Genome-wide association study of habitual physical activity in over 277,000 UK Biobank participants identifies novel variants and genetic correlations with chronotype and obesity-related traits.

Short Title: Genome-wide association study of habitual physical activity

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Abstract

Physical activity (PA) protects against a wide range of diseases. Engagement in habitual PA has been shown to be heritable, motivating the search for specific genetic variants that explain variation in habitual PA and may ultimately improve efforts to promote PA and target the best type of PA for each individual. We used data from the UK Biobank to perform the largest genome-wide association study of PA, using four measures based on self-report (n=277,656) and accelerometry (n=67,808). Replication was then sought in the Atherosclerosis Risk in Communities (ARIC) study (n=8,556). In the UK Biobank, we identified 17 genome-wide loci across the four PA measures. Interestingly, rs429358 of the *APOE* gene was the most strongly associated variant with any single PA measure and was at least nominally associated with three of the four PA measures examined. We also identified three loci (*DNAJC1*, *DCAF5*, and *PML*) consistently associated with PA across all four measures. Tissue enrichment analyses implicate the brain and pituitary gland as locations where PA-associated loci may exert their actions. Genetic correlation analyses suggest a positive genetic correlation of PA with early-morning chronotype and psychiatric traits, and a negative genetic correlation of PA with obesity-related traits. Using data from the GIANT consortium, we identify several loci that are associated with both increased waist circumference and decreased PA. Although very small effect sizes precluded replication of individual loci in ARIC, we found consistent overall genetic correlations of PA with other traits. These results provide new insight into the genetic basis of habitual PA, and the genetic links connecting PA and obesity.

Introduction

A physically active lifestyle has been shown to protect against a wide range of diseases, including cardiovascular disease, cancer, type-2 diabetes, and osteoporosis [1–4]. Levels of engagement in physical activity (PA) vary across individuals, and many people do not meet recommended levels to achieve health benefits. Although cultural, economic, and other environmental factors influence PA engagement [5,6], genetic factors also likely play a role. Understanding the genetic factors underlying inter-individual variation will better inform efforts to promote PA and potentially allow targeting the best type of PA for each person, what might be called "Precision Exercise Prescription".

Evidence of genetic factors underlying the propensity to exercise in humans has been demonstrated in a number of studies [7–14]. Several studies have utilized a candidate gene approach to identify specific genetic variants associated with a proclivity towards PA [8,15–19]. These studies generally focused on genes related to the serotonin and dopamine systems, energy metabolism, and neurotrophic factors. However, to our knowledge there have been only two previous reports of genome-wide association studies (GWAS) of PA [20,21], neither of which identified a locus at genome-wide significance, likely due to relatively small sample sizes. Thus, while previous work strongly suggests a genetic basis for engagement in PA, the genes that contribute strongly to this healthy lifestyle remain unknown.

In this study, we conduct the largest GWAS of PA to date, aiming to identify genetic variants associated with self-reported and accelerometry-based levels of habitual, leisure-time PA. We sought to identify variants in the UK Biobank, a large cohort study of 500,000 adults measured across a wide range of characteristics including genome-wide markers. We then examined the genetic correlation of PA with other traits, examined putative tissues where PA genes may exert their effects, and attempted to replicate our identified loci using self-reported PA in the Atherosclerosis Risk in Communities (ARIC) study.

Methods

Studies

Data from the UK Biobank study were used for discovery of variants. Briefly, the UK Biobank is a large prospective cohort study of approximately a half-million adults (ages 40-69) living in the United Kingdom (UK), recruited from 22 centers across the UK [22]. All participants provided written informed consent. For replication we used data from the ARIC study, which is a prospective cohort study of over 15,000 adults aged 45-64 years that took place in four United States communities. Details of the ARIC study can be found elsewhere [23]. To reduce the potential for confounding by population stratification, we included only individuals of white race/ethnicity in both studies.

Physical activity

In the UK Biobank, self-reported levels of physical activity during work and leisure time were measured via a touchscreen questionnaire, in a fashion similar to the International Physical Activity Questionnaire [24]. For moderate PA (MPA), participants were asked: "In a typical WEEK, on how many days did you do 10 minutes or more of moderate physical activities like carrying light loads, cycling at normal pace? (Do not include walking)". For vigorous PA (VPA), participants were asked: "In a typical WEEK, how many days did you do 10 minutes or more of vigorous physical activity? (These are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting)". For each of these questions, those who indicated 1 or more such days were then asked "How many minutes did you usually spend doing moderate/vigorous activities on a typical DAY". Participants were asked to include activities performed for work, leisure, travel and around the house. We excluded individuals who selected "prefer not to answer" or "do not know" on the above questions, those reporting not being able to walk, and individuals reporting more than 16 hours of either MPA or VPA per day. Those reporting >3hr/day of VPA or MPA were recoded to 3 hours, as recommended [25]. Moderate-to-vigorous PA (MVPA) was

88 calculated by taking the sum of total minutes/week of MPA multiplied by four and the total number of
89 VPA minutes/week multiplied by eight, corresponding to their metabolic equivalents, as previously
90 described [24,26].

91 Since heritability has previously been shown to be higher for intense/vigorous physical activity
92 [13], we also considered VPA on its own. Because the distribution of minutes/week of VPA was highly
93 skewed and zero-inflated, we chose to dichotomize minutes/week of VPA into those who reported 0 days
94 of VPA, and those reporting 3 or more days of VPA and also reporting a typical duration of VPA that is
95 25 minutes or greater.

96 Also, in the UK Biobank, approximately 100,000 participants wore an Axivity AX3 wrist-worn
97 accelerometer, as previously described [27]. We examined two measures derived from up to seven days
98 of accelerometer wear: overall acceleration average, and fraction of accelerations > 425 milli-gravities
99 (mg) [27]. Since the variable that is available in the UK Biobank is the fraction < 425 mg, we subtracted 1
100 from this variable. The 425 mg cutoff was chosen because this corresponds to an equivalent of vigorous
101 physical activity, as previously reported [28]. For both accelerometry variables, we excluded individuals
102 with less than three days (72 hours) of data, those not having data in each one-hour period of the 24-hour
103 cycle, and outliers with values more than 4 standard deviations above the mean.

104 For the replication study (ARIC), self-reported PA was assessed for sports/exercise, within the
105 previous year, based on a modification of the Baecke questionnaire [29,30]. The sport/exercise index is
106 based on responses to 4 items: frequency of participation in sports/exercise; frequency of sweating during
107 sports/exercise; a subjective rating of the frequency of participation in sports/exercise compared to others
108 in the same age group; the sum of frequency, duration, and intensity of up to 4 sports/exercises.

109

110 *Genotypes*

111 The majority of UK Biobank participants were genotyped with the Affymetrix UK Biobank
112 Axiom Array (Santa Clara, CA, USA), while 10% of participants were genotyped with the Affymetrix
113 UK BiLEVE Axiom Array. Detailed quality control and imputation procedures are described elsewhere
114 [31]. Imputation was performed using a combined panel of the Haplotype Reference Consortium [32] and
115 the UK10K haplotype resource [33]. Since corrections for potential problems with the position
116 assignment of the SNPs from the UK10K haplotype resource were not available at the time of analysis,
117 we only included SNPs imputed from the Haplotype Reference Consortium. To minimize the possibility
118 of confounding due to population stratification, only participants who self-identified as White/British
119 (European-descent), and who were not population outliers based on principal components analysis (PCA)
120 were included. Individuals were excluded based on unusually high heterozygosity or >5% missing rate, a
121 mismatch between self-reported and genetically-inferred sex, and on relatedness (i.e. samples not used in
122 primary PCA). SNP exclusions were made based on Hardy-Weinberg equilibrium ($p<1x10^{-6}$), high
123 missingness (>1.5%), low minor allele frequency (<0.1%), and low imputation quality (info<0.4).

124 In ARIC, participants were genotyped with the Affymetrix Genome-Wide Human SNP Array 6.0
125 (Affymetrix, Santa Clara, CA, USA). Standard quality control procedures were implemented prior to
126 imputation with IMPUTE2 [34], using all individuals in the 1,000 Genomes phase 1 integrated v3 release.
127 Quality-control procedures consisted of excluding SNPs with minor allele frequency < 1%, with
128 missingness >10%, and SNPs out of Hardy-Weinberg equilibrium ($p<1 \times 10^{-6}$), and excluding individuals
129 with SNP missingness > 10%. We used principal components for the European-ancestry group as
130 provided by ARIC in dbGaP. Briefly, LD pruning resulted in 71,702 SNPs that were used to derive
131 principal components. A total sample size of 8,556 participants was used in the analysis.

132

133 *Statistical analyses*

For the continuous variables in the UK Biobank (MVPA and accelerometry variables) we created an adjusted phenotype corresponding to the residual of the regression of the following independent variables on the respective dependent PA variable: age, sex, genotyping chip, first ten genomic principal components, center, season (month) at center visit or wearing accelerometer (coded 0 for Winter, 1 for Fall or Spring, and 2 for Summer). In sensitivity analyses, we considered the inclusion of the additional following covariates: levels of physical activity at work (coded as 0 by default, 1 for 'sometimes', 2 for 'usually', and 3 for 'always'), extent of walking or standing at work (coded similarly as previous variable), and the Townsend Deprivation Index (TDI; a composite measure of deprivation as previously described [35,36]). We also considered a third model in which body mass index (BMI) was included as an additional covariate. Since the MVPA and fraction of accelerations > 425 mg variables exhibited skewed distributions, we inverse-normalized these variables prior to inclusion in the models. Model residuals conformed to the assumptions of normality and homoscedasticity. For the categorical variables, we used logistic regression, including the same set of covariates listed above. We conducted two additional analyses. First, we sought to identify variants consistently associated with PA across all four measures. We thus searched for variants associated in the same direction, with $p<0.001$ with each of the four PA phenotypes. The prior probability under the null hypothesis for a SNP association at this level with all four phenotypes and with the same direction of association is $0.001 \times 0.0005 \times 0.0005 \times 0.0005 = 1.25 \times 10^{-13}$. However, it is important to note that these four phenotypes are correlated with each other. Second, given the observed strong and consistent negative genetic correlation of all PA measures with waist circumference we used summary statistics from the GIANT consortium [37] to identify loci that are consistently associated with all four measures of PA in the same direction ($p<0.01$ in each of four PA measures) and with waist circumference in the opposite direction ($p<0.01$).

Given the association that we identified with the rs428358 variant in *APOE*, we examined the association of the *APOE* ε4 genotype, using this SNP along with the rs7412 SNP. Individuals with homozygous CC genotypes at both of these SNPs were classified as homozygous for the APOE ε4 allele.

159 Individuals with homozygous CC genotypes at either SNP and heterozygous at the other SNP were
160 classified as being heterozygous for the ε4 allele. We excluded individuals heterozygous at both SNPs.
161 We assumed an additive model in association testing.

162 All genome-wide significant loci were examined in ARIC, where we modeled PA as a continuous
163 variable (as described above). We used multiple linear regression to model PA as a function of: age, sex,
164 first ten genomic principal components, BMI, center, season (coded in the same way as described above).
165 Residuals from this model conformed to the assumptions of normality and homoscedasticity, and were
166 used as the outcome in the genome-wide SNP association analysis. A replication was considered
167 successful if the p-value in ARIC was <0.0025, corresponding to a Bonferroni correction for 20 tests
168 performed. All GWAS analyses were performed with PLINK 2.0, assuming an additive genetic model
169 [38]. Additional analyses were performed with R statistical software[39]. To examine association of
170 genetic variants with gene expression patterns in different tissues, we used the web-based platform,
171 Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA GWAS) [40], which
172 uses data from GTEx [41].

173 We used the summary statistics from our GWAS to examine genetic correlation of PA with over
174 200 traits and diseases using LD score regression [42,43], implemented in an online interface
175 (http://ldsc.broadinstitute.org/). The genetics of these other traits and diseases are inferred from
176 previously published GWAS. A significant genetic correlation was considered to have a $p < 2.5 \times 10^{-4}$,
177 assuming a correction for 200 different tests, which is conservative given that many of the traits/diseases
178 tested are correlated with each other. LD score regression intercepts and chip heritability estimates were
179 also recorded.

180

181 **Results**

182 *Self-reported PA in UK Biobank*

183 A summary of self-report PA variables can be found in Table 1. BMI and TDI were consistently
184 negatively associated with these variables, whereas season and physical activity at work were consistently
185 positively associated with them (see Supplementary Table 1). Self-report PA measures were weakly
186 correlated with accelerometry-based measures (see Supplementary Table 2). 'Chip heritability' estimates
187 for both self-report PA measures were approximately 5% (Supplementary Table 3). LD score regression
188 intercepts (<1.02) suggest no significant systematic inflation of test statistics. In over 277,000 individuals,
189 we find ten loci significantly associated ($p < 5 \times 10^{-8}$) with MVPA and three loci with VPA (see Figure 1
190 and Table 2). Most notably, the C allele at SNP rs429358 in *APOE* is associated with higher self-reported
191 MVPA. This allele is also nominally associated with higher levels of other measures of PA (VPA: $p=8.4$
192 $\times 10^{-6}$; average acceleration: $p=3.7 \times 10^{-3}$). Testing the association of the Alzheimer's disease-associated
193 *APOE* ε4 allele with MVPA resulted in nearly identical findings. In models adjusted for other covariates,
194 this *APOE* variant remained genome-wide significant (see Supplementary Tables 4 and 5). We did not
195 observe any loci significantly associated with both MVPA and VPA. In models adjusting for additional
196 covariates, the results were very similar with slightly fewer loci reaching genome-wide significance for
197 MVPA, and slightly more for VPA (see Supplementary Tables 4 and 5 and Supplementary Figures 1 and
198 2). In ARIC, we observed no significant replication of any variant. However, we note similar direction of
199 association for 8 of the 13 variants, including the *APOE* SNP (see Table 2).

200

201 *Accelerometer-based PA in UK Biobank*

202 'Chip heritability' estimates for the accelerometry-based measures were higher (15% for average
203 acceleration, and 11% for fraction of accelerations >425 mg) than for self-report PA measures
204 (Supplementary Table 3). LD score regression intercepts (<1.009) suggest no significant systematic
205 inflation of test statistics. Three loci were found to be significantly associated with average acceleration
206 and one locus with fraction of accelerations >425 mg (see Table 2 and Figure 1).

207 We found three loci associated with each of the four PA measures at $p<0.001$, and with the same
208 direction of association (Table 3). These include an intronic variant in *DNAJC1*, a variant just upstream of
209 *DCAF5*, and a missense variant in *PML*. No SNP was successfully replicated in ARIC.

210

211 *Genetic correlation and tissue enrichment analysis*

212 We examined the genetic correlation between habitual PA and over 200 hundred other
213 traits/diseases. Most notably, we find highly significant negative genetic correlations of PA with waist
214 and hip circumference, body fat, obesity, BMI, and triglycerides (see Figure 2). This negative genetic
215 correlation with obesity and related traits is particularly accentuated for the accelerometry-derived PA
216 variables (see Figure 2). We found three potentially pleiotropic loci associated with both lower physical
217 activity and greater waist circumference (see Table 4), including the *DNAJC1* variant previously
218 identified as being consistently associated with PA. We find a positive genetic correlation with
219 chronotype (morning-type) and psychiatric traits, and a negative genetic correlation of self-reported PA
220 with educational attainment traits. Results remained very similar in GWAS models adjusted for activity at
221 work and TDI variables (see Supplementary Figure 3), except that the negative correlation with
222 educational attainment traits exhibited a reversed direction of association. Similarly, upon addition of
223 BMI as a covariate, the direction of genetic correlation between PA and obesity traits was reversed (see
224 Supplementary Figure 4). As we note below, caution is warranted in interpreting results from these
225 adjusted models. In ARIC, we found similar genetic correlations of PA with waist circumference (r_g=-
226 0.13), chronotype (r_g=0.04), and schizophrenia (r_g=0.32), although these do not reach statistical
227 significance.

228 Tissue enrichment analysis using eQTL data from GTEx implicate the brain and pituitary as
229 primary tissues through which the PA-associated loci may exert their effects (see Figure 3 and
230 Supplementary Figure 5).

231

232 **Discussion**

233 Given the importance of physical activity for multiple dimensions of health, and its' reported
234 heritability, we sought to identify genetic variants that are associated with engagement in habitual
235 physical activity, while considering important covariates such as season, physical activity at work, socio-
236 economic status, and BMI.

237 In the UK Biobank, with a very large sample size and multiple measures of PA, we identified
238 several genome-wide significant SNPs. Interestingly, a well-established variant in *APOE* (part of *APOE*
239 ε4 allele), strongly implicated in Alzheimer's disease [44,45], exhibited one of the strongest associations
240 with PA. How the *APOE* risk allele is associated with greater physical activity is not clear. An exercise
241 training study found that *APOE* ε4 carriers had a greater increase in aerobic capacity [46]. This increased
242 capacity could reinforce engagement in PA. Another potential explanation for our finding is that
243 individuals with a known family history of dementia or Alzheimer's disease purposefully increase their
244 levels of PA in order to avoid succumbing to these diseases. Nevertheless, it is important to note that this
245 association may lead to spurious gene-environment interactions [47]. This is particularly pertinent in the
246 case of the reported interactions of *APOE* with physical activity that suggest PA can have a beneficial
247 effect on Alzheimer's disease risk [e.g. 44–46]. Although this association remained after adjustment for
248 BMI and other covariates, it remains to be determined whether some residual confounding exists. None of
249 the identified loci were successfully replicated in the ARIC data, likely due to the very small effect sizes
250 observed in the UK Biobank, the smaller sample size in ARIC, and the different methods of measuring
251 physical activity in these studies. Additionally, it is important to note that none of the identified loci have
252 previously been found to be associated with PA or related traits [e.g. 16,17].

253 Previous studies have shown that BMI-associated genetic variants are also associated with PA
254 [51,52]. Similarly, we find an overall shared genetic basis for PA with several obesity-related traits,

255 suggesting that genetic risk for obesity coincides with genetic propensity for lower PA. There is likely a
256 complex set of genetic, environmental, and phenotypic factors that connect PA and obesity across the
257 lifespan, that involve many pleiotropic genetic factors. Although the direction of correlation is reversed
258 when BMI is included as a covariate, caution is warranted in interpreting results of genetic associations in
259 which heritable covariates are included in the association model [53]. Another major potential source of
260 bias is collider bias, which occurs when one controls for a variable (i.e. BMI) that is caused by both
261 another covariate (i.e. gene) and the outcome variable in the model (i.e. PA) [54,55].

262 Our study is strengthened by the large sample size, the availability of both self-reported and
263 accelerometer-based measures of PA, and the availability of a replication cohort from a different country.
264 However, we note several limitations. Given the relatively small genetic effect sizes observed for these
265 PA phenotypes, we were insufficiently powered to replicate associations in the much smaller sample size
266 in ARIC. Additional replication studies are thus needed to more robustly identify PA-associated loci.
267 Furthermore, the self-report measure of PA used in ARIC differed from the one used in the UK Biobank.
268 Both self-reported and accelerometer-based measures of PA are subject to various biases. Since both the
269 UK Biobank and ARIC cohorts are comprised of middle- to late-middle-aged adults, the extent to which
270 these results generalize to other age groups is not known. Furthermore, our results may not generalize to
271 other ethnic/racial groups.

272 In conclusion, our study revealed several important new findings. Effect sizes were generally
273 very small, given the very large sample size, variant allele frequencies, and modest p-values. *APOE*, a
274 major risk factor for Alzheimer's disease, is associated with higher levels of PA, which could importantly
275 lead to spurious *APOE*-by-PA interactions in epidemiological studies. We found a negative genetic
276 correlation of PA with obesity and related traits, suggesting extensive pleiotropy and complex
277 connections among PA and obesity. The identification of genetic factors that predispose to high or low
278 levels of physical activity will lead to a better understanding of the biological mechanisms underlying
279 these proclivities. It may also lead to the identification of individuals less likely to engage in and/or

adhere to physical activity, and consequently to the development of tailored behavioral strategies. Finally, the integration of genetic information with lifestyle and environmental information may point to how lifestyle/environmental factors interact with genetic factors to influence levels of PA.

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322

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450

451

452 **Figure Legends**

453 **Figure 1:** Manhattan plot of GWAS for self-reported MVPA and VPA and for accelerometer-based
454 average accelerations and fraction of accelerations > 425 mg. Negative log10-transformed p-value for
455 each SNP is plotted by chromosome and position (x-axis). The red and blue horizontal lines represent
456 thresholds for genome-wide significant and suggestive associations, respectively.

457

458 **Figure 2:** Genetic correlation of PA variables with other traits and diseases. Traits/diseases are ordered
459 from top to bottom in order of increasing p-value for the ten traits/diseases with strongest degree
460 (according to p-value) of genetic correlation with respective measure of PA. Horizontal position of bars
461 corresponds to the genetic correlation (r_g) between PA and the respective trait/disease. Error bars
462 represent 95% confidence intervals for r_g estimates. Bright green bars represent traits that showed a
463 correlation with p-value <2.5E-4, and light green bars represent traits with genetic correlation p<0.05. We
464 excluded highly redundant traits (e.g. obesity, overweight) after leaving higher ranked one in.

465

466 **Figure 3:** Results of tissue enrichment analysis using eQTL results from GTEx RNA-seq data for PA-
467 associated loci.

468 **Table 1: Summary of PA phenotypes in the UK Biobank**

Self-Report	
MVPA	Mean=1,646; SD=2,075; n=277,656
Vigorous PA: 0 vs. ≥3 days/week	71,739 cases; 119,866 controls
Accelerometry	
Average acceleration (milli-gravities)	Mean=27.93; SD=8.15; n=67,808
Fraction accelerations > 425 milli-gravities	Mean=0.0026 ; SD=0.0033 ; n=67,565

469 SD: standard deviation

470

471

472 **Table 2:** Summary of polymorphisms identified in the UK Biobank with association statistics in ARIC.

SNP ID	Chr.	Gene/Nearest Gene	Position	EA	EAF	Beta/OR	p-value	n	ARIC replication	
									Beta	p-value
MVPA										
rs429358	19	*APOE*	45,411,941	T	0.84	-0.023	4.98E-11	277,656	-0.026	0.260
rs72737787	9	*ZCCHC7*	37,336,741	G	0.65	-0.017	3.66E-10	277,656	-0.026	0.049
rs1043595	7	*CALU*	128,410,012	G	0.72	0.017	1.48E-09	277,656	0.014	0.310
rs1921981	21	*BACE2*	42,422,547	G	0.67	0.016	4.03E-09	277,656	0.021	0.106
rs3129981	6	HCG20	30,758,857	C	0.83	0.020	5.13E-09	277,656	0.007	0.730
rs921917	7	*C7orf72*	50,228,738	C	0.51	-0.015	1.19E-08	277,656	-0.007	0.568
rs12147808	14	*C14orf64*	98,618,705	C	0.79	-0.018	1.30E-08	277,656	-0.009	0.484
rs124672	8	*KCNK9*	140,722,178	A	0.71	-0.016	2.22E-08	277,656	0.003	0.840
rs148854222	5	*SLC1A3*	36,505,944	T	0.997	-0.137	2.87E-08	277,656	0.066	0.645
rs12142550	1	*HAX1*	154,258,549	C	0.75	0.016	4.60E-08	277,656	-0.011	0.461
Vigorous PA: 0 vs. ≥3 days/week										
rs6955240	7	*EXOC4*	133,581,873	G	0.61	1.044	9.57E-10	191,473	0.001	0.905
rs6667222	1	*HAX1*	154,253,661	A	0.75	1.046	9.55E-09	191,473	-0.014	0.340
rs6909774	6	*MMS22L*	97,687,471	A	0.25	1.044	3.34E-08	191,473	-0.035	0.014
Accelerometry – Average acceleration										
rs62055545	17	*MAPT-AS1*	43,964,561	C	0.78	-0.038	1.41E-09	67,808	0.006	0.680
rs34517439	1	*FUBP1*	78,450,517	C	0.88	0.044	4.23E-08	67,808	-0.010	0.635
rs4747438	10	*DNAJC1*	22,124,263	C	0.32	-0.030	4.62E-08	67,808	0.009	0.485
Accelerometry – Fraction accelerations > 425 milli-gravities										
rs10851869	15	*PML*	74,331,083	T	0.57	0.027	3.66E-08	67,565	0.015	0.227

473 EA refers to effect allele that Beta/OR corresponds to. EAF: effect allele frequency; proxy rs2732705 SNP was used
474 for rs62055545 in ARIC
475

476 **Table 3:** Loci consistently associated with PA across all four measures (each p<0.001).

					MVPA		VPA		AA		AF>425		ARIC PA	
SNP	Chr.	Nearest Gene	Position	Effect Allele	Beta	p	OR	p	Beta	p	Beta	p	Beta	p
rs7910002	10	*DNAJC1*	22050570	G	-0.01	8.7E-04	0.97	2.8E-04	-0.03	7.9E-08	-0.02	1.0E-04	0.005	0.716
rs10135643	14	*DCAF5*	69517406	A	0.01	6.5E-04	1.03	1.7E-04	0.02	4.6E-04	0.02	2.2E-04	0.023	0.064
rs5742915	15	*PML*	74336633	T	-0.01	3.7E-06	0.96	1.3E-07	-0.02	2.4E-05	-0.02	3.0E-06	0.002	0.873

477 AA: Average acceleration, AF>425: acceleration fraction greater than 425mg, ARIC PA: Physical
478 activity in ARIC study.

479

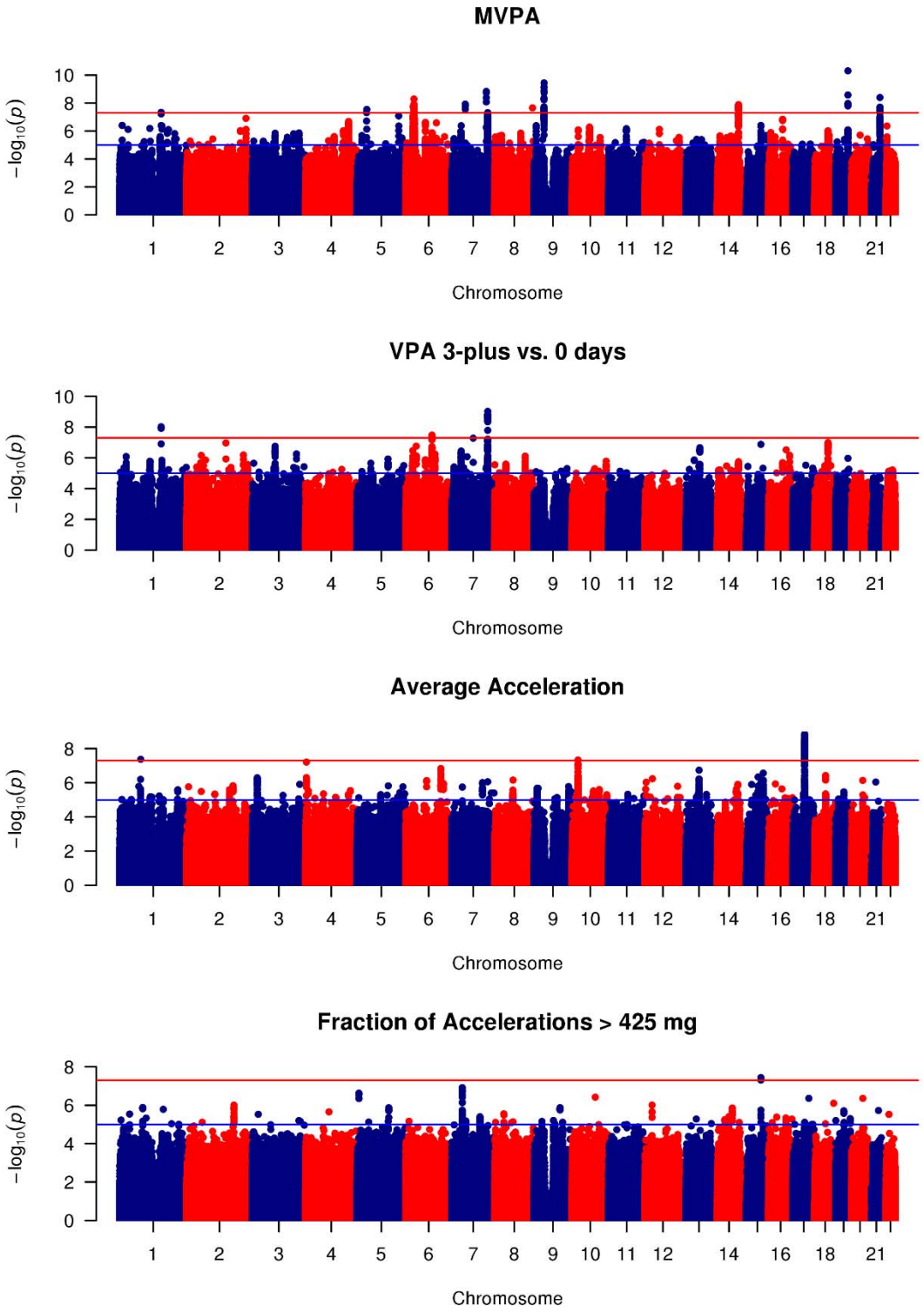
480 **Table 4:** Loci consistently associated with all four PA variables and with waist circumference from
481 GIANT consortium (each p<0.01)
482

					MVPA		VPA		AA		AF>425		Waist circum.	
SNP	Chr	Nearest Gene	Position	Effect Allele	Beta	p	OR	p	Beta	p	Beta	p	Beta	p
rs12993490	2	*CPS1*, *ERBB4*	211,953,629	C	0.01	4.1E-03	1.03	3.1E-04	0.02	4.4E-04	0.01	9.1E-03	-0.016	1.1E-03
rs7910002	10	*DNAJC1*	22,050,570	G	-0.01	8.7E-04	0.97	2.8E-04	-0.03	7.9E-08	-0.02	1.0E-04	0.015	7.5E-04
rs7250389	19	*CCNE1*	30,325,332	G	0.01	2.4E-03	1.03	1.7E-04	0.03	3.7E-06	0.02	3.5E-05	-0.02	2.1E-05

483 AA: Average acceleration, AF>425: acceleration fraction greater than 425mg

484
485

486 **Figure 1**



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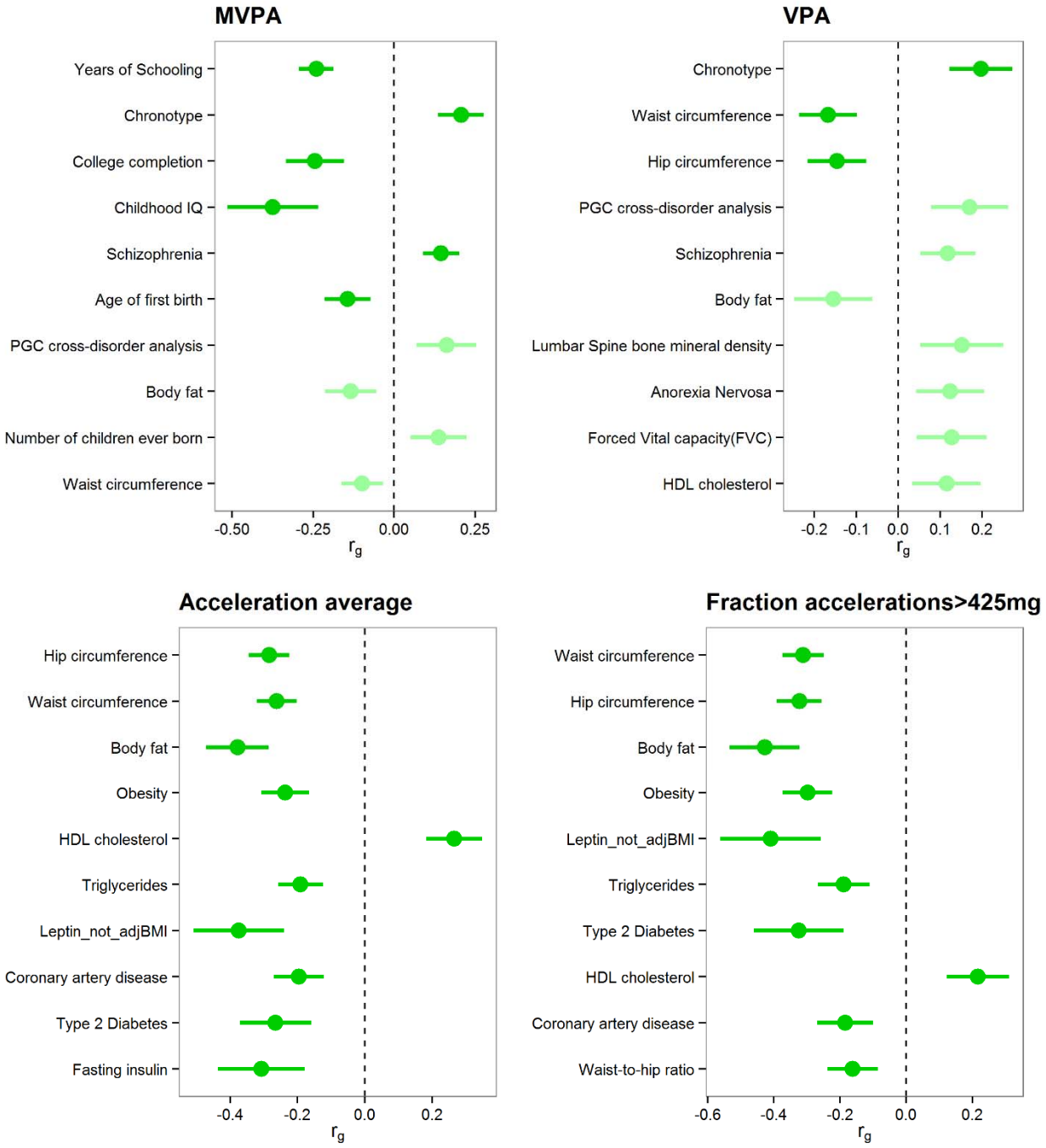
488 **Figure 2**



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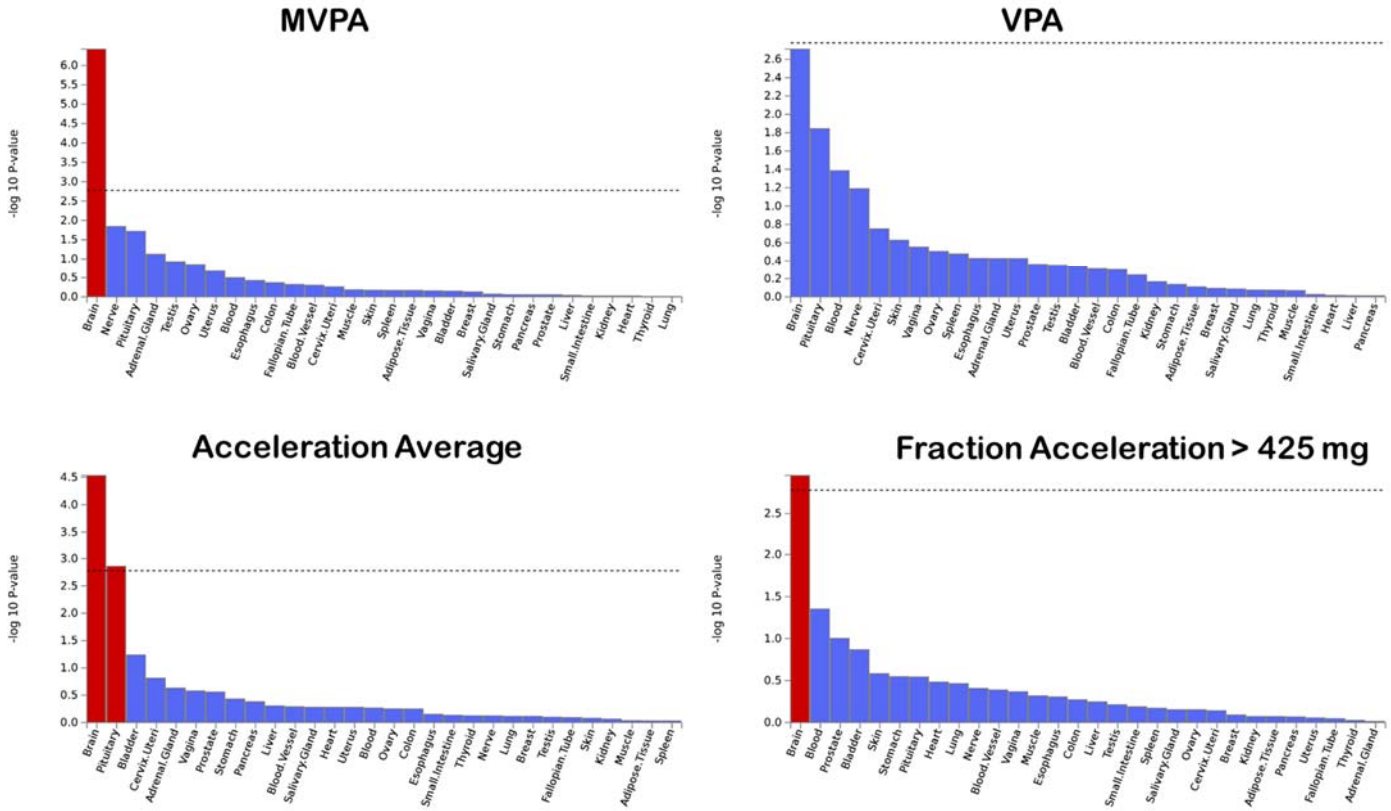
490 **Figure 3**



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