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Heritability and Sex-Specific Genetic Effects of Self-Reported Physical Activity in a Brazilian Highly Admixed Population

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Abstract

Introduction—The engagement in sports or habitual physical activity (PA) has shown an extensive protective role against multiple diseases such as cancer, obesity, and many others. Additionally, PA has also a significant impact on life quality, since it aids with managing stress, preserving cognitive function and memory, and preventing fractures in the elderly.

Objective—Considering there has been multiple evidence showing that genetic variation underpins variation of PA-related traits, we aimed to estimate the heritability (h^2) of these phenotypes in a sample from the Brazilian population and assess whether males and females differ in relation to those estimates.

Methods—2,027 participants from a highly admixed population from Baependi, MG, Brazil, had information regarding their PA and sedentary behavior (SB) phenotypes collected through a questionnaire (IPAQ-SF). After data cleaning and transformation procedures, we obtained four variables to be evaluated: total PA (TPA MET), walking time, (WK MET), moderate-vigorous PA (MVPA MET), and SB. A model selection procedure was performed using a singlestep covariate inclusion approach. We tested for BMI, waist, hip and neck circumferences, smoking, and depression separately, and performed correlation tests among covariates. Linear mixed models, selection procedure, and the variance components approach to estimate h^2 were implemented using SOLAR-Eclipse 8.3.1.

Results—We obtained estimates of 0.221, 0.109, 0.226, and 0 for TPA MET, WK MET, MVPA MET, and SB, respectively. We found evidence for gene-sex interactions, with males having higher

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Author Contributions

J.M.R.S.L, A.R.V.R.H, and J.M.P.S designed the research. J.M.R.S.L analyzed the data and wrote the main manuscript text. All authors reviewed the manuscript.

Disclosure Statement

The authors have no conflicts of interest to declare.

Statement of Ethics

All subjects provided written consent before participation.

sex-specific heritabilities than females for TPA MET and MVPA MET. In addition, we found higher estimates of the genetic variance component in males than females for most phenotypes.

Discussion/Conclusion—The heritability estimates presented in this work show a moderate heritable set of genetic factors affecting PA in a sample from the Brazilian population. The evaluation of the genetic variance component suggests segregating genetic factors in male individuals are more heterogeneous, which can explain why men globally tend to need to practice more intense PA than women to achieve similar health benefits. Hence, these findings have significant implications for the understanding of the genetic architecture of PA and might aid to promote health in the future.

Keywords

Sex-specific heritability; Polygenic mixed model; Model selection; Physical activity; Family study

Introduction

The engagement in sports or habitual physical activity (PA) has shown an extensive protective role against multiple diseases such as cancer, obesity and type-2 diabetes, and cognitive impairments [1–3]. Additionally, PA has also a significant impact on life quality, since it aids with managing stress, preserving cognitive function and memory, and preventing fractures in the elderly [4, 5]. Over the last three decades, there has been multiple evidence showing genetic contributions for these traits, such as the variants found in genes involved in the blood pressure control system, which is altered in response to exercise [6, 7]. In addition, a specific polymorphism in the ACTN-3 gene, which codes for a protein involved in the stability of muscle fiber's Z-band, has been consistently associated with strength, speed, and endurance phenotypes [7–9].

Aside from those candidate-gene studies, family-based investigations have also shown that there is a considerable genetic component underlying PA and PA-related traits. These study designs are especially suitable for the estimation of the proportion of phenotypic variance that is accounted for by additive genetic effects (heritability) and have, for instance, found values as high as 62 and 50% for vertical jump and flexibility, respectively [10, 11]. Nonetheless, most of the genetic studies of PA-related phenotypes have been conducted in European and American cohorts [7, 12–14] and, to our knowledge, very few have focused on the Brazilian population [15, 16]. This population is of particular interest because of its history of migration and high admixture, which accounts for its rich, unique, and diverse genetic background. Also, several governmental initiatives have been implemented over the past 10 years in Brazil in order to stimulate PA practice, reduce disease burden, and improve health and welfare, which shows how important the study of the genetic architecture of PA is.

Considering the understanding of how genetic variation underpins PA-related traits is still limited, especially in the Brazilian population, we sought to estimate the heritability of self-reported PA phenotypes and sedentary behavior (SB) in a Brazilian cohort from the Baependi municipality-MG, and evaluated whether there is a sex-specific genetic effect by means of heterogeneity in the genetic and environmental variance components. Since

moderate heritability estimates for a wide range of PA phenotypes have been found, and males and females are different in many biological aspects [17], we hypothesized that there is a considerable moderate genetic component underpinning the self-reported PA phenotypes and SB and that the heritability estimates differ among sexes.

Materials and Methods

Sample

This work is part of the Baependi Heart Study (BHS), a family-based investigation in a highly admixed population from Baependi, which is a small rural town located in the state of Minas Gerais, Brazil. Starting in 2006, the project has collected information regarding several variables including cardiovascular risk factors, social and demographic aspects, anthropometric measurements, tobacco and alcohol usage, and PA traits. Participants were recruited as described in Egan et al. [18] and provided written consent before participation. A dataset of 2,027 individuals, comprised of 829 males and 1,198 females distributed into 117 families, was evaluated for summary statistics and the estimation of the heritability of PA-related traits.

PA Phenotypes

PA and SB were measured with the International Physical Activity Questionnaire, short form (IPAQ-SF). This instrument has appropriate measurement properties that have been previously validated [19]. Participants answered questions about the intensity, frequency, and duration of their activities during one week, as well as about time spent in a sitting position. Following the IPAQ protocol, we cleaned the data and used standard energy expenditure values known as metabolic equivalent tasks (MET) for walking time (WK; MET = 3.3), moderate PA (MPA; MET = 4), and vigorous PA (VPA; MET = 8). Total PA (TPA MET), a linear combination of these three, was then calculated taking the sum of the MET-adjusted phenotypes. SB was maintained in minutes per day, as recommended [20].

Since the distributions of MPA and VPA MET traits were zeroinflated and highly skewed, we combined the MPA MET and VPA MET into moderate-vigorous PA MET (MVPA MET) as in Klimentidis et al. [13], using it as a response variable instead of MPA and VPA MET alone. Additionally, we also performed a normal inverse transformation of the traits as described previously [21]. These procedures successfully improved the model fitting properties and eliminated convergence issues in our analysis. All data cleaning and transformation procedures were performed using R Studio software.

Models and Statistical Analysis

In order to estimate heritabilities, we adopted a polygenic linear mixed model as follows:

$$y_{if} = \mu + X'_{if}\beta + g_{if} + \varepsilon_{if},$$

where μ is the trait mean, X_{if} is a vector with covariates, and β is a vector with the regression coefficients for the covariates. The components g_{if} and ε_{if} are the residual random genetic effects due to the polygenic term and the random error term, respectively. A common

assumption in this model is that g_{if} and ε_{if} are uncorrelated and follow a normal distribution with mean 0 and variances σ_g^2 and σ_e^2, respectively [22].

Regarding the fixed effects (covariates) used in the model, we opted for sex, age, age^2, and interactions between those, which comprise the model most recommended in genetic studies [15, 16, 23]. In order to account for the ancestry background in our sample, we also included and tested ancestry coefficients that are the two main principal components (pca1 and pca2) estimated for our sample from the Brazilian population as previously described [24]. Aside from these, we tested for the covariates BMI, waist, hip and neck circumferences, smoking, and depression, since they could be possibly related to the evaluated phenotypes. Hence, in order to select the best covariates in the models for heritability, we tested for each covariate separately and performed correlation tests for pairs of covariates. Since the individuals in our dataset are not independent, we partitioned the variances and covariances into genetic and environmental variance components and estimated the total, genetic, and environmental correlation coefficients using the Oualkacha algorithm for these anthropometric covariates [25]. If the covariates had p values < 0.05 and high correlation environmental coefficients, we decided to include only the covariate considered as having the most biological interactions with PA-related traits as well as the one most used in the literature.

The heritability estimates for PA traits were calculated through the variance components approach implemented in SOLAR-Eclipse 8.3.1 package. Assuming the trait follows a normal distribution, the covariance between traits for individuals i and i' is given by [15]:

$$\mathrm{Cov}(y_i, y_{i'}) = \begin{cases} \sigma_g^2 + \sigma_e^2 \text{ for } i = i' \\ 2\phi_{ii'}\sigma_g^2 \text{ for } i \neq i' \text{ and related.} \\ 0 \text{ for } i \neq i' \text{ and unrelated} \end{cases}$$

Hence, the heritability h^2 is defined by the formula:

$$h^2 = \sigma_g{}^2/\sigma_p{}^2,$$

where h^2 corresponds to the heritability, $\sigma_g{}^2$ to the variance accounted for by additive genetic effects, and $\sigma_p{}^2$ to the total phenotypic variance, so that $\sigma_p{}^2 = \sigma_g{}^2 + \sigma_e{}^2$ under the polygenic model. Heritability estimates were obtained by restricted maximum likelihood, and its significance was measured by the likelihood ratio statistics [26].

In order to evaluate genotype-by-sex interaction effects, four models were fitted with regard to the genetic and environment variance components as previously described [15]:

$$\mathrm{Cov}(y_i y_{i'}) = \begin{cases} \sigma^2_g,\ female + \sigma^2_e,\ female \text{ for } i = i' \text{ and female} \\ \sigma^2_g,\ male + \sigma^2_e,\ male \text{ for } i = i' \text{ and male} \\ 2\phi_{ii'}\sigma^2_g,\ female \text{ for } i = i',\ \text{related and female} \\ 2\phi_{ii'}\sigma^2_g,\ male \text{ for } i = i',\ \text{related and male} \\ 2\phi_{ii'}\sigma^2_g,\ female,\ male \text{ for } i = i',\ \text{related and } \neq \text{ sexes} \\ 0 \text{ for } i = i' \text{ and unrelated} \end{cases}$$

For the models in which a h^2 higher than 0 was found, we included an across-sex correlation parameter (ρ) and tested to check whether this was equal to 1 or not as previously performed [23]. This test and the comparison between these models to each other were run through the likelihood ratio test with $\alpha = 0.05$, obtaining sex-specific heritability estimates as previously described [15].

Results

Since the distributions of the traits of interest are nonnormal highly skewed, we also reported their median and interquartile ranges, as recommended [20]. The summary statistics for the evaluated phenotypes and covariates used in the models are presented in Table 1.

Heritability estimates for PA traits under the same models for the selection of covariates are displayed in Table 2. These preliminary estimates ranged from 0.104 to 0.249, among which MVPA MET and SB had the highest statistically significant values under the model adjusted for BMI. Regarding the inclusion of the ancestry coefficients, only the second principal component (pca2) was statistically significant, which decreased the heritability of SB to 0.078 when tested individually. Additional estimates also showed that the inclusion of pca2 in models with other covariates decreased the heritability to 0.07, however, with rejection of the alternative hypothesis in these cases (results not shown); e.g., no heritability was found for SB.

As the next and final step to select the appropriate model for each PA and SB phenotype, we assessed the correlations among BMI, waist, hip and neck circumference, smoking, and depression. Due to relatedness among the individuals, we partitioned the phenotype correlations to account for the segregating genetic effects, and evaluated only the environmental component to assess which covariates provide redundant information. Considering waist, hip, neck circumferences, and BMI had the highest environmental correlation coefficients (Table 3), we opted to use BMI as a covariate for all phenotypes (Table 2).

Once the covariates were selected, we stratified the variance components of the model for males and females in order to ascertain whether there is sex heterogeneity. Since the inclusion of pca2 led to the loss of significance of SB's heritability and decreased it to zero in additional estimates, it was only reasonable to stratify the models for TPA MET, WK MET, and MVPA MET. Hence, the likelihood ratio test showed that there are significant differences in both genetic and environmental variance components for all those phenotypes

(Table 4) ($p < 0.05$). For TPA MET and MVPA MET, males had higher heritability estimates, while female had a higher heritability value for WK. Regarding the variance components themselves, the genetic one was considerably higher in males for TPA MET and MVPA MET and slightly higher for WK MET in females. On the other hand, the difference in the environmental variance component estimate between males and females was more striking only for WK MET and MVPA MET, with males having higher values than females.

Discussion/Conclusion

Herein, after a model selection approach, we report low to moderate heritability estimates for self-reported PA-related phenotypes and no heritability for the SB trait in a sample from the Brazilian population. The lack of heritability for this phenotype was found after inclusion of pca2 in the model, which indicates that the putative heritability for SB in the other models was actually accounted for by population admixture structure instead of true segregating genetic factors that influence this phenotype. We also successfully found evidence for gene-sex interaction effects as shown by higher sex-specific heritabilities in males for TPA MET and MVPA MET traits.

In a sample from the Portuguese population, higher h^2 estimates were found, ranging from 28 to 45 %, except for MVPA, which was not evaluated in that study [23]. In contrast to those findings, the heritability of WK was much smaller in the sample from Baependi, which indicates that the variation in WK in our sample has a heritable genetic component with additive effects lower than the one in the Portuguese sample. These differences between our results and the ones found for the Portuguese population are not surprising, since it may reflect differences in how social-cultural and geopolitical populationspecific aspects affect the variability of exercise practice. In addition, the genetic background of these two populations is different because it reflects different admixture and ancestry degrees. It should be noted, however, that the comparison between these particular studies as well as with others across the literature should be taken cau-tiously, since investigations are heterogeneous regarding sample size, population stratification, study design, and PA assessment, measurement and analytical methods.

In particular, we assessed PA and SB phenotypes using a self-reported questionnaire, IPAQ-SF. Although this instrument has been widely used and was initially validated across multiple countries [19], its efficacy is still questionable. For instance, Ekelund et al. [27] compared the amount of PA objectively measured by an accelerometer and self-reported PA by the IPAQ-SF. Although these authors found a relatively high sensitivity for the IPAQ-SF (77%), its sensibility (true positive rate) was low (45%), which suggests this questionnaire tends to underestimate PA practice. On the other hand, Folley et al. [28] highlight that there can be overestimation of reported PA under specific situations, especially when related to sample stratification. Thus, aside from self-reported PA, it might be reasonable to evaluate other PA measurements as well as to adjust the measurements using other variables, in order to reduce bias and obtain more precise estimates.

Regarding the sex-specific genetic effects assessment, we did not stratify the model for SB because, in contrast to the results in Horimoto et al. [16], this phenotype had no significant

heritability here. A possible explanation for these contrasting results is that we included the two main principal components of ancestry to adjust for ancestry admixture in our study, as recommended [29]. Nonetheless, it should be note that, although Horimoto et al. [16] found differences in the variance components for other PA phenotypes, they measured PA and sedentary traits through a different questionnaire, which hinders an appropriate comparison among these studies.

In addition, it is important to highlight that, since h^2 is a proportion, the relation between the genetic and environmental variance components can vary in a diverse range of scenarios. For instance, it could be possible that only the genetic variance component would be different among sexes or perhaps the environmental one. However, considering that sex differences, including biological ones, are very noticeable in multiple cultures and populations, a scenario where both genetic and environmental variance components differ among sexes would likely be more reasonable.

Our present analysis is generally consistent with the third aforementioned scenario, in which there was a difference in both variance components for most phenotypes. The higher σ_e estimates found for males, especially in WK and MVPA phenotypes, indicate that sociocultural factors have more impact on the variability of the time spent walking and in MVPA in men than in women. On the other hand, the higher σ_g estimates for men in TPA and MVPA phenotypes implies that segregating additive genetic effects have more impact on the variability of total and moderate-vigorous time spent in PA. Also, the higher genetic variance in men suggests that the genetic factors segregating amongst male subjects are more heterogeneous. These results have important implications: since segregating genetic factors are more heterogeneous, their resulting effects might be more scattered, and consequently not as strong as in females. This can at least partially explain why men tend to need to practice more intense PA than women to achieve similar health benefits [17].

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Table 1.

Summary statistics of physical activity-related phenotypes and covariates

Traits	Mean±SD	Median	1Q	3Q
Waist circumference, cm	91.46±12.10	91	83	99
Hip circumference, cm	98.53±9.59	97	92	104
Neck circumference, cm	35.62±3.66	35	33	38
BMI, kg/cm^2	25.88±5.08	25.1	22.3	28.7
Smoking, cigarettes/week	3.04±5.09	1	1	28
Depression	11.25±9.55	9	4	16
TP A MET, MET×min/week	872.7±1,591.54	297	0	990
WK MET, MET×min/week	357.2±581.43	0	0	594
MPA MET, MET×min/week	321.7±886.21	0	0	0
VPA MET, MET×min/week	193.4±840.88	0	0	0
MVPA MET, MET×min/week	515.4±1,384.96	0	0	240
SB, min/week	1,596± 1,030.31	1,350	840	2,160

TPA, total physical activity; MET, metabolic equivalent tasks; WK, walking time; MPA, moderate physical activity; VPA, vigorous physical activity; MVPA, moderate-vigorous physical activity; SB, sedentary behavior.

Table 2.

Covariate selection and heritability estimates of physical activity and sedentary behavior phenotypes

	TPA MET			WK MET			MVPA MET			SB		
	h^2	SD	*n*	h^2	SD	*n*	h^2	SD	*n*	h^2	SD	*n*
No covariates	0.215 *	0.04	2,021	0.112 *	0.04	2,027	0.224 *	0.04	2,022	0.186 *	0.04	2,018
SexA	0.21 *, ♦	0.04	2,021	0.112 *	0.04	2,027	0.217 *, ♦	0.04	2,022	0.234 *, ♦	0.04	2,018
SexA + waist	0.213 *, ♦	0.04	1,855	0.106 *, ♦	0.04	1,860	0.224 *, ♦	0.04	1,856	0.248 *, ♦	0.04	1,860
SexA + BMI	0.221 *, ♦	0.04	1,861	0.109 *, ♦	0.04	1,866	0.226 *, ♦	0.04	1,862	0.249 *, ♦	0.04	1,858
SexA + hip	0.214 *, ♦	0.04	1,847	0.107 *, ♦	0.04	1,852	0.217 *	0.04	2,022	0.235 *, ♦	0.04	1,844
SexA + neck	0.216 *, ♦	0.04	1,861	0.104 *, ♦	0.04	1,866	0.224 *, ♦	0.04	1,862	0.247 *, ♦	0.05	1,858
SexA + depression	0.236 *	0.05	1,544	0.112 *	0.04	2,017	0.232 *	0.05	1,544	0.226 *	0.04	2,018
SexA + smoking	0.21 *	0.04	2,021	0.112 *	0.04	2,027	0.217 *	0.04	2,022	0.245 *, ♦	0.12	707
SexA + peal	0.210 *	0.04	2,021	0.112 *	0.04	2,027	0.217 *	0.04	2,022	0.233 *	0.04	2,018
SexA + pca2	0.210 *	0.04	2,021	0.112 *	0.04	2,027	0.217 *	0.04	2,022	0.078 *, ♦	0.06	921

TPA, total physical activity; MET, metabolic equivalent tasks; WK, walking time; MVPA, moderate-vigorous physical activity; SB, sedentary behavior; SexA, age, age^2, sex, and their interactions; waist, waist circumference; BMI, body mass index; hip, hip circumference; neck, neck circumference; pca1, first principal component; pca2, second principal component.

* *p* value of h^2 <0.05.

♦ Covariate´s *p* value <0.05.

Table 3.

Correlation estimates of covariates for non-independent individuals

Correlation tests	ρ_T	ρ_g	ρ_e
Waist-hip	0.77	0.89	0.68
Waist-neck	0.48	0.85	0.38
Waist-BMI	0.73	0.85	0.67
Waist-smoking	0.06	0.49	0.07
Waist-depression	0.04	0.3	−0.03
Hip-neck	0.30	0.82	0.08
Hip-BMI	0.68	0.88	0.55
Hip-smoking	−0.04	0.03	−0.11
Hip-depression	0.07	0.24	0.02
Neck-BMI	0.74	0.93	0.69
Neck-smoking	0.45	−0.36	0.80
Neck-depression	0.20	0.04	0.22
BMI-smoking	0.34	−0.23	0.69
BMI-depression	0.30	−0.06	0.39
Smoking-depression	0.27	−0.04	0.39

ρT, ρg, and ρe correspond to the total, genetic, and environmental estimates, respectively.

Table 4.

Final results of model selection and sex-specific heritabilities for physical activity-related phenotypes

Phenotype	TPA MET	WK MET	MVPA MET
Covariates in the selected model	SexA + BMI	SexA + BMI	SexA + BMI
ρ_{fm} (P value)	0.75 (0.38)	0.234 (0.06)	1 (1.00)
Selected model	Both	Both	Both
(p value)	(4.4e-05)	(9.4e-05)	(9.2e-12)
Model with no heterogeneity			
h^2	0.221	0.109	0.226
Model with heterogeneity			
h^2_f	0.148	0.127	0.169
h^2_m	0.349	0.089	0.32
σ_{gf}	0.328	0.299	0.283
σ_{ef}	0.787	0.785	0.629
σ_{gm}	0.581	0.292	0.493
σ_{em}	0.794	0.933	0.719

TPA, total physical activity; MET, metabolic equivalent tasks; WK, walking time; MVPA, moderate-vigorous physical activity; SexA, age, age^2, sex, and their interactions; h^2_f, female heritability; h^2_m, male heritability; σ_g and σ_e, square root of the genetic and environmental variance components, respectively.

p values for ρ estimators and the comparison between the model with no heterogeneity and the model with heterogeneity in at least one variance component through the likelihood ratio test are presented.