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Genotypic Variations Associated with Changes in Body Mass in Response to Endurance Training

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ABSTRACT

This study investigates the extent to which different genotypes can explain changes in body mass following an 8-week running program, in a UK population. Participants were randomly assigned to either a training ($n = 17$) or control group ($n = 21$). Participants' diets were not altered, only the exercise regime was manipulated to isolate effects. The exercise group completed a periodized running program consisting of 20–30 min, over an agreed route, three times per-week, whilst the control groups refrained from daily exercise. Participants were screened at the end of the study for 1,000 gene variants using a DNA test kit. Results demonstrated a significant reduction in body mass, within the exercise, compared to the control group ($p = .002$). This reduction in body mass varied significantly ($p = .024$) between individuals within the exercise group. Moreover, genetic analysis identified 17 single nucleotide polymorphisms (SNPs) associated with this variation ($r^2 = .74$; $p < .001$). These findings indicate that individuals with specific alleles are better predisposed to weight-management, compared to their counterparts, following an exercise program. This study helps to bridge the gap between population health and exercise science and can inform research in the application of genetics to help develop individually tailored health interventions.

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For decades, obesity and unhealthy weight gain have continued to be a major issue for society which places an ever-increasing burden on health systems and the economy (McLaughlin et al., 2017). The Health Survey for England data estimates approximately 64% of adults in the UK are either overweight or obese (HSE, 2022), which are major risk factors for cardiovascular disease, cardiometabolic disease, type 2 diabetes, and increased mortality (Swift et al., 2014). Clinically significant weight loss (>5%) has repeatedly shown improvements in metabolic health markers, decreased health risks and comorbidities (Wing et al., 2011); hence, clinical guidelines advocate that these individuals should proactively attempt to reduce bodyweight (Jensen et al., 2014). It is well recognized that physical activity (PA) can contribute to weight loss and mitigate some of the negative effects of obesity, but there are many individual barriers to PA (Swift et al., 2013). These include limited access to facilities and/or organized PA and exercise for some populations which may impede people's ability to lose weight. Nevertheless, there are many exercise regimes that can be undertaken at home, or in open spaces that require minimal resources, e.g. going for outdoor runs (Strongman et al., 2022; Swain et al., 2023). Yet, despite almost unanimous acceptance of these benefits, many individuals still struggle to achieve and maintain sustained weight losses.

Weight loss occurs when the body is in energy deficit, either because of reduced dietary energy intake, increased energy expenditure, or both. Creating an energy deficit through increased energy expenditure, in the form of PA, also has benefits that are unrelated to weight loss. High levels of PA and cardiorespiratory fitness are inversely associated with all-cause mortality (Swift et al., 2013), and it has been reported that higher fitness levels are associated with fewer metabolic complications at any age and across different weight status groups (Ortega et al., 2013). Studies investigating the effects of aerobic exercise on weight loss suggest that programs with the minimum levels of PA recommendations (~150 min moderate, ~75 min vigorous, or a combination of both) without dietary restriction may induce modest weight loss (~2–3 kg) over periods ranging from 8 weeks to 1 year (Bellicha et al., 2021). Additionally, exercise interventions have shown to reduce the loss of lean body mass, increase visceral fat loss and facilitate maintenance of weight losses (Weiss et al., 2017). Despite these positive benefits, not all studies have reported weight loss and the individual responses are often highly variable, with large inter-individual variability in weight change (ranging from −14 to +2 kg) in response to the same exercise interventions (King et al., 2008).

A key factor that can influence these outcomes to PA is an individual's genetic profile (Luglio et al., 2015). Genetic factors have shown to contribute significantly to weight management, due to variations in energy expenditure, appetite and endocrine mechanisms, lipid metabolism, adipogenesis, thermogenesis and cell differentiation (Deram & Villares, 2009). Previous family studies on monozygotic twins have

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demonstrated significant influences of genetic factors, on body mass index (BMI), in response to PA (Hopkins et al., 2012). For example, the PPARGC1A gene interacts with a broad range of transcription factors which modulate energy expenditure, fat burning, weight management and obesity (Csép et al., 2017). Although previous studies have linked exercise-induced adaptations to particular genes, there is a paucity of research regarding specific alleles of these genes (Chung, Keiller, Roberts et al., 2021). This is a fundamental flaw, as there are many variants of a gene (often associated with single nucleotide polymorphisms [SNPs]) and alternative alleles of a specific SNP can often result in different responses to the same intervention (Chung et al., 2023). SNPs are the most common type of genetic variation among people and therefore are commonly used to compare a gene sequence. Each SNP represents a difference in a single DNA-building block, called a nucleotide, and these can be used to understand individual differences. This highlights the importance of personalized strategies and the critical requirement of identifying individual SNPs and reporting specific genotypes.

Moreover, this also means that the influence of allelic variation and identification of specific SNPs on changes in body mass in response to endurance training has yet to be fully understood. Accordingly, the purpose of this study was to engage a cohort of physically inactive UK adults in an 8-week aerobic training program and identify the SNPs and allelic variations associated with changes in body mass. We hypothesized that 8 weeks of endurance training could reduce body mass, but participants would improve at different rates, and that this could be explained, in part, by their genetic differences.

Materials and methods

Participants

Ethical approval was granted by the researchers' institutional ethics board (FSE_19_864). A G*Power *a-priori* analysis determined a sample of $n = 34$ (17 per group) with $\alpha = 0.05$, $\beta = 0.80$, two-tailed and anticipated effect = 1.0. This calculation was based on a study including 12 systematic reviews post aerobic training on weight loss (King et al., 2008). Participants aged between 20 and 40 years provided written, informed consent. All participants were British, from the UK Midlands and East Anglia region. Participants completed a pre-exercise health questionnaire (PAR-Q) to screen for any injuries, or health conditions. If any items were scored negatively, participants were excluded from the study. Participants did not undertake any exercise training prior to the study and were classed as inactive. Participants were instructed to maintain their usual dietary intake for the full duration of the study and not to change any normal lifestyle routines.

Study design

Forty-five participants were randomly assigned into one of the two groups (exercise group [EG] and control group [CG]), using a repeated measures design. Participant's height (m) and body mass (kg) were recorded at the same time of day and at the start of each test in weeks 0 and 8. BMI was determined using the World Health Organization (WHO) standard protocols (WHO, 1995) and the participants' nutritional health status was categorized according to WHO guidelines for their age range (WHO, 2010).

To assess the additional benefits of the training, a Cooper 12-min run test (Cooper, 1968) was performed at baseline (week 0) and post-study (end of week 8) using total distance traveled (km) in a 12-min period. This was used as a field-based estimate of cardiorespiratory fitness, where it can be indirectly calculated to assess if participants improved aerobic ability during the 8 weeks of training (Bandyopadhyay, 2015). The rationale for a field-based intervention was due to necessity in line with restrictions during the COVID-19 pandemic following the UK's second national lockdown in 2021. Participants were instructed to perform all runs at the same time of day, over the same route, and on a flat surface, where possible. The STRAVA running app (Strava Inc., freemium model) utilizing Global Positioning System (GPS) technology was employed to record distance (km), duration (min), route (location), and the time and date completed. Additionally, session rating of perceived exertion (sRPE CR-10) (Borg, 1998) was recorded 30 min after each run for determination of overall session exertion (Foster et al., 2001).

For all training and assessment sessions, participants were instructed to wear appropriate sportswear, have fasted for at least 3 hr, and remain well hydrated with water only. All participants recorded their exercise and physical activity habits using an online training diary that was monitored daily (Foster et al., 2017). A genotyping test kit (DNA Health, Muhdo Health Ltd, Ipswich, UK) was used for the collection of genetic information. For further details, refer to Collins and Heasman (2022) and Chung et al. (2023).

Training intervention

The training consisted of three weekly outdoor runs, increasing in duration from 20 to 30 min, over a period of 8 weeks. For each session, participants aimed for an overall sRPE of 7. Participants familiarized themselves with the CR-10 scale and ensured that it was subjectively calibrated to their perceived exertion based on Borg's qualitative descriptors prior to the study commencing (1998). The session duration was increased to enhance the overall training load by 10% each week, for training progression, whilst sRPE remained constant (Düking et al., 2020). Weekly training duration was reduced on the weeks when a Cooper 12-min run test was completed, ensuring there was still a consistent 10% progression in training load overall (for further information see Chung et al. (2023)). Any additional activities completed outside of the training prescription were recorded in the online personal training diary to track total training volume and loads.

Genotype analysis

DNA test kits were provided by Muhdo health Ltd. (Martlesham Heath, Ipswich, England). Participants provided a 2 mL passive saliva sample in a uniquely coded plastic tube (GeneFiX™ Saliva DNA/RNA Collection), prefilled with

nontoxic stabilization buffer. This allowed storage and transport at room temperature without degradation, for a maximum of 30 days. All samples were immediately sent to Eurofins Global Laboratory (Certification: ISO 17,025:2017) for analysis.

Phosphate buffered saline was mixed to prevent any premature cell rupture, and cell recovery was accomplished using standard extraction procedures. Recovered cells and assay medium (Cell Lysis Solution Infinium, GoldenGate) were loaded into chip wells for Illumina multiplex sequencing. The custom chips (Illumina® Infimum HumanOmni BeadChip) with bound DNA sequences, containing 1,000 target SNPs, were scanned using a Microarray Scanner (iScan, Illumina, San Diego, CA, USA). These SNPs have previously been identified through GWAS to be associated with athletic ability, health, and fitness. Three probes were used, in both forward and reverse orientations with 3-repeats for determination of alleles and nucleotides with an accuracy report of 99.99%. For the complete list of all SNPs included within the DNA chip, please refer to the UK Data Service (https://doi.org/10.5255/UKDA-SN-856799).

Statistical analysis

All data were reported as mean ± standard deviation (SD) and data analysis was performed using the statistical package JASP 0.16.2.0. All variables were assessed for parametric assumptions, using the Shapiro–Wilk test of normality and Levene's test for homogeneity of variance, with an alpha of $p \leq .05$. Changes in body mass in both exercise and control groups were initially assessed using two-way mixed ANOVA and Eta-squared. Significant results were further evaluated using independent samples and paired sample t-tests, as appropriate. Equivalent non-parametric tests were used where data failed to meet parametric assumptions. A Spearman's rho correlation test was implemented to evaluate relationships. Cohen's *d* effect size (ES) and 95% Confidence Intervals (CI) were also calculated. The ES was defined as small = 0.20–0.49, medium = 0.50–0.79, and large ≥0.80 (Cohen, 2013).

Pearson's chi-square (χ^2) was used to screen potential body mass change-associated SNPs. As the χ^2 analysis provided no information about the magnitude of response and the SNP data were often non-parametric, a Kruskal–Wallis H-test was employed for these data, followed by Dunn's multiple pairwise comparisons, to confirm which allelic combinations were significant. Fisher's exact test determined whether the SNP's allelic distributions were in line with established European frequencies and calculated Hardy–Weinberg equilibrium (HWE).

A moderation analysis tested changes in body mass (kg) as the dependent variable, pre-mass as a covariant, and intervention groups multiplied by summed allele scores as independent variables (interaction term) to determine any moderate relationships. Finally, positive alleles (SNPs associated with body mass change) were summed (polygenetic score) for each participant and were equally weighted; homozygosity for associated alleles scored 2, whilst heterozygosity scored 1 and homozygosity, with no allele association, scored 0. The resultant allelic scores were summed and subjected to regression analysis with the change in body mass (%) using methods to those described in the previous literature (Burgess & Thompson, 2013; Chung et al., 2023).

Results

Participant characteristics

Of the original 45 participants, seven did not return consistent genetic calls and were excluded from further analysis. The remaining 38 participants (males: $n = 21$; females: $n = 17$) were split into one of the two groups: (EG [$n = 17$: 5 females and 12 males], age: 31 ± 8 years, height: 1.79 ± 0.09 m, body mass: 81.8 ± 15.63 kg, and BMI 25.3 ± 3.59 kg·m^2 and CG [$n = 21$: 12 females and 9 males], age: 28 ± 5 years, height: 1.71 ± 0.08 m, body mass: 73.2 ± 15.26 kg, and BMI 24.8 ± 4.28 kg·m^2) were included for the final analysis of the study, where all baseline variables were normally distributed. There were non-significant differences in any baseline characteristics, except for height, when comparing groups ($p = .005$). Table 1 displays participant information as well as group means across measured variables.

Body mass

Baseline body mass was normally distributed across all participants. Independent samples t-test found no significant differences in baseline results, when comparing EG against CG (t(36) = 0.351, $p = .73$, ES = 0.38 [95% CI: −2.68 to 2.39]), with Levene's test showing homogeneity between groups at baseline.

Over the 8-week intervention, the training diaries revealed that the EG totaled a training load of 50,811 ± 2,258 AU (arbitrary units), in comparison to the CG at 23,512 ± 4,178 AU, which was significantly greater ($p < .001$; ES = 1.65 [95% CI: 0.98–2.33]). The EG showed a significant decrease in body mass equating to −1.63 ± 2.71% (−1.46 ± 2.41 kg) (t(16) = 2.624, $p = .018$, ES = 0.64 [95% CI: 0.09–0.82]). Although the CG showed a slight increase in body mass of 0.65 ± 1.45% (0.45 ± 0.95 kg), this change was not significant (t(20) = −2.069, $p = .052$, ES = 0.45 [95% CI: −0.30 to 0.001]). These differences were more apparent when comparing the changes between groups (t(36) = −3.328, $p = .002$, ES = 1.09 [95% CI: −3.678 to −0.893]). Figure 1 shows each participant's change in body mass and groups.

Notably, the change in body mass in the EG varied significantly ($p = .024$; ES = 0.60 [95% CI: −3.03 to 1.31]) between individuals, confirming inter-individual differences in their response to exercise (Figure 1). This difference could not be accounted for by variation in training loads alone (regression = 0.159; $p = .88$). Eta-squared also showed that only 24% (95% CI: 0.37–0.435) of the variance between participants were accounted for by the training program itself.

Cardiorespiratory fitness

Both groups were normally distributed for Cooper run scores (EG = D (17), 0.965, $p = .723$; CG = D (21), 0.972, $p = .776$). Independent samples t-test showed no significant differences between baseline scores between the EG (2.26 ± 0.47 km) and

Table 1. Participant characteristics. Study cohort including both groups over all relevant variables.

Participant no.	Group	Height (m)	Baseline body mass (kg)	Post body mass (kg)	Δ Body mass (kg)	Δ Body mass (%)	Baseline BMI (kg/m^2)	Post BMI (kg/m^2)	Baseline Cooper run (km)	Post Cooper run (km)	Δ Cooper run (%)
1	EG	1.83	87.00	79.00	−8.00	−9.20	25.98	23.59	2.45	2.26	−7.76
2	EG	1.85	92.50	91.20	−1.30	−1.41	27.03	26.65	2.07	2.54	22.71
3	EG	1.68	59.00	59.50	0.50	0.85	20.99	21.17	1.76	2.09	18.75
4	EG	2.04	105.00	107.00	2.00	1.90	25.23	25.71	2.33	2.63	12.88
5	EG	1.80	89.00	88.50	−0.50	−0.56	27.47	27.31	2.17	2.41	11.11
6	EG	1.75	69.00	69.00	0.00	0.00	22.53	22.53	2.54	2.71	6.69
7	EG	1.78	90.26	88.97	−1.29	−1.43	28.55	28.14	1.40	1.71	22.14
8	EG	1.80	86.20	84.82	−1.38	−1.60	26.60	26.18	2.31	2.42	4.76
9	EG	1.80	91.65	89.50	−2.15	−2.35	28.29	27.62	2.43	2.59	6.62
10	EG	1.73	57.10	57.10	0.00	0.00	19.08	19.08	3.42	3.64	6.43
11	EG	1.80	76.80	76.80	0.00	0.00	23.70	23.70	1.88	2.28	21.28
12	EG	1.69	61.00	60.70	−0.30	−0.49	21.38	21.28	1.85	2.24	20.87
13	EG	1.88	96.00	91.00	−5.00	−5.21	27.16	25.75	2.41	2.64	9.33
14	EG	1.81	111.00	107.50	−3.50	−3.15	33.88	32.81	2.20	2.39	8.64
15	EG	1.73	75.40	73.50	−1.90	−2.52	25.19	24.56	2.88	3.15	9.50
16	EG	1.70	75.00	72.00	−3.00	−4.00	25.90	24.86	1.80	2.29	26.79
17	EG	1.84	72.00	73.00	1.00	1.39	21.23	21.53	2.59	2.86	10.56
Mean		**1.79**	**81.99**	**80.53**	**−1.46**	**−1.63**	**25.31**	**24.85**	**2.26**	**2.52**	**12.43**
SD		**0.09**	**15.63**	**15.00**	**2.41**	**2.71**	**3.59**	**3.29**	**0.47**	**0.43**	**8.67**
18	CG	1.65	55.00	56.00	1.00	1.82	20.20	20.57	1.95	1.93	−0.83
19	CG	1.73	73.00	75.00	2.00	2.74	24.39	25.06	2.25	2.17	−3.56
20	CG	1.68	75.00	75.00	0.00	0.00	26.57	26.57	1.63	1.60	−1.84
21	CG	1.65	54.00	55.00	1.00	1.85	19.83	20.20	1.69	1.61	−4.76
22	CG	1.63	54.00	55.00	1.00	1.85	20.43	20.81	2.05	2.05	0.00
23	CG	1.70	82.00	82.00	0.00	0.00	28.31	28.31	1.87	1.89	1.07
24	CG	1.87	69.00	71.00	2.00	2.90	19.73	20.30	1.98	2.43	22.76
25	CG	1.65	89.90	88.90	−1.00	−1.11	33.02	32.65	1.91	2.04	6.81
26	CG	1.65	61.90	62.30	0.40	0.65	22.74	22.88	1.30	1.38	6.15
26	CG	1.64	56.00	54.00	−2.00	−3.57	20.82	20.08	2.22	2.20	−0.90
28	CG	1.73	100.90	101.30	0.40	0.40	33.71	33.85	2.30	2.27	−1.30
29	CG	1.85	69.00	69.00	0.00	0.00	20.16	20.16	2.65	2.94	10.94
30	CG	1.73	75.50	75.30	−0.20	−0.26	25.31	25.24	2.63	2.44	−7.22
31	CG	1.67	70.00	71.00	1.00	1.43	25.10	25.46	1.90	1.87	−1.69
32	CG	1.82	105.00	105.00	0.00	0.00	31.70	31.70	2.42	2.05	−15.29
33	CG	1.88	98.40	98.70	0.30	0.30	27.84	27.93	2.00	2.09	4.84
34	CG	1.62	68.00	68.30	0.30	0.44	25.91	26.02	1.90	1.96	3.16
35	CG	1.66	62.20	63.00	0.80	1.29	22.57	22.86	2.10	2.21	5.24
36	CG	1.66	62.50	62.50	0.00	0.00	22.58	22.58	2.28	2.31	1.32
37	CG	1.75	74.80	75.20	0.40	0.53	24.42	24.56	1.67	1.74	4.19
38	CG	1.76	82.00	84.00	2.00	2.44	26.47	27.12	1.88	1.92	1.71
Mean		**1.71**	**73.24**	**73.69**	**0.45**	**0.65**	**24.85**	**25.00**	**2.03**	**2.05**	**1.47**
SD		**0.08**	**15.26**	**15.19**	**0.95**	**1.45**	**4.28**	**4.21**	**0.33**	**0.34**	**7.39**

EG = Exercise group; CG = Control group; Δ = the change from baseline to post 8-week scores.

CG (2.03 ± 0.33 km) (t(36) = 1.816, p = .078, ES = 0.59 [95% CI: −0.03 to 0.50]).

Following the 8 weeks of training the EG significantly improved their running distance and correspondingly their cardiorespiratory fitness compared to baseline scores by 0.26 ± 0.16 km (equivalent to 12.43 ± 8.67%) (t (16) = −6.744, p < .001, ES = 1.64 [95% CI: −0.34 to −0.176]), whilst the CG showed no significant changes (0.02 ± 0.16 km [1.47 ± 7.39%], p = .489, ES = 0.15, [95% CI: −0.35 to 0.98]). Furthermore, when comparing the two groups, the, improvements in the EG were significantly greater than CG (t(36) = 4.137, p = .001, ES = 1.38 [95% CI: 5.68–16.25]) demonstrating the positive effects of the training program.

Genotypes

A total of 285 SNPs (28.5%) showed no allelic variation between participants and were manually removed from the dataset prior to statistical analysis. Dunn's multiple pairwise comparisons revealed that 17 SNPs were positively associated with a decrease in body mass (Table 2). Fisher's Exact test calculated HWE as standard, found no significant differences in the allele frequencies with those expected within the European population. Independent samples t-test confirmed that there were no significant differences between allele scores when comparing EG and CG (t(36) = 0.434, p = .667, [95% CI: −2.09 to 3.22]), confirming that the groups were constructed at random and that allele frequencies are even.

For the exercise intervention group, there was a significant association between the changes in body mass and the number of positive alleles that participants possessed (r^2 = .74; p < .001). Conversely, those in the control group did not observe any significant association for the allele scores and the change in body mass (r^2 = .001; p = .874) shown in Figure 2(a).

Linear Regression model further showed that both summed alleles scores and intervention groups, had independent effects on the change in body mass (p = .013 and 0.014, respectively) when viewed separately. However, more importantly, when both independent variables were combined (interaction term) using Moderation analysis, the model summary predicted 62.2% of the variance within the change in body mass is accounted for

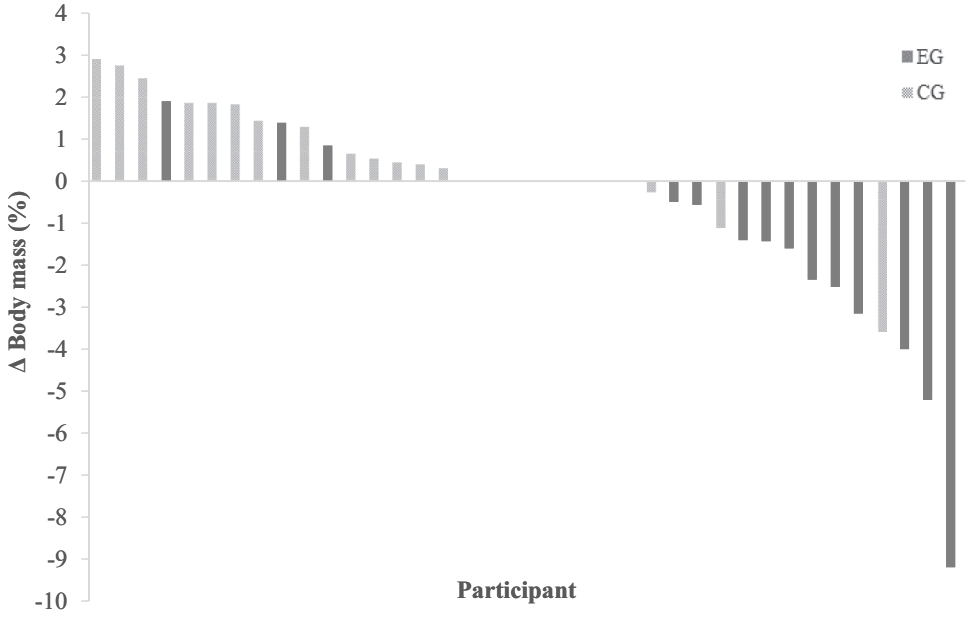

Figure 1. Waterfall plot of change in body mass (%). This is separated for each participant and highlighted the group they are in. Each participant number is presented outside of the bar as a data label. Where EG = Exercise group and CG = Control group.

Table 2. Alphabetical list of genes. Genes associated with decreases in BMI, together with initial χ2 values and Dunn's test *p*-values.

Gene*	Position	rs number	SNP alleles	Positive allele	Type	χ2	Dunn test
BDNF	Chr 11/27658369	4923460	GT	G	Upstream Var	0.006	0.016
BDNF	Chr 11/27635242	6265	GA	G	Missense Coding	0.006	0.016
CHRNA5	Chr 15/78590583	16969968	GA	A	Missense Coding	0.005	0.036
COL1A1	Chr 17/50200388	1800012	GT	T	Intron Var	0.026	0.035
CPT1B	Chr 22/50578924	5770917	TC	T	Upstream Var	0.021	0.038
FGF5	Chr 4/80263187	16998073	AT	T	Intron Var	0.024	0.041
HCP5	Chr 11/31466217	41298364	CT	C	Upstream Var	0.036	0.017
LIN28B	Chr 6/104942078	1475120	CT	C	Upstream Var	0.026	0.019
POU3F2	Chr 6/98582900	12206087	GA	G	Upstream Var	0.042	0.032
PPARGC1A	Chr 4/23874211	3774923	GA	G	3′-UTR	0.023	0.043
PPARGC1A	Chr 4/23813084	3736265	GA	G	Missense Coding	0.023	0.049
PPARGC1A	Chr 4/23793441	10028665	CT	T	Intron Var	0.025	0.039
SMAD3	Chr 15/67450305	17228058	AG	G	Upstream Var	0.011	0.013
SOD2	Chr 6/159692840	4880	TC	C	Missense Coding	0.019	0.044
TBX3	Chr 12/114914926	2384550	GA	A	Upstream Var	0.039	0.049
TDRD9	Chr 14/104017953	10149470	AG	G	Intron Var	0.004	0.011
VRK2	Chr 2/57980939	15183395	AG	A	Intron Var	0.031	0.011

Note. Or the nearest gene. SNV = single nucleotide variation; Var = Variant; Positive allele = allele associated with improved body mass scores; *Or nearest gene; 3′-UTR = three prime untranslated region.

by the interaction (summed allele scores*group). The interaction term was significantly associated with the change in body mass at $p = .001$, shown in Figure 2(b). Thus, those participants with more positive alleles for the genes listed in Table 2, demonstrated greater decreases in body mass, only when following the 8-week intervention (Figure 2).

Discussion

The aim of this study was to investigate genetic associations with changes in body mass, following an endurance-based running program, within a previously inactive UK population. Participants within the EG showed significant decreases in body mass ($p = .018$), whereas the control group displayed a small, but non-significant increase. This is outlined in Figure 1 and shows that the majority of those that lost weight belonged to the exercise group. Critically, the change in body mass was significantly different ($p = .024$) between individuals in the EG, a difference that could not be accounted for by exercise loads alone (24% of the variance explained). Further, 17 SNPs were positively associated with decreases in body mass and the number of these "favorable" SNPs participants possessed displayed a significant linear correlation ($r^2 = .74$; $p < .001$). Moderation analysis confirmed an interaction effect with the dependent variable (Body mass) and independent variable (summed allele scores * intervention group), predicting 62.2% of the variance in the change in body mass and significant interactions at $p = .001$. These findings demonstrate that the inter-individual variability in the responsiveness to endurance training can be largely explained by the number of "favorable" SNPs an individual possesses only when integrated with exercise (Figure 2). Such findings concur with previous studies, which have reported significant associations with reductions in BMI attributable to genetic factors (Leońska-Duniec et al., 2019; Lin et al., 2019). However, very few studies have been

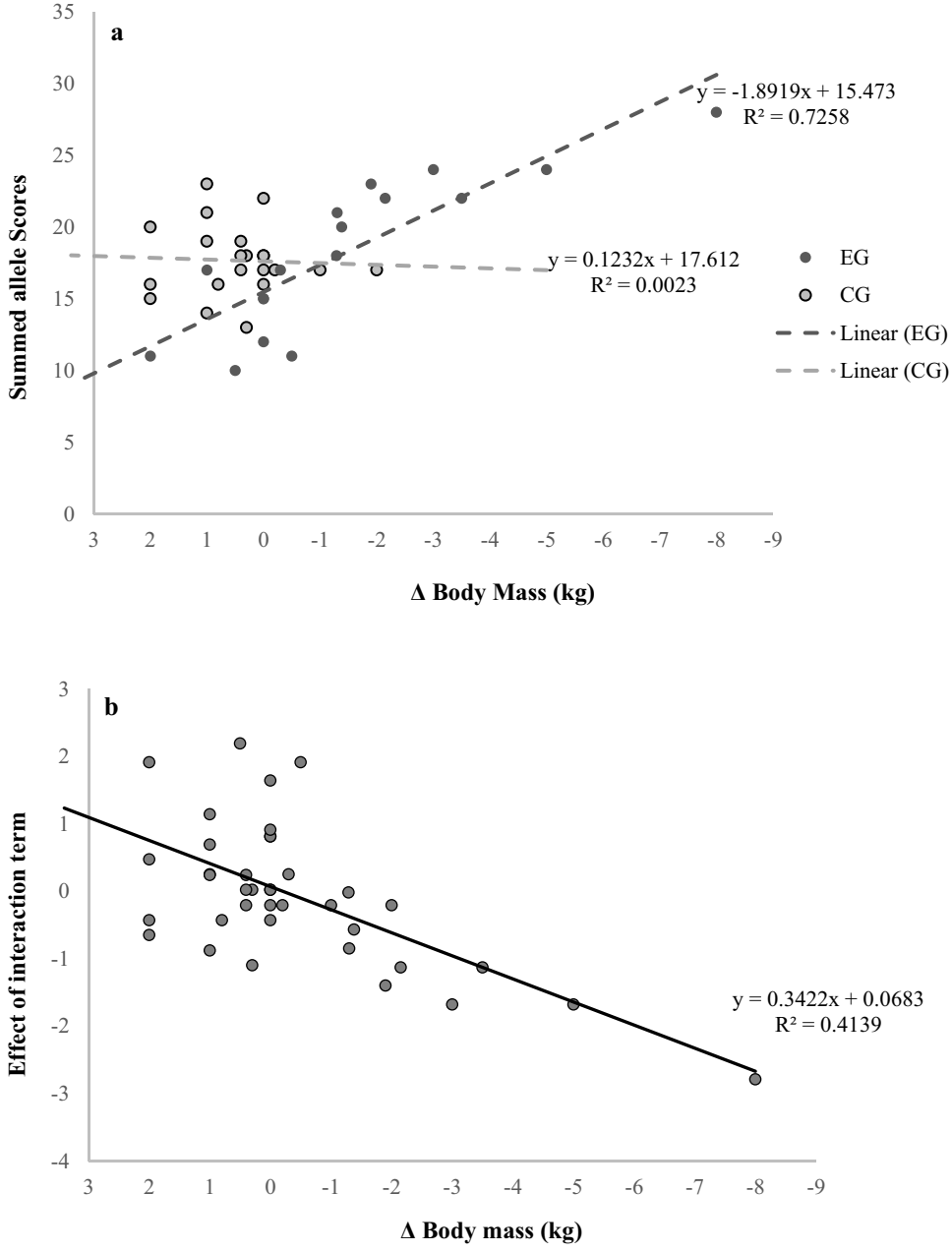

Figure 2. A depiction of the interaction between alleles and body mass over both intervention groups separately (panel A) and a moderator analysis plot representing the effect of the interaction term (the intervention grouping multiplied by summed allele scores (panel B).

performed under realistic field-based settings and reviewed multiple genotypes.

Of the 17 SNPs identified, 13 were found in regions of the genome that are non-protein coding: seven upstream variants, five intron variants, and one 3'UTR (Table 2). Such non-coding DNA (ncDNA) accounts for the majority of the human genome and includes sequences that are transcribed into a variety of RNA molecules, which have regulatory functions, including gene promoters and enhancers (Jo & Choi, 2015; Pagni et al., 2022). The remaining four SNPs were missense coding single nucleotide variations (SNVs), which may cause a change in the overall structure and function of a protein (Jo & Choi, 2015). Interestingly, the SNPs identified in this study fall into two distinct groups: 1) Those associated with genes (PPARGC1A; COL1A; CPT1B; BDNF; HCP5; SOD2; FGF5; SMAD3; TBX3) involved in the control of diet, adiposity and/or energy metabolism; 2) Those associated with genes (CHRNA5; VRK2; LIN28B; TDRD9; POU3F2) involved in intelligence and/or psychological conditions, particularly depressive illness.

Genes associated with diet, adiposity and energy metabolism

PPARGC1A (peroxisome proliferator-activated receptor-coactivator (PGC-1-α)) is a key regulator of energy metabolism, playing a central role in the regulation of cellular metabolism, mitochondrial biogenesis, oxidative muscle fiber development and has roles in the regulation of both carbohydrate and lipid metabolism (Csép et al., 2017). PGC-1-α is also

associated with disorders such as obesity, diabetes, and cardiomyopathy (Csép et al., 2017) and within the context of this study, rs3736265, and rs3774923 have a significant relationship with the change in body mass (Yoneda et al., 2008).

SMAD3 (SMAD family member 3 protein) is a TGFβ-activated transcriptional modulator, which regulates obesity-induced glucose and lipid abnormalities (Laulajainen-Hongisto et al., 2020). SMAD3-deficient adipocytes demonstrate a marked increase in mitochondrial biogenesis, with a corresponding increase in basal respiration. SMAD3 also acts as a repressor of PPARGC1A expression (Yadav et al., 2011). Hence, it is plausible that participants with these two positive alleles have an enhanced metabolism response associated with exercise.

HCP5 is a TGFβ-induced LncRNA which is transcriptionally regulated by SMAD3 (Kulski, 2019). HCP5 promotes adipogenic differentiation, and recent studies have identified differentially methylated sites within, or neighboring, the HCP5 gene sequence, associated with epigenetic regulation of disease-related phenotypes, including obesity (Kulski, 2019). Moreover, HCP5 is involved in the upregulation of PPARGC1A and carnitine palmitoyl transferase 1 (CPT1), which increases fatty acid oxidation (Wu et al., 2020).

CPT1B (carnitine palmitoyl transferase 1B) catalyzes the rate-limiting step of transport of cytoplasmic long-chain acyl-coenzyme A into the mitochondrial matrix, in both striated muscle and brown adipose tissue. The ability to increase fatty acid oxidation (FAO), in response to dietary lipids is impaired in the skeletal muscle of obese individuals (Maples et al., 2015). Honda et al. (2022) showed a significant interaction between obesity and rs5770917 ($p = .0089$). Interestingly, BDNF rs6265, which reduces CBP1 activity, also correlates with obesity (Ricci et al., 2021).

BDNF (brain-derived neurotrophic factor) gene polymorphisms, including rs6265, correlate with BMI and can be considered a genetic determinant of obesity (Akbarian et al., 2018). This has been confirmed by GWAS for both rs6265 and rs4923460 (Marcos-Pasero et al., 2021). Mechanistic studies, reviewed by Sandrini et al. (2018), have demonstrated that reductions in BDNF expression, BDNF haploinsufficiency, or missense mutations, including rs6265, are associated with hyperphagia, weight gain, and obesity. These observations could explain why some individuals failed to lose body mass regardless of exercise as well as some of the variance observed (Table 1 and Figure 1).

SOD2 (superoxide dismutase 2) studies have shown that increases in activity are correlated with obesity, with over 90% of obese people processing the C/T genotype of rs4880 (Ricci et al., 2021). In a diet and exercise intervention study, which required those to walk at a "brisk pace" for 30 min per day, the C/T SOD2 genotype, rs4880, showed a statistically significant decrease in BMI, in agreement with the findings of this study (Monda et al., 2010).

FGF5 (fibroblast growth factor 5) rs16998073 is an intron variant, previously identified by GWAS, targeted at adiposity traits, metabolic syndrome and hypertension (Monda et al., 2010). A study of associations of hypertension-related SNPs with obesity risk, identified three polymorphisms, including FGF5 rs16998073 in this study. Interaction analyses among these loci indicated a potential gene interaction between methylenetetrahydrofolate reductase (MTHFR) and FGF5 (Fu et al., 2018). Eta-analysis has also demonstrated a significant relationship between homocysteine and obesity risk *via* MTHFR (Fu et al., 2019).

TBX3 (Transcription factor T-box 3) is expressed in hypothalamic neurons involved in sensing and governing energy status, and human TBX3 haploinsufficiency has been linked with obesity (Quarta et al., 2019). Mutations in TBX3 are also considered a monogenic cause of obesity, with TBX3 having a role in the development of hypothalamic melanocortin neurons, which play an important role in the weight regulation pathway in humans (Xu et al., 2020).

COL1A1 codes for type-I collagen and would not immediately appear to have a direct link with obesity and energy metabolism. However, a recent study examining the risk of acute musculoskeletal soft tissue injuries noted that the rs1800012 (G/T) allele was associated with increased body mass (Gibbon et al., 2020). Interestingly, rs1800012 is a Sp1-binding site polymorphism (Posthumus et al., 2009). This is significant because the adiponectin gene ADIPOQ (adipocyte C1q and collagen domain containing) promoter has an SP1-binding site and serum adiponectin concentrations are decreased in those with obesity.

Genes associated with intelligence and psychological conditions

There is a strong association between depression and obesity (Torgersen et al., 2022), and longitudinal studies suggest that the direction of causality runs from low intelligence to obesity, suggesting shared causal biological mechanisms (Milaneschi et al., 2019). Whilst this relationship is clearly multifactorial and complex, research demonstrates a strong genetic component (Milano et al., 2020).

CHRNA5 (cholinergic receptor nicotinic alpha 5): Smoking is known to influence bodyweight, a relationship partly explained by the effect of nicotine on appetite (Thorgeirsson et al., 2013). In this connection, a GWAS of smoking behavior noted that CHRNA5 rs1051730 is correlated with reduced BMI in smokers. This is of relevance for this study since rs16969968 is in perfect linkage disequilibrium with rs1051730 (Li & Yue, 2018). Moreover, the rs16969968 GA and AA genotypes are associated with increased ability to cease smoking, and individuals with recurrent depression were significantly less likely to quit smoking compared to those with no history of depression (Tomaz et al., 2018).

VRK2 (vaccinia-related kinase 2) and SNPs near this gene have shown consistent correlations with multiple psychiatric disorders, including major depressive disorders (MDD), which display strong heritability (~0.80). Rs1518395 showed genome-wide significant associations (MDD $p = 4.32 \times 10^{-12}$) (Li & Yue, 2018). Furthermore, a study of 15 genetic loci, associated with risk of MDD, revealed that rs1518395 was the second most significant variant and also had a significant interaction with obesity (Hyde et al., 2016).

LIN28B (Lin-28 homolog B) rs1475120 has been shown to have a significant association with MDD (Hyde et al., 2016; Katsuki et al., 2019), whilst longitudinal analyses (Ong et al., 2011) have revealed age-dependent associations between LIN28B genotype and bodyweight ($p < .001$). However, it is

unclear how this applies to this study cohort as appetite and feeding were not monitored.

TDRD9 (tudor domain containing 9) in a meta-analytical study of 450,619 individuals showed evidence of substantial polygenic overlap between depression and change in body mass (Torgersen et al., 2022). Of 13,900 trait-variants influencing depression and 11,000 trait-variants influencing bodyweight, 9,500 were shared, with a Dice coefficient of 0.76 (SD 0.08). Further research uncovered significant upregulation of the TDRD9 gene in human type 2 diabetes-specific adipose tissue proteome and transcriptome in obesity (Carruthers et al., 2021).

POU3F2 (POU Class 3 homeobox 2): GWAS identified three independent SNPs of genome-wide significance, including rs9320913, for educational attainment (Rietveld et al., 2013). This is relevant because rs12206087 is in close linkage disequilibrium for rs9320913 ($r^2 = .99$) (Rietveld et al., 2014). Small deletions are linked to intellectual disability and obesity (Kasher et al., 2016). Sniekers et al. (2017) identified 25 loci, including POU3F2 (rs12206087) and TDRD9 (rs10149470), that were associated with high intelligence. It is therefore suggested that there is a significant negative association between IQ and obesity (Jacob et al., 2020). Therefore, those with positive alleles for genes associated with intelligence and psychological conditions may make healthier lifestyle choices.

The findings in this study confirm the relevance and potential application of genetics within exercise and weight management. As observed, the human genome plays a crucial role and has many interactions with exercise-based responses and adaptations. This study serves to bridge the gap between population health and exercise sciences. It aims to enhance the research in the application of genetics to develop and aid individually tailored health interventions and exercise protocols to tackle health conditions, such as obesity.

Multiple comparisons

A potential criticism of this study is that it used a relatively small number of participants and multiple statistical tests, hence the probability of type I statistical error increases. Under such circumstances, the Bonferroni correction is usually considered necessary to adjust p-values (Armstrong, 2014). Equally, arguments have been made against adjusting p-values, as this increases the probability of type II error. Additionally, this weakens the statistical detectability of significance, creating false negatives. In this case, four observations suggest that the associated alleles have been identified correctly and therefore do not need to be adjusted: 1) Within the 17 SNPs identified, PPARGC1A and BDNF are disproportionately represented. It is highly unlikely that a set of false positive allelic associations would repeatedly identify the same gene. Accordingly, the probability of identifying the PPARGC1A gene three times, independently, at random, from 715 SNPs, is $1.25 \times 10–4$; hence, the expected probability for this gene to be erroneously identified from this dataset, is 0.089%; 2) PPARGC1A SNPs, rs3736265 and rs3774923, are in strong linkage disequilibrium (Lai et al., 2008), indicating that their simultaneous identification is very unlikely to be a false positive; 3) Ten (CPT1B, HCP5, SMAD3, PPARGC1A, CPT1B, BDNF, POU3F2, TDRD9, VRK2, LIN28B) of the 14 genes identified demonstrate functional interrelationships; 4) All the SNPs identified in this study have been previously associated with specifically weight-related traits within the research literature.

For this study, we have displayed the results at face value with full transparency. A mixture of tests, such as A Dunn's multiple pairwise comparisons, the Fisher's Exact test and Hardy–Weinberg equilibrium (HWE), were used to confirm that our allele frequencies represent the European population, and that identification of allele comparisons is correct. If Bonferroni adjustments are applied, this would change the significant threshold value to 0.00007. Inherently, this level of significance causes statistical issues in none of GWAS studies. Therefore, caution is required when applying these adjustments.

Limitations

Participants were advised to maintain their normal diet where possible and did not report any changes. However, accurately measuring dietary intake in a free-living environment is challenging and underreporting has been shown to increase with physical activity (Waterworth et al., 2022). At the time of design, it was therefore decided that assessment of dietary intake would place an unnecessary burden on participants and was not monitored. Additionally, it is important to acknowledge that this data was collected during the COVID-19 pandemic where collection methods were limited. This study would have also benefited from measurements of body composition, such as muscle mass and body fat, to support the measurements of body mass and determine the specific efficacy of the training program.

Although sample size may have been adequate for variables such as Cooper run performance and change in body mass (confirmed with the *post-hoc* power), a larger sample size for the allele subgroups was desirable. This is because not all samples were successfully analyzed in this study and there are inherent issues with sub-grouping. In particular, the relatively small group sizes meant that many low-frequency alleles were not represented in our analysis, consequently excluding specific genes that might still be relevant. However, such SNPs should not be disregarded as some rare, but potentially significant variants could be identified with larger sample sizes. Another limitation that must be addressed is the genotype DNA chip that was used. Although Muhdo Health Ltd justifies the SNP selection with research literature evidence, the chip only has 1,000 SNPs, whereas other chips can have thousands. It is likely, therefore, that interactions may have been omitted.

Conclusion

This study found that an individual's change in body mass in response to exercise is, to a large degree, determined by their specific genetic profile. This concurs with previous heritability studies that have reported a range between 24% and 81% (Lin et al., 2019) which encompasses the variability noted in this study. Whilst genetic factors are undoubtedly important, it is clear that lifestyle factors, including exercise, are also

important to modify body mass. Given that obesity is a burgeoning challenge to society, a comprehensive knowledge of how genes and their alleles affect the body's responses to exercise would revolutionize the individualization and effectiveness of exercise programs (Chung et al., 2023; Leońska-Duniec et al., 2019). This is an emerging area of science, and further research is required to elucidate the links between individual genetic polymorphisms and exercise adaptations.

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Data availability statement

All relevant data are publicly available and within the contents of this manuscript or supporting documents and cited. The complete genetic data files collected for this study have been published within the UK Data Service (https://doi.org/10.5255/UKDA-SN-856799) as '*1000 SNP Genotypes of UK adults, 2021–2023*' and is publicly available to access.

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