Etiology and Pathophysiology

Genetic factors in exercise adoption, adherence and obesity

M. P. Herring¹, M. H. Sailors² and M. S. Bray¹,³

¹Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA; ²Department of Symptoms Research, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; ³Department of Nutritional Sciences, University of Texas at Austin, Austin, Texas, USA

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Address for correspondence: MS Bray, Department of Nutritional Sciences, University of Texas at Austin, T.S. Painter Hall, Room 5.32, 103 W. 24th Street, Austin, TX 78705, USA.
E-mail: mbray@austin.utexas.edu

Summary

Physical activity and exercise play critical roles in energy balance. While many interventions targeted at increasing physical activity have demonstrated efficacy in promoting weight loss or maintenance in the short term, long term adherence to such programmes is not frequently observed. Numerous factors have been examined for their ability to predict and/or influence physical activity and exercise adherence. Although physical activity has been demonstrated to have a strong genetic component in both animals and humans, few studies have examined the association between genetic variation and exercise adherence. In this review, we provide a detailed overview of the non-genetic and genetic predictors of physical activity and adherence to exercise. In addition, we report the results of analysis of 26 single nucleotide polymorphisms in six candidate genes examined for association to exercise adherence, duration, intensity and total exercise dose in young adults from the Training Interventions and Genetics of Exercise Response (TIGER) Study. Based on both animal and human research, neural signalling and pleasure/reward systems in the brain may drive in large part the propensity to be physically active and to adhere to an exercise programme. Adherence/compliance research in other fields may inform future investigation of the genetics of exercise adherence.

Keywords: Energy expenditure, genes, physical activity, variation.

Introduction

Obesity has been increasingly recognized as a world-wide public health issue with far-reaching impact on quality of life, the global economy and the burden on medical health care. Numerous strategies focused on behaviour modification, nutrition, physical activity, psychology, social support and other putative underpinnings of obesity have been developed to promote weight loss. Many of these have proven efficacious in the short term, but long-term success and adherence to such programmes generally has remained elusive. Although physical activity is associated with immediate health and psychological benefits, even in the absence of weight loss, the statistics on the prevalence of sedentarism go hand-in-hand with that of obesity. While we understand a great deal about how to impact obesity through diet, exercise and behaviour, what we do not have a good understanding of is why adhering to such programmes is so very difficult for many. Exercise adherence research has generally focused on the psychological, social and demographic aspects of adherence, with relatively little emphasis on its potential biological basis. Although physical activity has been demonstrated to have a strong genetic component in both animals and humans, there is a dearth of knowledge in the role of genetic variation as a driving force for physical activity and exercise adherence. In this review, we provide an overview of the genetic and non-genetic predictors of physical activity and adherence, along...
Obesity, energy balance and physical activity

Obesity results primarily from an imbalance between energy intake and energy expenditure, which may be influenced by a myriad of environmental and behavioural factors. The first law of thermodynamics, which states that energy is neither created nor destroyed but is converted from one form to another, also applies to living organisms. The energy balance equation states that body mass remains constant when caloric intake equals caloric expenditure. Any chronic imbalance (too much energy or a deficit of energy) can result in a change of body mass. If the caloric value of food intake exceeds the energy loss due to heat and work, it is converted to stored energy in endogenous forms such as glycogen, cellular protein and triglycerides stored in adipose. If the caloric intake of food is less than the energy output from work and heat, these endogenous stores will be utilized, resulting in reduced body mass. Energy imbalance in an obese state is largely driven by excessive caloric consumption that is not offset by physical activity or other alterations in metabolism. Although the energy balance equation appears very simplistic in nature, in reality it is remarkably complex involving metabolic, physiological, nutritional, psychological and genetic influences, as well as the complex interrelation among these factors, that potentially affect both sides of the energy balance equation.

The two components of energy balance that are under an individual's volitional control are energy expended during physical activity and dietary energy intake, although a component of both may be non-volitional. Physical activity is defined as 'any bodily movement produced by skeletal muscles that results in energy expenditure;' exercise is a subcategory of physical activity that is 'planned, structured, repetitive, and purposive' (1). Although approximately 60% of US adults self-report engaging in the recommended volume of physical activity (~500 MET min week⁻¹) (2), fewer than 5% actually meet this criterion when physical activity is objectively estimated using accelerometry and less than 2.5% meet recommended levels of vigorous physical activity necessary for improved fitness (3). Considerable weight gain can occur in a person with a constant level of energy intake but reduced level of energy expenditure; this is especially true during aging, in which lowered energy expenditure due to slowing metabolism and decreased lean body mass combined with less physical activity are often not matched by decreased food intake (4). Few present day jobs require strenuous physical activity, and even fewer people compensate for reduced work-related or other physical movement with regular voluntary physical activity. The current rates of physical inactivity among all age groups are particularly alarming given the increased risk for morbidity and mortality associated with a lifetime of physical inactivity (5–10).

Predictors of physical activity

Studies have repeatedly demonstrated that physically active individuals are less likely to gain weight over time (11–14). What factors separate the physically active from the inactive? Income, socioeconomic status, education, gender, age and raceethnicity have all been reported to influence physical activity levels, either positively or negatively (15). Nevertheless, both animal and human studies have provided evidence that the propensity to be physically active may also be driven at least in part by genes.

Evidence from animal research

In animals, spontaneous physical activity levels diverge widely with type of rodent strain (16–18) and selective breeding experiments have produced colonies of high active and low active rodents with distinctively different predispositions for voluntary physical activity (19–21). The most active mouse strains demonstrate physiologic changes consistent with enhanced physical performance, including increased cardiac contractility and cardiac hypertrophy (18), indicating that physiological adaptation and fitness may be a factor that drives activity. Conversely, differences in behavioural parameters are observed in animals selectively bred for high physical activity in which access to the running wheel is limited in order to prevent a 'training effect'. Compared to less active controls, animals bred for high activity demonstrate increased signs of stress when running is denied, enhanced preference for wheel running over other activities and increased neuronal activity associated with physical activity, suggesting that behavioural traits may be targeted by the breeding process (22). Through the use of backcrosses and intercrosses between high active and low active strains of mice, gene mapping studies in animals have delineated multiple quantitative trait loci (QTL) that are distinct for running duration, distance and speed (17,23). Similar mapping studies in mice selectively bred for high voluntary wheel running have also identified novel exercise QTL, some of which are sex-specific (24). Each of the loci identified explains only a small portion of the variance in activity traits, and there is little overlap between the QTL identified in within-strain breeding crosses versus multiple strain crosses, suggesting that the molecular mechanisms driving physical activity are highly complex and potentially population- and/or context-specific.
Candidate genes

The dopamine receptor 1 (Drd1) and nascient helix loop helix 2 (Nhlh2) genes are among the most strongly supported of the candidate genes identified within the mouse QTL activity studies (25,26); both of these genes meet the criteria of having functional relevance, localizing within an identified QTL, containing sequence variation that is predictive of a functional difference in the protein, exhibiting gene expression differences between high active and low active animals and producing a phenotypic change when the gene is manipulated (25). Animal studies of dopaminergic activity have shown decreased initiation of spontaneous movement, akinesia, abnormal gait and postural issues among dopamine receptor-deficient mice (27,28). In addition, reduced dopamine receptors are thought to contribute to age-related declines in overall physical activity (29). Knockout models of the Nhlh2 gene demonstrate adult-onset obesity that is largely the consequence of decreased spontaneous activity driven by reduced motivation and ability to perform moderate physical activity (30). Both Drd1 and Nhlh2 have also been implicated in feeding behaviour (31,32). Nhlh2 has been demonstrated to influence the melanocortin pathway, in which mutations have been shown to produce monogenic forms of obesity in humans and which has repeatedly been implicated in the risk for and development of obesity in genome-wide association studies (33,34). Nhlh2 has been shown to transcriptionally regulate the melanocortin 4 receptor (Mec4r) and proconvertase-1 genes; thus, Nhlh2 transcriptional activity may directly influence human and rodent body weight homeostasis through both feeding and physical activity (35). In addition to Drd1 and Nhlh2, the transcription factor Ap2, alpha (Tcfap2a) gene was identified in mapping studies of high active and low active mice as a QTL candidate gene that interacts with the dopamine pathway by regulating the promoter activity of the D1 receptor gene (36); interestingly, this gene is also a key factor in adipocyte differentiation in animals and humans.

Six candidate genes (insulin induced gene 2; suppressor of cytokine signalling 2; DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, Y-linked; arrestin domain containing 4; prolylcarboxypeptidase, angiotensinase C; and interleukin 15) were recently identified by genome-wide eQTL in mice brain for their potential action in voluntary physical activity and body composition (37). Other QTL candidate physical activity mouse genes include myostatin (Gdf8), glucose transporter 4 (Slc2a4) and 3-phosphoadenosine 5-phosphosulfate synthase (38). The candidate genes identified through QTL mapping in rodents reflect a notable overlap between physical activity and obesity-related traits. The relevance of these gene pathways to energy balance is of potential importance.

Evidence from human subjects research

In humans, physical activity has been shown to aggregate in families. Children of physically active parents are significantly more likely to be active than those with inactive parents, even after controlling for familial environment and role modelling (39). The heritability of physical activity, or amount of trait variability accounted for by variation in genes, varies both with the type of population studied and the instrument used to assess physical activity. Heritability estimates in the scientific literature range from 9% in Mexican–American families (40) to almost 80% in European twins, with the highest concordance reported for vigorous physical activity (41–45). The compendium of heritability research in physical activity provides substantial support for the role of genes in influencing the natural tendency to be physically active.

The Human Gene Map for Performance and Health-related Fitness Phenotypes lists a number of genes that have been identified to be associated with exercise performance and response to exercise training (46). These genes interact with physical activity and/or exercise to influence multiple physiological outcomes, including body size/mass, adiposity, blood lipids and glucose, and haemodynamics (46). The biological functions of these genes are consistent with the fitness phenotypes observed in animal models of physical activity and provide insight as to the types of physiologic processes that might drive the capacity for physical activity. Nevertheless, physical changes associated with genes whose expression or action can be altered by exercise may be distinctly different from genes that directly influence the propensity to be active or inactive.

Multiple QTLs for physical activity have been identified in human linkage studies (46), with candidate gene regions containing both metabolic and satiety signalling genes (47–49). In two separate studies, both common and rare variation within the Mec4r gene was associated with self-reported physical inactivity (47,50); these effects were demonstrated in both non-Hispanic whites from the Quebec Family Study as well as Mexican–Americans from the San Antonio Heart Study. In a study of the leptin receptor (LEPR) Gln223Arg variant in Pima Indians, Stefan et al. reported that homozygotes for the Arg223-encoding allele of LEPR had lower 24 h energy expenditure (P = 0.04) and physical activity levels (P = 0.007) compared to Gln homozygotes (48).

Neural/reward systems and physical activity

Components of neural reward systems appear to be central factors in influencing physical activity in both animals and humans. Much of the empirical research has focused on neurotransmitters and neurotrophic peptides, including brain monoamines (i.e. dopamine and serotonin) and...
brain-derived neurotrophic factor (BDNF), due in large part to the plausible role of these neurobiological factors in voluntary locomotor activity, motivation and reward processing (51–53).

Serotonin

The serotonin system has been strongly associated with both food intake and physical activity levels, and multiple pharmacological treatments for obesity target the serotonin system (54). Animals lacking a functional serotonin receptor 2C (Htr2c) are both hyperphagic and hyperactive but also have substantial reductions in the energy cost of physical activity, resulting in late-onset obesity (55). Extensive RNA editing of the Htr2c gene results in multiple isoforms associated with variability in energy metabolism and eating behaviour (56). In humans, the serotonin system is associated with a number of psychological and mood disorders (e.g. depression, anxiety, schizophrenia, bipolar disease, etc.), many of which are also associated with obesity (57). Recently, Carr et al. identified the A/G variant rs6314 within the HTR2A gene as a moderator of food reinforcement on body mass index (BMI), with rs6314 variation being predictive of both high and low BMI based on the level of food reinforcement (58). Drug targets of both the serotonin 5-HT2A and 5-HT2C receptors have demonstrated efficacy in reducing the symptoms of depression and anxiety while inducing hypophagia and reducing body weight (57).

Dopamine

The dopamine system is a key regulator of motor movement and motivational behaviours, and variation in genes within the dopamine system has also been associated with human and animal physical activity and activity-related pathogenesis, including attention-deficit/hyperactivity disorder (59), self-reported physical activity (60) and Parkinson’s disease (61). Variation in the DRD4 gene has been associated with increased longevity in both animals and humans, and the effect was strongly correlated with physical activity levels (62). Acute treadmill running increases dopamine release (63) and turnover (64) and chronically up-regulates D2 receptors in rats (65).

Brain-derived neurotrophic factor

The BDNF gene has also been implicated in physical activity behaviour in animal and human studies. Mice bred to be physically active have higher levels of hippocampal BDNF compared to their wild-type counterparts (66), and exercise has been shown to induce BDNF expression, which may play a critical role in enhanced cognitive function following exercise training (67). In overweight and obese subjects, 10 weeks of aerobic exercise training was associated with increased serum and platelet BDNF, along with significant improvements in multiple metabolic parameters (68). Bryan et al. reported that motivational affect associated with exercise was a function of whether and how long a person had been performing an acute bout of exercise and that changes in affect were mediated by variation in the BDNF gene (69). Positive affect increased with greater duration of acute exercise, and carriers of the BDNF 196A allele showed a more pronounced increase in positive affect compared to 196G/G homozygotes. Increases in heart rate associated with exercise duration were also associated with both alterations in mood and variation in BDNF, suggesting that mood may be influenced by the interaction between physiologic changes and genetic variation (69).

It is clear from the available evidence from rodent models and studies of humans summarized above that genes play a substantial role in influencing physical activity behaviour. However, less is known about which factors influence the propensity to adhere to physical activity or exercise programmes.

Defining adherence

Adherence can be defined as commitment to a behavioural standard established as part of a negotiated agreement, alliance or contract, particularly in the context of behavioural change, therapeutic intervention and/or medical treatment (70,71). Healthcare providers often favour the word ‘adherence’ to ‘compliance’ because it implies that a treatment plan is based on a negotiated therapeutic alliance between patient and physician (70). In the context of medical research, adherence rates have typically been reported as a percentage of the prescribed dose of a medical treatment actually completed across a specific time period (70). Similarly, research on exercise behaviour change has traditionally defined exercise adherence based on an attendance criterion (i.e. minimum percentage of prescribed exercise sessions actually attended). Early trials of exercise often defined adherence as a session attendance of 60–80% resulting in a commonly reported finding that approximately half of participants dropped out within the first 6 months before the salutary benefits of exercise were realized or identified (72–74). These disappointing adherence rates are comparable to the poor rates shown for adherence to medication after the first 6 months of pharmacotherapy among patients with chronic medical conditions (70,75–77).

Non-genetic predictors of adherence

Variables identified as being associated with exercise and physical activity adherence include age, education, gender, ethnicity, previous activity, dietary habits, smoking, occupation and social support (15,78–81). Subjects who
reported they were physically active and had a moderate level of aerobic fitness were the most likely to continue to exercise (80). Higher body weight and body fat was associated with non-adherence to exercise (73,82). Social-cognitive variables (e.g. self-efficacy, self-motivation, perceived barriers, social support, personality and outcome expectancy value) have consistently been shown to influence exercise adoption and adherence (15,83). Perceived self-efficacy or belief in one’s capabilities to achieve a behavioural goal, is among the most consistent and strongest psychological predictors/mediators of exercise adoption and adherence (15,84–86). High self-motivation and a tendency to set goals and strive to reach them by emphasizing effort, determination and persistence following the setting of a goal, are both positively associated with exercise adherence (87–89). In addition, social support and perceived barriers to physical activity, including perceived lack of time and injury/illness, also can strongly influence exercise behaviour (15,79,90,91).

Exercise intensity and perceived effort have both been found to be negatively associated with exercise adoption and adherence (15,92). Nevertheless, intensity is often neglected in clinical trials of the predictors of exercise behaviour, which have primarily been limited to activity type in population surveys (93). Compliance with intensity prescription can be measured by the use of computerized systems that automatically adjust work rate to maintain heart rate at the prescribed level (94). However, even with the use of monitoring devices, participants’ self-regulated compliance with heart rate prescriptions drift during prolonged trials even when completion rates are high (95). We recently reported significant associations between exercise dose (based on intensity and duration of accumulated exercise sessions) and improved body weight, percent body fat, fasting cholesterol and fasting glucose, reiterating the importance of quantifying compliance with prescribed exercise dose as a component of exercise adherence (96).

Exercise adherence and genetic variation

Although a substantial amount of research in humans describes the demographic, psychological, social and behavioural components of adherence, very few studies have directly examined the association between genetic variation and exercise adherence. This may be due to lack of availability of samples for genotyping in exercise intervention studies, lack of consent for the use of DNA in intervention studies not focused on genetic analysis, and/or lack of study designs that follow the natural attrition of subjects from an intervention without interference from the study investigators. In one of the few genetic studies with available adherence data, Thompson et al. determined genotype at a common 287-bp insertion (I)/deletion (D) polymorphism in intron 16 in the angiotensin converting enzyme (ACE) gene and examined I/D genotype for association to exercise adherence defined by session attendance. The investigators reported that adherence to exercise training was significantly higher in I carriers than in D homozygotes (97). The ACE I/D polymorphism was not associated to maximal oxygen uptake, BMI, skinfold thickness and serum lipids in this study, and the authors hypothesized that the genetic predisposition to adhere to an exercise regimen may drive response to exercise, rather than vice versa (97).

Because the dopamine and serotonin pathways have been implicated in physical activity behaviour in both animals and humans, we conducted a focused analysis of 26 single nucleotide polymorphisms (SNPs) in six genes within these pathways (BDNF, BDNF opposite strand [BDNFOS], DRD2, DRD4, HTR2A and HTR2C) in 885 participants (males = 333, females = 552) from the Training Interventions and Genetics of Exercise Response (TIGER) Study. The TIGER Study is a large epidemiologic study designed to identify genetic variation associated with physiological response and adherence to an aerobic exercise programme (98). The exercise intervention is consistent with recommendations for vigorous physical activity and consists of at least 30 min of aerobic exercise performed 3 days per week for up to 30 weeks at 65%–85% of maximum heart rate reserve. Each exercise session is documented through the use of computerized heart rate monitors. During the first phase of the study, four comparable cohorts were recruited in each of four years (2004–2008), and more than 42,000 exercise sessions were recorded. The racial/ethnic groups most frequently represented by the majority of participants in this study were non-Hispanic white (28.5%), African–American (27.3%), Hispanic (23.7%) and Asian (7.4%). Exercise exposure is quantified by adjusting total exercise time by exercise intensity and summing the adjusted minutes across all exercise sessions to create a summary score representing total exercise dose (the heart rate physical activity score, HRPAS) (96). Adherence in the TIGER Study is defined as meeting the minimum prescribed exercise dose or HRPAS for each cohort.

All analyses were conducted using Stata software, version 11.2 (Stata Corp., College Station, TX, USA). Nominal significance was set a P-value of 0.05 and Bonferroni-corrected significance at a P-value of 0.001 (0.05/26 variants for each outcome). A total of 82 ancestry–informative markers were genotyped to obtain individual estimates of ancestral genetic admixture in order to reduce potential confounding from population stratification (99). Linear regression, adjusted for age, gender and race/ethnicity was used to examine differences in physiologic and performance traits by adherence/non-adherence status. Logistic regression, adjusted for age, gender, BMI and genetic admixture was used to examine the association between genotype and exercise adherence, defined as
meeting or not meeting the minimum prescribed exercise dose (HRPAS). Linear regression, adjusted for age, gender, BMI and genetic admixture, was used to examine the association between genotype and quantitative measures of HRPAS, average exercise intensity, average exercise heart rate and average exercise session duration.

Table 1 depicts the mean values for the non-genetic predictors of exercise adherence in adherent and non-adherent subjects based on HRPAS cut-points in the TIGER Study. Adherent subjects exercised at a significantly higher exercise intensity and average heart rate and for a longer duration, and had significantly lower values for BMI, body weight, and waist and hip circumferences. Baseline measures of aerobic fitness and cardiovascular function (estimated VO2max, resting heart rate, systolic and diastolic blood pressure) were not associated with exercise adherence in the TIGER Study, as shown in Table 1. The continuous measure of HRPAS was significantly associated with both African and European admixture, providing evidence for a genetic component to this measured trait; however, adherence defined by HRPAS cut-points was not associated with genetic admixture.

A summary of the genotype frequencies for the DNA sequence variants examined in this study is provided in Supporting Information (Table S1). Variants examined in this study included either tagging SNPs or non-synonymous coding region variants (as noted in Table S1). After controlling for the covariates listed above, rs6314 within the HTR2A gene was nominally associated with both exercise adherence (P < 0.005) and exercise dose (HRPAS, P < 0.006). Within the HTR2C gene, rs5946015 was associated with exercise adherence (P < 0.005) and duration (P < 0.03) and rs1801412 was associated with average exercise intensity (P < 0.05). Within the DRD4 gene, rs3758653 was associated with mean exercise duration (P < 0.04). Average values for the significant quantitative phenotypes reported above by genotype are provided in Fig. 1. Variants in the DRD2, BDNF, and BDNFOS genes were not associated with adherence or other exercise parameters in this study.

Our results provide suggestive evidence that dopaminergic and serotonergic pathways may play a role in exercise tolerance and adherence in humans, just as they appear to do in animals. A strength of the TIGER Study is that subjects are allowed to self-select their exercise intensity and duration, within a defined exercise protocol, allowing for the examination of factors that influence the variability in these parameters. Self-selected intensity and duration provide an indication of exercise tolerance, which may be influenced by both physical fitness as well as psychological measures. Both subject recruitment and genotyping are ongoing in the TIGER Study; thus, more definitive conclusions regarding the role of neural pathways in exercise adherence can be made with a larger and more powerful data set.

Exercise adherence, compulsion and addiction

Although relatively little is known about the genetics of exercise adherence, such studies may be informed by genetic analyses of similar types of behaviours. As depicted in Fig. 2, non-adherence and adherence might be considered part of a continuum of behaviour that would include both compulsive and addictive behaviours. Compulsive behaviour is defined as performing an act persistently and repetitively without it leading to an actual reward or

### Table 1 Characteristics of adherent and non-adherent subjects

<table>
<thead>
<tr>
<th></th>
<th>Adherent Mean ± SD</th>
<th>Non-adherent Mean ± SD</th>
<th>P</th>
<th>Effect size (η²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21.3 ± 3.0</td>
<td>21.2 ± 3.0</td>
<td>0.55</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.2 ± 19.8</td>
<td>78.4 ± 22.4</td>
<td>0.03</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.1 ± 9.4</td>
<td>168.5 ± 9.0</td>
<td>0.38</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>80.2 ± 14.0</td>
<td>83.2 ± 16.4</td>
<td>0.02</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Hip (cm)</td>
<td>102.0 ± 12.1</td>
<td>104.0 ± 12.5</td>
<td>0.04</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>WHR</td>
<td>0.79 ± 0.08</td>
<td>0.80 ± 0.08</td>
<td>0.25</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>26.4 ± 6.0</td>
<td>27.5 ± 6.8</td>
<td>0.04</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>114.6 ± 12.8</td>
<td>115.6 ± 13.0</td>
<td>0.81</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>66.8 ± 9.3</td>
<td>67.2 ± 10.8</td>
<td>0.56</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Resting heart rate (bpm)</td>
<td>73.9 ± 12.1</td>
<td>74.2 ± 12.3</td>
<td>0.40</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Percent body fat</td>
<td>24.8 ± 9.4</td>
<td>25.3 ± 9.4</td>
<td>0.10</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Estimated VO₂max (mL kg⁻¹ min⁻¹)</td>
<td>38.2 ± 7.5</td>
<td>38.7 ± 7.6</td>
<td>0.60</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Average exercise intensity (%HRR)</td>
<td>68.7 ± 5.3</td>
<td>65.0 ± 6.5</td>
<td>&lt;0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Average duration (min)</td>
<td>38.7 ± 3.5</td>
<td>37.0 ± 3.8</td>
<td>&lt;0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Average heart rate</td>
<td>158.0 ± 7.1</td>
<td>152.9 ± 9.0</td>
<td>&lt;0.01</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender and race/ethnicity.
%HRR, percent heart rate reserve; BMI, body mass index; BP, blood pressure; bpm, beats per minute; SD, standard deviation; WHR, waist-hip ratio.
pleasure, while addiction is the persistent use of a mood altering substance or behaviour, despite adverse dependency consequences (100). Typically, when one speaks of addiction, the immediate thought is of illicit drug or alcohol abuse. However, exercise in both animal models and humans is a potentially addictive, self-rewarding and a highly motivation-driven behaviour (101–103), and excessive physical exercise fits the criteria for a behavioural addiction (104). Exercise dependence occurs when an individual exercises excessively either for the sole purpose of psychological gratification resulting from exercise (primary) (105) or to accomplish a separate goal such as weight loss (secondary) (106). Exercise dependence may be considered an extreme of exercise adherence and conceptualized as an addictive behaviour that can result in detriments to health (106).

The heritability of addiction has been estimated to be 0.48 to 0.58 (107), and addiction is now considered a disease of the brain caused by the impact of the behaviour/drug on the brain which may then be modified by environmental or genetic factors (108). Risk for substance addiction has been associated with genetic variation in neurochemical pathways including monoamine and opioid systems, dynorphins, gamma-aminobutyric acid, endocannabinoids, neuropeptide Y, galanin, orexin, substance P, melanocortins, leptin, glutamine and glucocorticoids (109). Importantly, genes involved in dopamine and serotonin systems which are thought to be associated with exercise behaviour and adherence are also associated with addictive/compulsive behaviour. For example, SNPs within the HTR2A gene have been associated with cocaine dependence (110) and pathological gambling (111), while variation in HTR1B was associated with alcohol, cocaine and heroin dependence (112). The A1 allele of the Taq1A polymorphism (rs1800497) within the DRD2 gene is among the most consistently replicated variants associated with alcohol dependence (113), while variation in DRD4 has been implicated in motivation to drink among heavy drinkers (114). More recent evidence showed that CpGs in HTR2B, HTR3A and DRD4 were hypermethylated in alcohol-dependent cases compared with controls among European-Americans (115), suggesting that genetic variation and epigenetic modifications in these genes may play critical roles in addictive behaviour. As described above, significant overlap may exist in the mechanisms underlying addictive behaviours and exercise adherence; examining the overlap between the genetic factors that play a role in these conditions may provide valuable insight to both areas of research.

Conclusions and future directions

What is clear from the existing literature is that the genetic basis of exercise adherence is a vastly understudied area of science. As McBride et al. noted, no single variable explains and/or predicts exercise adoption and adherence, reiterating the continued need for conceptual models of how the independent effects and interrelations of biological, psychological and environmental factors putatively influence adherence (116). In a comprehensive examination of the implications of the Human Genome Project, Green et al. included the statement that at least one of the outcomes
of the project is the potential to use ‘genomics-based information to change risk behaviour.’ In order to improve intervention adherence, a better understanding of the predisposition to healthy and risk behaviours that results from the complex interplay of biological, psychological, environmental, genetic and epigenetic factors is needed. Future investigations of the genetics of exercise adherence can be informed by genetic analyses of similar behaviours (i.e. addictive/compulsive behaviours), which could be considered on a continuum that includes adherence and non-adherence.

Conflict of interest statement
None.

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Supporting information
Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12089

Table S1. Genotype frequencies for neural-related gene variants.

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