos induced transient knockdown of physical activity related proteins. PLoS One. 2013; 8(4):e61472.
101. Tsao T-S, Li J, Change KS *et al.* Metabolic adaptations in skeletal muscle overexpressing glut4: Effects on muscle and physical activity. FASEB J. 2001; 15:958-69.
102. Meek TH, Eisenmann JC and Garland Jr. T. Western diet increases wheel running in mice selectively bred for high voluntary wheel running. Int J Obes (Lond). 2010; 34(6):960-9.
103. Pistilli EE, Bogdanovich S, Garton F *et al.* Loss of il-15 receptor alpha alters the endurance, fatigability, and metabolic characteristics of mouse fast skeletal muscles. J Clin Invest. 2011; 121(8):3120-32.
104. O'Neill HM, Maarbjerg SJ, Crane JD *et al.* Amp-activated protein kinase (AMPK) {beta}1{beta}2 muscle null mice reveal an essential role for AMPK in maintaining mitochondrial content and glucose uptake during exercise. Proc Natl Acad Sci U S A. 2011; 108(38): 16092-7.
105. Ferguson DP, Dangott LJ, Schmitt EE, Vellers HL and Lightfoot JT. Differential skeletal muscle proteome of high- and low-active mice. J Appl Physiol. 2014; 116(8):1057-67.
106. De Geus EJC and De Moor MHM. A genetic perspective on the association between exercise and mental health. Ment Health Phys Act. 2008; 1 (2):53-61.
107. Thorndike EL. A proof of the law of effect. Science. 1933; 77(1989):173-5.
108. Ekkekakis P, Hall EE and Petruzzello SJ. Variation and homogeneity in affective responses to physical activity of varying intensities: An alternative perspective on dose-response based on evolutionary considerations. J Sports Sci. 2005; 23 (5):477-500.
109. Kwan BM and Bryan A. In-task and post-task affective response to exercise: Translating exercise intentions into behaviour. Br J Health Psychol. 2010; 15(Pt 1):115-31.

110. Ruby MB, Dunn EW, Perrino A, Gillis R and Viel S. The invisible benefits of exercise. Health Psychol. 2011; 30(1):67-74.

111. Dunton GF and Vaughan E. Anticipated affective consequences of physical activity adoption and maintenance. Health Psychol. 2008; 27(6):703-10.

112. Rhodes RE and Kates A. Can the affective response to exercise predict future motives and physical activity behavior? A systematic review of published evidence. Ann Behav Med. 2015; 49(5):715-31.

113. Schneider ML and Graham DJ. Personality, physical fitness, and affective response to exercise among adolescents. Med Sci Sports Exerc. 2009; 41(4):947-55.

114. Williams DM, Dunsiger S, Ciccolo JT, Lewis BA, Albrecht AE and Marcus BH. Acute affective response to a moderate-intensity exercise stimulus predicts physical activity participation 6 and 12 months later. Psychol Sport Exerc. 2008; 9(3):231-45.

115. Williams DM, Dunsiger S, Jennings EG and Marcus BH. Does affective valence during and immediately following a 10-min walk predict concurrent and future physical activity. Ann Behav Med. 2012; 44(1):43-51.

116. De Moor MH, Beem AL, Stubbe JH, Boomsma DI and De Geus EJ. Regular exercise, anxiety, depression and personality: A population-based study. Prev Med. 2006; 42(4):273-9.

117. Rhodes RE and Smith NE. Personality correlates of physical activity: A review and meta-analysis. Br J Sports Med. 2006; 40(12):958-65.

118. Wilkinson AV, Gabriel KP, Wang J *et al.* Sensation-seeking genes and physical activity in youth. Genes Brain Behav. 2013; 12(2):181-8.

119. Wilson KE, Das BM, Evans EM and Dishman RK. Personality correlates of physical

activity in college women. Med Sci Sports Exerc. 2015; 47(8):1691-7.

120. Polderman TJ, Benyamin B, De Leeuw CA, Sullivan PF, Van Bochoven A, Visscher PM and Posthuma D. Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nat Genet. 2015; 47(7):702-9.

121. Dishman RK, Motl RW, Sallis JF *et al.* Self-management strategies mediate self-efficacy and physical activity. Am J Prev Med. 2005; 29(1):10-8.

122. MaCauley D, McCrum EE, Stott G *et al.* Levels of physical activity, physical fitness and their relationship in the Northern Ireland Health and Activity Survey. Int J Sports Med. 1998; 19(7):503-11.

123. Nigg CR. Explaining adolescent exercise behavior change: A longitudinal application of the transtheoretical model. Ann Behav Med. 2001; 23(1):11-20.

124. Posner MI and Rothbart MK. Toward a physical basis of attention and self regulation. Phys Life Rev. 2009; 6(2):103-20.

125. Aaltonen S, Kaprio J, Vuoksimaa E, Huppertz C, Kujala UM and Silventoinen K. Genetic architecture of motives for leisure-time physical activity: A twin study. Scand J Med Sci Sports. 2016; 27(11): 1431-41.

126. Powers SK and Howley ET. Exercise Physiology: Theory and Application to Fitness and Performance, 10th Edition. New York, NY: McGraw Hill; 2017.

127. Schutte NM, Nederend I, Hudziak JJ, De Geus EJ and Bartels M. Differences in adolescent physical fitness: A multivariate approach and meta-analysis. Behav Genet. 2016; 46(2):217-27.

128. Schutte NM, Nederend I, Hudziak JJ, Bartels M and De Geus EJ. Twin-sibling study and meta-analysis on the heritability of maximal oxygen consumption. Physiol Genomics.

2016; 48(3):210-9.

129. Bouchard C, An P, Rice T *et al.* Familial aggregation of VO2max response to exercise training: Results from the Heritage Family Study. J Appl Physiol (1985). 1999; 87(3):1003-8.

130. Yancey AK, Grant D, Kurosky S, Kravitz-Wirtz N and Mistry R. Role modeling, risk, and resilience in California adolescents. J Adolesc Health. 2011; 48(1):36-43.

131. Huppertz C, Bartels M, De Zeeuw EL *et al.* Individual differences in exercise behavior: Stability and change in genetic and environmental determinants from age 7 to 18. Behav Genet. 2016; 46(5):665-79.

132. Roy EJ and Wade GS. Role of estrogens in androgen-induced spontaneous activity in male rats. J Comp Physiol Psychol. 1975; 89(6):573-9.

133. Bowen RS, Ferguson DP and Lightfoot JT. Effects of aromatase inhibition on the physical activity levels of male mice. J Steroids Horm Sci. 2011; 1(1):1-7.

134. Bowen RS, Knab AM, Hamilton AT, McCall JR, Moore-Harrison TL, and Lightfoot JT. Effects of supraphysiological doses of sex steroids on wheel running activity in mice. J Steroids Horm Sci. 2012; 3(2):110.

135. Stewart CC. Variations in daily activity produced by alcohol and by changes in barometric pressure and diet, with a description of recording methods. Am J Physiol. 1898; 1 (1):40-56.

136. Epling WF and Pierce WD. Activity-based anorexia: A biobehavioral perspective. Int J Eat Disord. 1988; 7 (4):475-85.

137. Verhagen LA, Luijendijk MC and Adan RA. Leptin reduces hyperactivity in an animal model for anorexia nervosa via the ventral tegmental area. Eur Neuropsychopharmacol.

2011; 21(3):274-81.

138. Yamada Y, Colman RJ, Kemnitz JW, Baum ST, Anderson RM, Weindruch R and Schoeller DA. Long-term calorie restriction decreases metabolic cost of movement and prevents decrease of physical activity during aging in rhesus monkeys. Exp Gerontol. 2013; 48(11):1226-35.

139. Casper RC. The ‘drive for activity’ and “restlessness” in anorexia nervosa: Potential pathways. J Affect Disord. 2006; 92(1):99-107.

140. Sternheim L, Danner U, Adan R and Van Elburg A. Drive for activity in patients with anorexia nervosa. Int J Eat Disord. 2015; 48(1):42-5.

141. Acosta W, Meek TH, Schutz H, Dlugosz EM and Garland Jr. T. Preference for western diet coadapts in high runner mice and affects voluntary exercise and spontaneous physical activity in a genotype-dependent manner. Behav Processes. 2017; 135:56-65.

142. Vellers HL, Letsinger AC, Walker NR, Granados JZ and Lightfoot JT. High fat high sugar diet reduces voluntary wheel running in mice independent of sex hormone involvement. Front Physiol. 2017; 8:628.

143. Lenard NR and Berthoud HR. Central and peripheral regulation of food intake and physical activity: Pathways and genes. Obesity (Silver Spring). 2008; 16 Suppl 3:S11-22.

144. Stefan N, Vozarova B, Del Parigi A *et al.* The gln223arg polymorphism of the leptin receptor in Pima Indians: Influence on energy expenditure, physical activity and lipid metabolism. Int J Obes Relat Metab Disord. 2002; 26(12):1629-32.

145. Teerds KJ, De Rooij DG and Keijer J. Functional relationship between obesity and male reproduction: From humans to animal models. Hum Reprod Update. 2011; 17(5):667-83.

146. Jean A, Laurent L, Bockaert J *et al.* The nucleus accumbens 5-htr$_4$-cart pathway ties

anorexia to hyperactivity. Transl Psychiatry. 2012; 2:e203.

147. Schmitt EE, Vellers HL, Porter WW and Lightfoot JT. Environmental endocrine disruptor inhibits voluntary physical activity in mice. Med Sci Sports Exerc. 2016; 48 (7):1251-8.

148. Hiramatsu L, Kay JC, Thompson Z *et al.* Maternal exposure to western diet affects adult body composition and voluntary wheel running in a genotype-specific manner in mice. Physiol Behav. 2017; 179:235-45.

149. Eclarinal JD, Zhu S, Baker MS, Piyarathna DB, Coarfa C, Fiorotto ML and Waterland RA. Maternal exercise during pregnancy promotes physical activity in adult offspring. FASEB J. 2016; 30(7):2541-8.

150. Garland Jr. T, Cadney MD and Waterland RA. Early-life effects on adult physical activity: Concepts, relevance, and experimental approaches. Physiol Biochem Zool. 2017; 90(1):1-14.

151. Garland Jr. T, Zhao M and Saltzman W. Hormones and the evolution of complex traits: Insights from artificial selection on behavior. Integr Comp Biol. 2016; 56(2):207-24.

Figure Legends:

Figure 1 – Percentage of surveyed BRFSS adults with 30+ minutes of physical activity five or more days/week (1996-2000) OR percentage with 30+ minutes of physical activity or 20+ minutes of vigorous activity five or more days/week.

Figure 2 - Conceptual model for the main physiological systems involved in physical activity and its regulation. 1) The brain is the behavioral control center integrating pre-set information from the activity-stat (see text) with ongoing motivational state. 2) Duration and intensity of physical activity will depend on cardiorespiratory fitness, partly by viscerosomatic signals (e.g. becoming out of breath) that affect motivational state. 3) Muscle is the mechanism of action (effector) and performance capability of this unit, as well as the cardiorespiratory system, is necessary but not sufficient for physical activity. Effects of biological, including genetic/genomic and environmental factors, with many interactive effects, will determine individual differences in the functioning of these physiological systems and hence the level of physical of physical activity.

Figure 3 - Research directions to further unravel the biological regulation of physical activity level. The three major sources of individual differences in physical activity level are genetic variants, environmental influences, and their interplay. Strategies to understand the biology of physical activity regulation and the contribution of genetic and environmental factors are numbered 1 to 9. Studies of humans and of animal models play complementary roles. The ultimate goal is to identify safe and effective environmental and/or pharmacological interventions that can increase the level of physical activity.

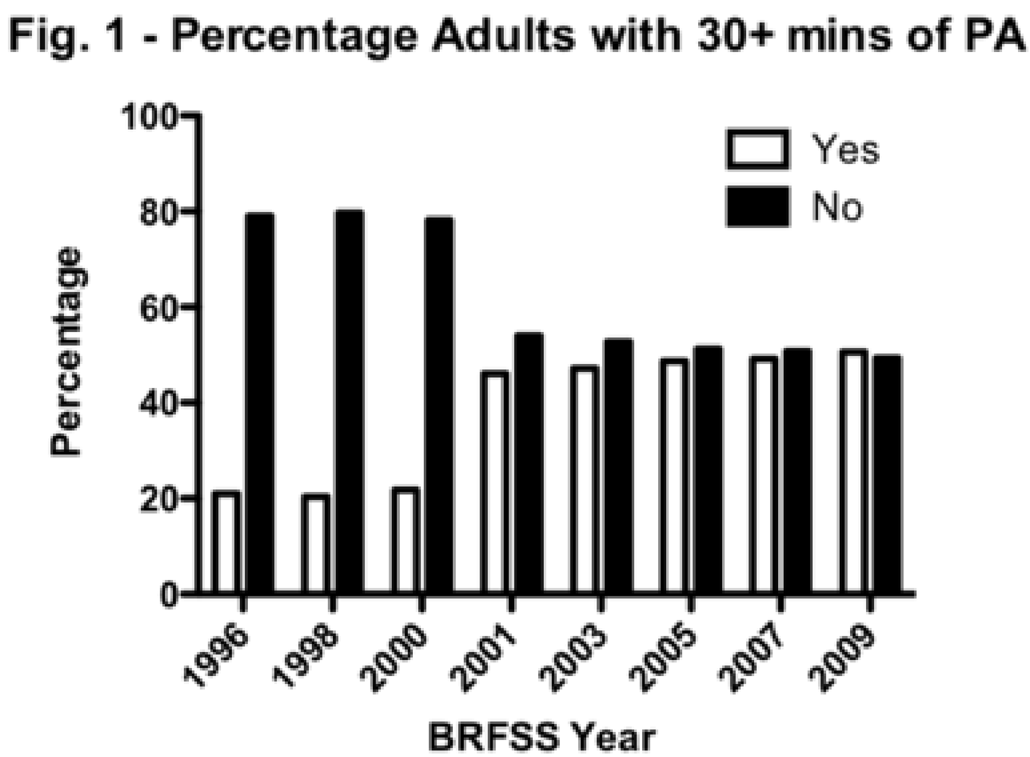
Fig. 1 - Percentage Adults with 30+ mins of PA
Percentage
100
80
60
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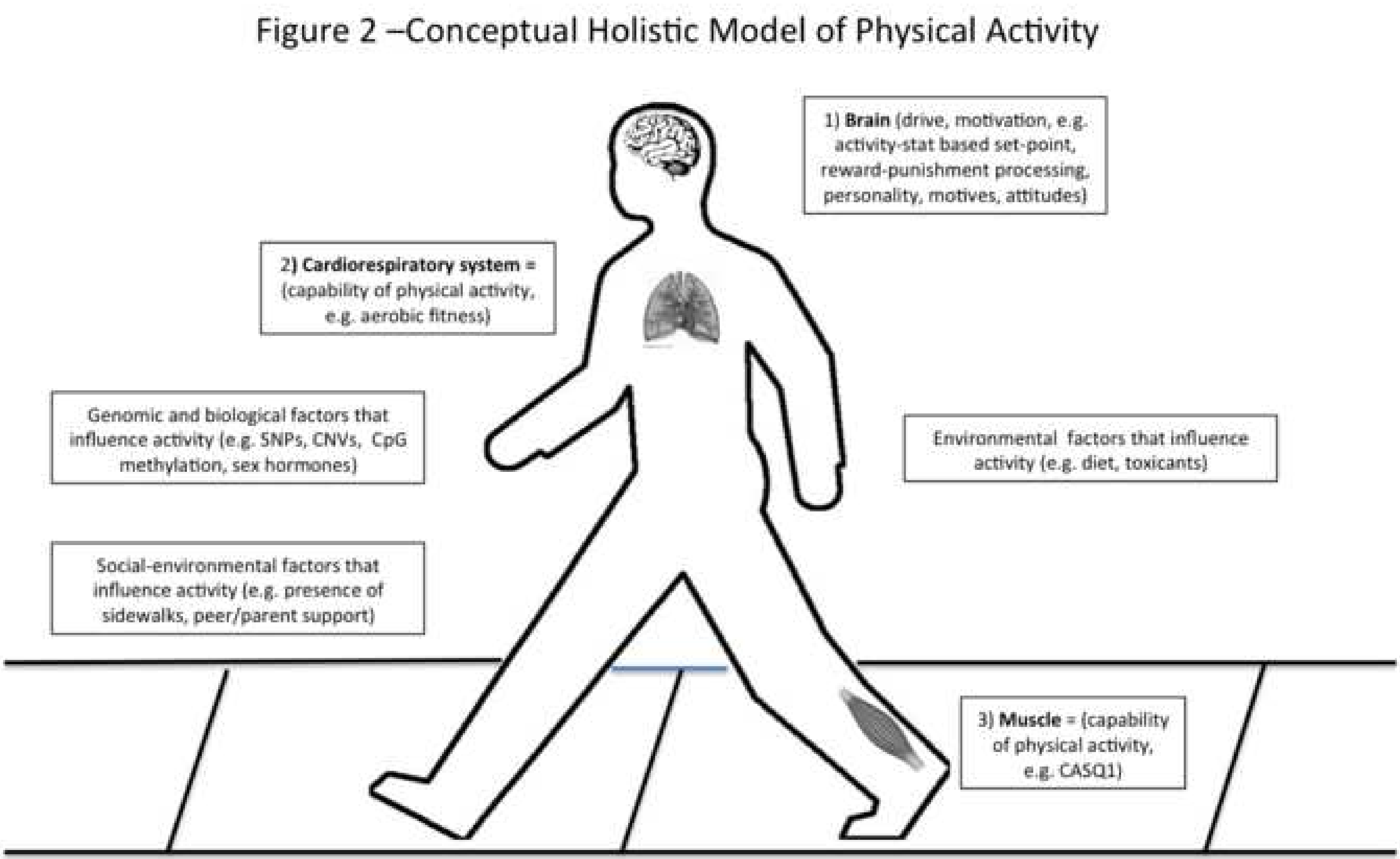
Figure 2 –Conceptual Holistic Model of Physical Activity
1) **Brain** (drive, motivation, e.g. activity-stat based set-point, reward-punishment processing, personality, motives, attitudes)
2) **Cardiorespiratory system** = (capability of physical activity, e.g. aerobic fitness)
Genomic and biological factors that influence activity (e.g. SNPs, CNVs, CpG methylation, sex hormones)
Environmental factors that influence activity (e.g. diet, toxicants)
Social-environmental factors that influence activity (e.g. presence of sidewalks, peer/parent support)
3) **Muscle** = (capability of physical activity, e.g. CASQ1)

Figure 3

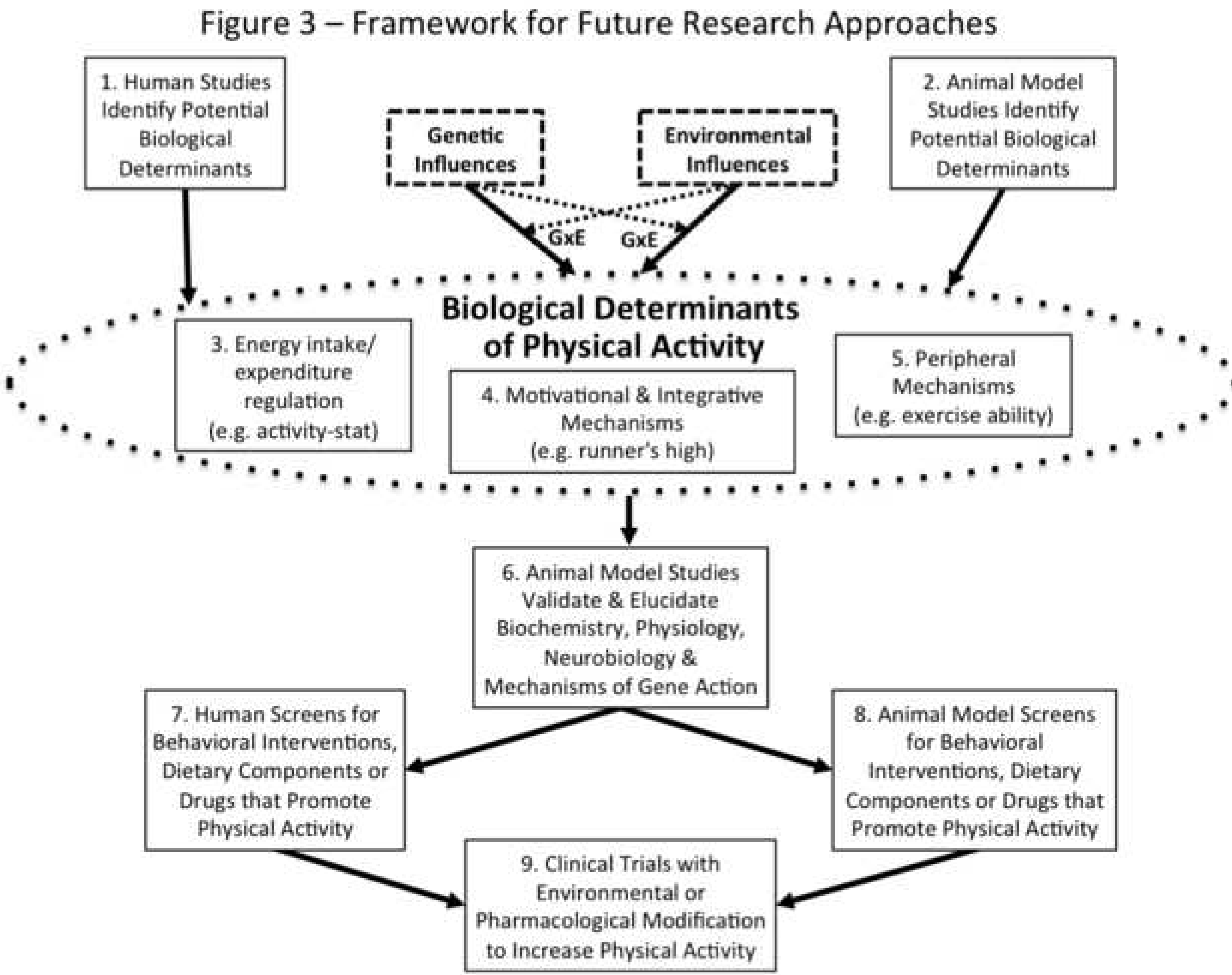
Figure 3 – Framework for Future Research Approaches
1. Human Studies Identify Potential Biological Determinants
Genetic Influences
Environmental Influences
2. Animal Model Studies Identify Potential Biological Determinants
GxE
GxE
Biological Determinants of Physical Activity
3. Energy intake/ expenditure regulation (e.g. activity-stat)
4. Motivational & Integrative Mechanisms (e.g. runner's high)
5. Peripheral Mechanisms (e.g. exercise ability)
6. Animal Model Studies Validate & Elucidate Biochemistry, Physiology, Neurobiology & Mechanisms of Gene Action
7. Human Screens for Behavioral Interventions, Dietary Components or Drugs that Promote Physical Activity
8. Animal Model Screens for Behavioral Interventions, Dietary Components or Drugs that Promote Physical Activity
9. Clinical Trials with Environmental or Pharmacological Modification to Increase Physical Activity