Genome-wide physical activity interactions in adiposity – a meta-analysis of 200,452 adults

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Abstract

Physical activity (PA) may modify the genetic effects that give rise to increased risk of obesity. To identify adiposity loci whose effects are modified by PA, we performed genome-wide interaction meta-analyses of BMI and BMI-adjusted waist circumference and waist-hip ratio from up to 200,452 adults of European (n=180,423) or other ancestry (n=20,029). We standardized PA by categorizing it into a dichotomous variable where, on average, 23% of participants were categorized as inactive and 77% as physically active. While we replicate the interaction with PA for the strongest known obesity-risk locus in the *FTO* gene, of which the effect is attenuated by ~30% in physically active individuals compared to inactive individuals, we do not identify additional loci that are sensitive to PA. In additional genome-wide meta-analyses adjusting for PA and interaction with PA, we identify 11 novel adiposity loci, suggesting that accounting for PA or other environmental factors that contribute to variation in adiposity may facilitate gene discovery.

Author Summary

Decline in daily physical activity is thought to be a key contributor to the global obesity epidemic. However, the impact of sedentariness on adiposity may be in part determined by a person's genetic constitution. The specific genetic variants that are sensitive to physical activity and regulate adiposity remain largely unknown. Here, we aimed to identify genetic variants whose effects on adiposity are modified by physical activity by examining ~2.5 million genetic variants in up to 200,452 individuals. We also tested whether adjusting for physical activity as a covariate could lead to the identification of novel adiposity variants. We find robust evidence of interaction with physical activity for the strongest known obesity risk-locus in the *FTO* gene, of which the body mass index-increasing effect is attenuated by ~30% in physically active individuals compared to inactive individuals. Our analyses indicate that other similar gene-physical activity interactions may exist, but better measurement of physical activity, larger sample sizes, and/or improved analytical methods will be required to identify

them. Adjusting for physical activity, we identify 11 novel adiposity variants, suggesting that accounting for physical activity or other environmental factors that contribute to variation in adiposity may facilitate gene discovery.

Introduction

In recent decades, we have witnessed a global obesity epidemic that may be driven by changes in lifestyle such as easier access to energy-dense foods and decreased physical activity (PA) [1]. However, not everyone becomes obese in obesogenic environments. Twin studies suggest that changes in body weight in response to lifestyle interventions are in part determined by a person's genetic constitution [2-4]. Nevertheless, the genes that are sensitive to environmental influences remain largely unknown.

Previous studies suggest that genetic susceptibility to obesity, assessed by a genetic risk score for BMI, may be attenuated by PA [5, 6]. A large-scale meta-analysis of the *FTO* obesity locus in 218,166 adults showed that being physically active attenuates the BMI-increasing effect of this locus by ~30% [7]. While these findings suggest that *FTO*, and potentially other previously established BMI loci, may interact with PA, it has been hypothesized that loci showing the strongest main effect associations in genome-wide association studies (GWAS) may be the least sensitive to environmental and lifestyle influences, and may therefore not make the best candidates for interactions [8]. Yet no genome-wide search for novel loci exhibiting SNP×PA interaction has been performed. A genome-wide meta-analysis of genotype-dependent phenotypic variance of BMI, a marker of sensitivity to environmental exposures, in ~170,000 participants identified *FTO*, but did not show robust evidence of environmental sensitivity for other loci [9]. Recent genome-wide meta-analyses of adiposity traits in >320,000 individuals uncovered loci interacting with age and sex, but also suggested that very large sample sizes are required for interaction studies to be successful [10].

Here, we report results from a large-scale genome-wide meta-analysis of SNP×PA interactions in adiposity in up to 200,452 adults. As part of these interaction analyses, we also

examine whether adjusting for PA or jointly testing for SNP's main effect and interaction with PA may identify novel adiposity loci.

Results

Identification of loci interacting with PA

We performed meta-analyses of results from 60 studies, including up to 180,423 adults of European descent and 20,029 adults of other ancestries to assess interactions between ~2.5 million genotyped or HapMap-imputed SNPs and PA on BMI and BMI-adjusted waist circumference (WC_{adjBMI}) and waist-hip ratio (WHR_{adjBMI}) (**Tables S1-S5**). Similar to a previous meta-analysis of the interaction between *FTO* and PA [7], we standardized PA by categorizing it into a dichotomous variable where on average ~23% of participants were categorized as inactive and ~77% as physically active (**see Methods and Table S6**). On average, inactive individuals had 0.99 kg/m^2 higher BMI, 3.46 cm higher WC, and 0.018 higher WHR than active individuals (**Tables S4 and S5)**.

Each study first performed genome-wide association analyses for each SNP's effect on BMI in the inactive and active groups separately. Corresponding summary statistics from each cohort were subsequently meta-analyzed, and the SNP×PA interaction effect was estimated by calculating the difference in the SNP's effect between the inactive and active groups. To identify sex-specific SNP×PA interactions, we performed the meta-analyses separately in men and women, as well as in the combined sample. In addition, we carried out meta-analyses in European-ancestry studies only and in European and other-ancestry studies combined.

We used two approaches to identify loci whose effects are modified by PA. In the first approach, we searched for genome-wide significant SNP×PA interaction effects ($P_{INT}<5x10^{-8}$). As shown in **Figure 1**, this approach yielded the highest power to identify *cross-over* interaction effects where the SNP's effect is directionally opposite between the inactive and active groups. However, this approach has low power to identify interaction effects where the SNP's effect is directionally concordant between the inactive and active groups (**Figure 1**). We identified a genome-wide

significant interaction between rs986732 in *cadherin 12 (CDH12)* and PA on BMI in European-ancestry studies ($beta_{INT}$=-0.076 SD/allele, $P_{INT}=3.1x10^{-8}$, n=134,767) (**Table S7**). The interaction effect was directionally consistent but did not replicate in an independent sample of 31,097 individuals ($beta_{INT}$=-0.019 SD/allele, P_{INT}=0.52), and the pooled association P value for the discovery and replication stages combined did not reach genome-wide significance (N_{TOTAL}=165,864; $P_{INT-TOTAL}=3x10^{-7}$) (**Figure S1**). No loci showed genome-wide significant interactions with PA on WC_{adjBMI} or WHR_{adjBMI}. *CDH12* encodes an integral membrane protein mediating calcium-dependent cell-cell adhesion in the brain, where it may play a role in neurogenesis [11]. While *CDH12* rs4701252 and rs268972 SNPs have shown suggestive associations with waist circumference ($P=2x10^{-6}$) and BMI ($P=5x10^{-5}$) in previous GWAS [12, 13], the SNPs are not in LD with rs986732 ($r^2<0.1$).

In our second approach, we tested interaction for loci showing a genome-wide significant main effect on BMI, WC_{adjBMI} or WHR_{adjBMI} (**Tables S7-S12**). We adjusted the significance threshold for SNP×PA interaction by Bonferroni correction (P=0.05/number of SNPs tested). As shown in **Figure 1**, this approach enhanced our power to identify interaction effects where there is a difference in the magnitude of the SNP's effect between inactive and active groups when the SNP's effect is directionally concordant between the groups. We identified a significant SNP×PA interaction of the *FTO* rs9941349 SNP on BMI in the meta-analysis of European-ancestry individuals; the BMI-increasing effect was 33% smaller in active individuals ($beta_{ACTIVE}$=0.072 SD/allele) than in inactive individuals ($beta_{INACTIVE}$=0.106 SD/allele, $P_{INT}=4x10^{-5}$). The rs9941349 SNP is in strong LD (r^2 = 0.87) with *FTO* rs9939609 for which interaction with PA has been previously established in a meta-analysis of 218,166 adults [7]. We identified no loci interacting with PA for WC_{adjBMI} or WHR_{adjBMI}.

In a previously published meta-analysis [7], the *FTO* locus showed a geographic difference for the interaction effect where the interaction was more pronounced in studies from North America than in those from Europe. To test for geographic differences in the present study, we performed additional meta-analyses for the *FTO* rs9941349 SNP, stratified by geographic origin (North America vs. Europe). While the interaction effect was more pronounced in studies from North America

480 ($beta_{INT}$=0.052 SD/allele, P=5x10^{-4}, N=63,896) than in those from Europe ($beta_{INT}$=0.028 SD/allele,
481 P=0.006, N=109,806), we did not find a statistically significant difference between the regions
482 (P=0.14).
483
484 **Explained phenotypic variance in inactive and active individuals**
485 We tested whether the variance explained by ~1.1 million common variants (MAF≥1%) differed
486 between the inactive and active groups for BMI, WC_{adjBMI}, and WHR_{adjBMI} [14]. In the physically active
487 individuals, the variants explained ~20% less of variance in BMI than in inactive individuals (12.4% vs.
488 15.7%, respectively; $P_{difference}$=0.046), suggesting that PA may reduce the impact of genetic
489 predisposition to adiposity overall. There was no significant difference in the variance explained
490 between active and inactive groups for WC_{adjBMI} (8.6% for active, 9.3% for inactive; $P_{difference}$=0.70) or
491 WHR_{adjBMI} (6.9% for active, 8.0% for inactive; $P_{difference}$=0.59).
492 To further investigate differences in explained variance between the inactive and active
493 groups, we calculated variance explained by subsets of SNPs selected based on significance
494 thresholds (ranging from P=5x10^{-8} to P=0.05) of PA-adjusted SNP association with BMI, WC_{adjBMI} or
495 WHR_{adjBMI} [15] (**Table S13**). We found 17-26% smaller explained variance for BMI in the active group
496 than in the inactive group at all P value thresholds (**Table S13**).
497
498 **Identification of novel loci when adjusting for PA or when jointly testing for SNP**
499 **main effect and interaction with PA**
500 Physical activity contributes to variation in BMI, WC_{adjBMI}, and WHR_{adjBMI}, hence, adjusting for PA as a
501 covariate may enhance power to identify novel adiposity loci. To that extent, each study performed
502 genome-wide analyses for association with BMI, WC_{adjBMI}, and WHR_{adjBMI} while adjusting for PA.
503 Subsequently, we performed meta-analyses of the study-specific results. We discovered 10 genome-
504 wide significant loci (2 for BMI, 1 for WC_{adjBMI}, 7 for WHR_{adjBMI}) that have not been reported in
505 previous GWAS of adiposity traits (**Table 1**, **Figures S2-S4**).

To establish whether additionally accounting for SNP×PA interactions would identify novel loci, we calculated the joint significance of PA-adjusted SNP main effect and SNP×PA interaction using the method of Aschard et al [16]. As illustrated in **Figure 1**, the joint test enhanced our power to identify loci where the SNP shows simultaneously a main effect and an interaction effect. We identified a novel BMI locus near *ELAVL2* in men ($P_{JOINT}=4x10^{-8}$), which also showed suggestive evidence of interaction with PA ($P_{INT}=9x10^{-4}$); the effect of the BMI-increasing allele was attenuated by 71% in active as compared to inactive individuals ($beta_{INACTIVE}=0.087$ SD/allele, $beta_{ACTIVE}=0.025$ SD/allele) (**Table 1, Figures S2-S4**).

To evaluate the effect of PA adjustment on the results for the 11 novel loci, we performed a look-up in published GIANT consortium meta-analyses for BMI, WC_{adjBMI}, and WHR_{adjBMI} that did not adjust for PA [17, 18] (**Table S22**). All 11 loci showed a consistent direction of effect between the present PA-adjusted and the previously published PA-unadjusted results, but the PA-unadjusted associations were less pronounced despite up to 40% greater sample size, suggesting that adjustment for PA may have increased our power to identify these loci.

The biological relevance of putative candidate genes in the novel loci, based on our thorough searches of the literature, GWAS catalog look-ups, and analyses of eQTL enrichment and overlap with functional regulatory elements, are described in **Box 1** and **Box 2**. As the novel loci were identified in a PA-adjusted model, where adjusting for PA may have contributed to their identification, we examined whether the lead SNPs in these loci are associated with the level of PA. More specifically, we performed look-ups in GWAS analyses for the levels of moderate-to-vigorous intensity leisure-time PA (n=80,035), TV-viewing time (n=28,752), and sedentary behavior at work (n=59,381) or during transportation (n=15,152) [personal communication with Marcel den Hoed, Marilyn Cornelis, and Ruth Loos]. However, we did not find significant associations when correcting for the number of loci that were examined (P>0.005) (**Table S16**).

Identification of secondary signals

In addition to uncovering 11 novel adiposity loci, our PA-adjusted GWAS and the joint test of SNP main effect and SNP×PA interaction confirmed 148 genome-wide significant loci (50 for BMI, 58 for WC_{adjBMI}, 40 for WHR_{adjBMI}) that have been established in previous main effect GWAS for adiposity traits (**Tables S7-S12, Figure S4**). The lead SNPs in eight of the previously established loci (5 for BMI, 3 for WC_{adjBMI}), however, showed no LD or only weak LD (r^2<0.3) with the published lead SNP, suggesting they could represent novel secondary signals in known loci (**Table S17**). To test whether these eight signals are independent of the previously published signals, we performed conditional analyses [19]. Three of the eight SNPs we examined, in/near *NDUFS4*, *MEF2C-AS1* and *CPA1*, were associated with WC_{adjBMI} with $P<5x10^{-8}$ in our PA-adjusted GWAS even after conditioning on the published lead SNP, hence representing novel secondary signals in these loci (**Table S17**).

Enrichment of the identified loci with functional regulatory elements

Epigenetic variation may underlie gene-environment interactions observed in epidemiological studies [20] and PA has been shown to induce marked epigenetic changes in the genome [21]. We examined whether the BMI or WHR_{adjBMI} loci reaching $P<1x10^{-5}$ for interaction with PA (13 loci for BMI, 5 for WHR_{adjBMI}) show overall enrichment with chromatin states in adipose, brain and muscle tissues available from the Roadmap Epigenomics Consortium [22]. However, we did not find significant enrichment (**Tables S18 and S19**), which may be due to the limited number of identified loci. The lack of significant findings may also be due to the assessment of chromatin states in the basal state, which may not reflect the dynamic changes that occur when cells are perturbed by PA [23].

We also tested whether the loci reaching $P<5x10^{-8}$ in our PA-adjusted GWAS of BMI or WHR_{adjBMI} show enrichment with chromatin states and found significant enrichment of the BMI loci with enhancer, weak transcription, and polycomb-repressive elements in several brain cell lines, and with enhancer elements in three muscle cell lines (**Tables S20 and S21**). We also found significant enrichment of the WHR_{adjBMI} loci with enhancer elements in three adipose and six muscle cell lines,

with active transcription start sites in two adipose cell lines, and with polycomb-repressive elements in seven brain cell lines. The enrichment of our PA-adjusted main effect results with chromatin annotations in skeletal muscle in particular, the tissue most affected by PA, could highlight regulatory mechanisms that may be influenced by PA.

Discussion

In this genome-wide meta-analysis of more than 200,000 adults, we do not find evidence of interaction with PA for loci other than the established *FTO* locus. However, when adjusting for PA or jointly testing for SNP main effect and interaction with PA, we identify 11 novel adiposity loci, suggesting that accounting for PA or other environmental factors that contribute to variation in adiposity may increase power for gene discovery.

Our results suggest that if SNP×PA interaction effects for common variants exist, they are unlikely to be of greater magnitude than observed for *FTO*, the BMI-increasing effect of which is attenuated by ~30% in physically active individuals. The fact that common SNPs explain less of the BMI variance among physically active compared to inactive individuals indicates that further interactions may exist, but larger meta-analyses, more accurate and precise measurement of PA, and/or improved analytical methods will be required to identify them. We found no difference between inactive and active individuals in variance explained by common SNPs in aggregate for WC_{adjBMI} or WHR_{adjBMI}, and no loci interacted with PA on WC_{adjBMI} or WHR_{adjBMI}. Therefore, PA may not modify genetic influences as strongly for body fat distribution as for overall adiposity. Furthermore, while differences in variance explained by common variants may be due to genetic effects being modified by PA, it is important to note that heritability can change in the absence of changes in genetic effects, if environmental variation differs between the inactive and active groups. Therefore, the lower BMI variance explained in the active group could be partly due to a potentially greater environmental variation in this group.

While we replicated the previously observed interaction between *FTO* and PA [7], it remains unclear what biological mechanisms underlie the attenuation in *FTO*'s effect in physically active individuals, and whether the interaction is due to PA or due to confounding by other environmental exposures. While some studies suggest that *FTO* may interact with diet [24-26], a recent meta-analysis of 177,330 individuals did not find interaction between *FTO* and dietary intakes of total energy, protein, carbohydrate or fat [27]. The obesity-associated *FTO* variants are located in a super-enhancer region [28] and have been associated with DNA methylation levels [29-31], suggesting that this region may be sensitive to epigenetic effects that could mediate the interaction between *FTO* and PA.

In genome-wide analyses for SNP main effects adjusting for PA, or when testing for the joint significance of SNP main effect and SNPxPA interaction, we identify 11 novel adiposity loci, even though our sample size was up to 40% smaller than in the largest published main effect meta-analyses [17, 18]. Our findings suggest that accounting for PA may facilitate the discovery of novel adiposity loci. Similarly, accounting for other environmental factors that contribute to variation in adiposity could lead to the discovery of additional loci.

In the present meta-analyses, statistical power to identify SNPxPA interactions may have been limited due to challenges relating to the measurement and statistical modeling of PA [5]. Of the 60 participating studies, 56 assessed PA by self-report while 4 used wearable PA monitors. Measurement error and bias inherent in self-report estimates of PA [32] can attenuate effect sizes for SNP×PA interaction effects towards the null [33]. Measurement using PA monitors provides more consistent results, but the monitors are not able to cover all types of activities and the measurement covers a limited time span compared to questionnaires [34]. As sample size requirements increase nonlinearly when effect sizes decrease, any factor that leads to a deflation in the observed interaction effect estimates may make their detection very difficult, even when very large population samples are available for analysis. Finally, because of the wide differences in PA assessment tools used among the participating studies, we treated PA as a dichotomous variable, harmonizing PA into

inactive and active individuals. Considerable loss of power is anticipated when a continuous PA variable is dichotomized [35]. Our power could be enhanced by using a continuous PA variable if a few larger studies with equivalent, quantitative PA measurements were available.

In summary, while our results suggest that adjusting for PA or other environmental factors that contribute to variation in adiposity may increase power for gene discovery, we do not find evidence of SNP×PA interaction effects stronger than that observed for *FTO*. While other SNP×PA interaction effects on adiposity are likely to exist, combining many small studies with varying characteristics and PA assessment tools may be inefficient for identifying such effects [5]. Access to large cohorts with quantitative, equivalent PA variables, measured with relatively high accuracy and precision, may be necessary to uncover novel SNP×PA interactions.

Methods

Main Analyses

Outcome traits - BMI, WC_{adjBMI} and WHR_{adjBMI}

We examined three anthropometric traits related to overall adiposity (BMI) or body fat distribution (WC_{adjBMI} and WHR_{adjBMI}) [36] that were available from a large number of studies. Before the association analyses, we calculated sex-specific residuals by adjusting for age, age², BMI (for WC_{adjBMI} and WHR_{adjBMI} traits only), and other necessary study-specific covariates, such as genotype-derived principal components. Subsequently, we normalized the distributions of sex-specific trait residuals using inverse normal transformation.

Physical activity

Physical activity was assessed and quantified in various ways in the participating studies of the meta-analysis (**Tables S1 and S6**). Aiming to amass as large a sample size as possible, we harmonized PA by categorizing it into a simple dichotomous variable – physically inactive vs. active – that could be

derived in a relatively consistent way in all participating studies, and that would be consistent with previous findings on gene-physical activity interactions and the relationship between activity levels and health outcomes. In studies with categorical PA data, individuals were defined inactive if they reported having a sedentary occupation and being sedentary during transport and leisure-time (<1 h of moderate intensity leisure-time or commuting PA per week). All other individuals were defined physically active. Previous studies in large-scale individual cohorts have demonstrated that the interaction between *FTO*, or a BMI-increasing genetic risk score, with physical activity, is most pronounced approximately at this activity level [6, 37, 38]. In studies with continuous PA data, PA variables were standardized by defining individuals belonging to the lowest sex- and age-adjusted quintile of PA levels as inactive, and all other individuals as active. The study-specific coding of the dichotomous PA variable in each study is described in **Table S6**.

Study-specific association analyses

We included 42 studies with genome-wide data, 10 studies with Metabochip data, and eight studies with both genome-wide and Metabochip data. If both genome-wide and Metabochip data were available for the same individual, we only included the genome-wide data (**Table S1**). Studies with genome-wide genotyped data used either Affymetrix or Illumina arrays (**Table S2**). Following study-specific quality control measures, the genotype data were imputed using the HapMap phase II reference panel (**Table S2**). Studies with Metabochip data used the custom Illumina HumanCardio-Metabo BeadChip containing ~195K SNPs designed to support large-scale follow-up of known associations with metabolic and cardiovascular traits [39]. Each study ran autosomal SNP association analyses with BMI, WC_{adjBMI} and WHR_{adjBMI} across their array of genetic data using the following linear regression models in men and women separately: 1) active individuals only; 2) inactive individuals only; and 3) active and inactive individuals combined, adjusting for the PA stratum. In studies that included families or closely related individuals, regression coefficients were estimated using a variance component model that modeled relatedness in men and women combined, with sex as a

660 covariate, in addition to the sex-specific analyses. The additive genetic effect for each SNP and
661 phenotype association was estimated using linear regression. For studies with a case-control design
662 (**Table S1**), cases and controls were analyzed separately.

663 All studies were conducted according to the Declaration of Helsinki. The studies were
664 approved by the local ethical review boards and all study participants provided written informed
665 consent for the collection of samples and subsequent analyses.

666

667 **Quality control of study-specific association results**

668 All study-specific files for the three regression models listed above were processed through a
669 standardized quality control protocol using the EasyQC software [40]. The study-specific quality
670 control measures included checks on file completeness, range of test statistics, allele frequencies,
671 trait transformation, population stratification, and filtering out of low quality data. Checks on file
672 completeness included screening for missing alleles, effect estimates, allele frequencies, and other
673 missing data. Checks on range of test statistics included screening for invalid statistics such as P-
674 values >1 or <0, negative standard errors, or SNPs with low minor allele count (MAC, calculated as
675 MAF*N, where MAF is the minor allele frequency and N is the sample size) and where SNPs with
676 MAC<5 in the inactive or the active group were removed. The correctness of trait transformation to
677 inverse normal was examined by plotting 2/median of the standard error with the square root of the
678 sample size. Population stratification was examined by calculating the study specific genomic control
679 inflation factor (λ_{GC}) [41]. If a study had λ_{GC}>1.1, the study analyst was contacted and asked to revise
680 the analyses by adjusting for principal components. The allele frequencies in each study were
681 examined for strand issues and miscoded alleles by plotting effect allele frequencies against the
682 corresponding allele frequencies from the HapMap2 reference panel. Finally, low quality data were
683 filtered out by removing monomorphic SNPs, imputed SNPs with poor imputation quality (r2_hat
684 <0.3 in MACH [42], observed/expected dosage variance <0.3 in BIMBAM [43], proper_info <0.4 in
685 IMPUTE [44]), and genotyped SNPs with a low call-rate (<95 %) or that were out of Hardy-Weinberg

equilibrium ($P<10^{-6}$).

Meta-analyses

Beta-coefficients and standard errors were combined by an inverse-variance weighted fixed effect method, implemented using the METAL software [45]. We performed meta-analyses for each of the three models (active, inactive, active + inactive adjusted for PA) in men only, in women only, and in men and women combined. Study-specific GWAS results were corrected for genomic control using all SNPs. Study-specific Metabochip results as well as the meta-analysis results for GWAS and Metabochip combined were corrected for genomic control using 4,425 SNPs included on the Metabochip for replication of associations with QT-interval, a phenotype not correlated with BMI, WC_{adjBMI} or WHR_{adjBMI}, after pruning of SNPs within 500 kb of an anthropometry replication SNP. We excluded SNPs that 1) were not available in at least half of the maximum sample size in each stratum; 2) had a heterogeneity I^2 >75%, or 3) were missing chromosomal and base position annotation in dbSNP.

Calculation of the significance of SNP×PA interaction and of the joint significance of SNP main effect and SNP×PA interaction

To identify SNP×PA interactions, we used the EasyStrata R package [46] to test for the difference in meta-analyzed beta-coefficients between the active and inactive groups for the association of each SNP with BMI, WC_{adjBMI} and WHR_{adjBMI}. Easystrata tests for differences in effect estimates between the active and inactive strata by subtracting one beta from the other ($\beta_{active} - \beta_{inactive}$,) and dividing by the overall standard error of the difference as follows:

$$Z_{diff} = \frac{\beta_{active} - \beta_{inactive}}{\sqrt{SE^2_{active} - SE^2_{inactive} - 2\,r * SE^2_{active} * SE^2_{inactive}}}$$

where *r* is the Spearman rank correlation coefficient between β_{active} and $\beta_{inactive}$ for all genome-wide SNPs. The joint significance of the SNP main and SNP×PA interaction effects was estimated using the

method by Aschard et al. [16] which is a joint test for genetic main effects and gene-environment interaction effects where gene-environment interaction is calculated as the difference in effect estimates between two exposure strata, accounting for 2 degrees of freedom.

Testing for secondary signals

Approximate conditional analyses were conducted using GCTA version 1.24 [19]. In the analyses for SNPs identified in our meta-analyses of European-ancestry individuals only, LD correlations between SNPs were estimated using a reference sample comprised of European-ancestry participants of the Atherosclerosis Risk in Communities (ARIC) study. In the analyses for SNPs identified in our meta-analyses of all ancestries combined, the reference sample comprised 93% of European-ancestry individuals and 6% of African ancestry participants from ARIC, as well as 1% of CHB and JPT samples from the HapMap2 panel, to approximate the ancestry mixture in our all ancestry meta-analyses. To test if our identified SNPs were independent secondary signals that fell within 1 Mbp of a previously established signal, we used the GCTA --cojo-cond command to condition our lead SNPs on each previously established SNP in the same locus.

Replication analysis for the *CDH12* locus

The replication analysis for the *CDH12* locus included participants from the EPIC-Norfolk ($N_{INACTIVE}$=4,755, N_{ACTIVE}=11,526) and Fenland studies ($N_{INACTIVE}$=1,213, N_{ACTIVE}=4,817), and from the random subcohort of the EPIC-InterAct Consortium ($N_{INACTIVE}$=2,154, N_{ACTIVE}=6,632). PA stratum-specific estimates of the association of *CDH12* with BMI were assessed and meta-analyzed by fixed effects meta-analyses, and the differences between the PA-strata were determined as described above.

Examining the influence of BMI, WC_{adjBMI} and WHR_{adjBMI}-associated loci on other complex traits and their potential functional roles

736 **NHGRI-EBI GWAS Catalog Lookups**

737 To identify associations of the novel BMI, WC_{adjBMI} or WHR_{adjBMI} loci with other complex traits in
738 published GWAS, we extracted previously reported GWAS associations within 500 kb and r^2>0.6 with
739 any of the lead SNPs, from the GWAS Catalog of the National Human Genome Research Institute and
740 European Bioinformatics Institute [47] (**Table S8**).

741

742 **eQTLs**

743 We examined the *cis*-associations of the novel BMI, WC_{adjBMI} or WHR_{adjBMI} loci with the expression of
744 nearby genes from various tissues by performing a look-up in a library of >100 published expression
745 datasets, as described previously by Zhang et al [48]. In addition, we examined *cis*-associations using
746 gene expression data derived from fasting peripheral whole blood in the Framingham Heart
747 Study[49] (n=5,206), adjusting for PA, age, age^2, sex and cohort. For each novel locus, we evaluated
748 the association of all transcripts ±1 Mb from the lead SNP. To minimize the potential for false
749 positives, we only considered associations where our lead SNP or its proxy (r^2>0.8) was either the
750 peak SNP associated with the expression of a gene transcript in the region, or in strong LD (r^2>0.8)
751 with the peak SNP.

752

753 **Overlap with functional regulatory elements**

754 We used the Uncovering Enrichment Through Simulation method to combine the genetic association
755 data with the Roadmap Epigenomics Project segmentation data [22]. First, 10,000 sets of random
756 SNPs were selected among HapMap2 SNPs with a MAF >0.05 that matched the original input SNPs
757 based on proximity to a transcription start site and the number of LD partners (r^2>0.8 in individuals of
758 European ancestry in the 1000 Genomes Project). The LD partners were combined with their original
759 lead SNPs to create 10,000 sets of matched random SNPs and their respective LD partners. These
760 sets were intersected with the 15-state ChromHMM data from the Roadmap Epigenomics Project
761 and resultant co-localizations were collapsed from total SNPs down to loci, which were then used to

762 calculate an empirical P value when comparing the original SNPs to the random sets. We examined
763 the enrichment for all loci reaching $P<10^{-5}$ for SNP×PA interaction combined, and for all loci reaching
764 $P<5x10^{-8}$ in the PA-adjusted SNP main effect model combined. In addition, we examined the variant-
765 specific overlap with regulatory elements for each of the index SNPs of the novel BMI, WC_{adjBMI} and
766 WHR_{adjBMI} loci and variants in strong LD ($r^2>0.8$).
767
768 **Estimation of variance explained in inactive and active groups**
769 We compared variance explained for BMI, WC_{adjBMI} and WHR_{adjBMI} between the active and inactive
770 groups using two approaches. First, we used a method previously reported by Kutalik et al [15], and
771 selected subsets of SNPs based on varying P value thresholds (ranging from $5x10^{-8}$ to 0.05) from the
772 SNP main effect model adjusted for PA. Each subset of SNPs was clumped into independent regions
773 using a physical distance criterion of <500kb, and the most significant lead SNP within the respective
774 region was selected. For each lead SNP, the explained variance was calculated as:

$$r^2 = \frac{1}{1+\frac{N}{\left(\Phi^{-1}\left(\frac{P}{2}\right)\right)^2}} - \frac{1}{N}$$

775
776 in the active and inactive groups separately, where *N* is the sample size and *P* is the P value for SNP
777 main effect in active or inactive strata. Finally, the variance explained by each subset of SNPs in the
778 active and inactive strata was estimated by summing up the variance explained by the SNPs.
779 Second, we applied the LD Score regression tool developed by Bulik-Sullivan et al [14] to
780 quantify the proportion of inflation due to polygenicity (heritability) rather than confounding (cryptic
781 relatedness or population stratification) using meta-analysis summary results. LD Score regression
782 leverages LD between causal and index variants to distinguish true signals by regressing meta-
783 analysis summary results on an 'LD Score', i.e. the cumulative genetic variation that an index SNP
784 tags. To obtain heritability estimates by PA strata, we regressed our summary results from the
785 genome-wide meta-analyses of BMI, WC_{adjBMI} and WHR_{adjBMI}, stratified by PA status (active and

inactive), on pre-calculated LD Scores available in HapMap3 reference samples of up to 1,061,094 variants with MAF≥1% and N>10th percentile of the total sample size.

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TOK and RJFL conceived and designed the study. TOK, MAC, RJFL and KLM coordinated the collection of genome-wide association and interaction study results from the participating studies. The association and interaction results were contributed by AVS, TBH, GE, LJL, and VG (AGES study); KEN, MG, AJ, KY, EB, and PGL (ARIC study); JBW, NGM, and GWM (AUSTWIN study); DPS (B58C study); GC, LJP, JH, AWM, ALJ, and JB (BHS study); MF, CB, MS, TR, SS, and BS (CARDIA study); YW, JBB, LSA, and KLM (CLHNS study); ZK, PMMV, TC, SB, GW, and PV (COLAUS study); KK, ASH, KH, SM, VS, and MP (COROGENE study); JM, IR, and CH (Croatia-Korcula study); VV, IK, and OP (Croatia-Vis study); LY, DT, BB, MM, AB, and PF (DESIR study); RR, TAL, PK, MH, KS, and RM (DR's EXTRA study); TH, TE, and AM (EGCUT study); JL, RAS, SB, CL, and NJW (Ely study); JL, JHZ, RL, RAS, SB, CL, and NJW (EPIC-Norfolk study); AD, NA, and CMvD (ERF study); IBB, MFF, and LB (Family Heart Study); JL, RAS, SB, CL, RJFL, and NJW (Fenland study); FX, NLHC, EL, JP, PJG, CSF, CTL, and LAC (FramHS); MB, FSC, KLM, and RNB (FUSION study); JT, LK, TE, HP, CS, and HAK (FUSION2 study); LFB, SLRK, MAJ, and PAP (GENOA study); SA, FR, IB, GH, and PWF (GLACIER study); JE, CO, LB, ML, AE, and JOJ (GOOD study); TSA, TH, LP, GD, and TIAS (GOYA study); JEH, DJP, SP, LJH, and BHS (GS study); SS, YCC, MF, JRO, and ARS (HAPI Heart study); MH, MA, AL, and HV (Health06 study); LQ, TH, and QQ (HPFS study); JAS, JDF, WZ, and DRW (HRS study); KH, OLH, AUJ, LLB, AJW, and KK (HUNT2 study); TT, DH, and SB (InCHIANTI study); MNH, JMJ, KF, NG, and OP (Inter99 study); TWW, IMH, MO, GG, HG, and AP (KORA3 study); KS, CHo, CHu, RR, BT, and MMN (KORA4 study); WZ, BL, WRS, STT, JCC, and JSK (LOLIPOP study); MEK, GED, TBG, GS, JH, and WM (LURIC study); UL, CH, LL, SB, and LH (MEC study); KL, AGB, LJRT, JAN, and YL (MESA study); ML, JK, AS, HS, PSC, and NN (METSIM study); WJP, GvG, YM, and BWJHP (NESDA study); AM, CML, MIM, TT, JA, and MRJ (NFBC66 study); LQ, TH, and QQ (NHS study); DK, KKO, JL, and AW (NSHD study); ÅJ and UG (NSPHS study); EJCdG, CH, MdM, JJH, DIB, and GW (NTR study); PN, AFW, NDH, SW, HC, and JFW (ORCADES study); CB, JB, MCV, CB, and LP (QFS study); DP, MW, and TMF (RISC study); NVR, MCZ, FR, AH, and AGU (RS1 study); JLBG, SS, FB, AM, GRA, and FC (SardiNIA study); ATe, HV, UV, MD, SG, and MN (SHIP study); RM, IP, and AT (Sorbs study); PJvdM, JVvVO, IMN, HS, AJO, and CAH (TRAILS study); LQ and MM (TwinsUK study); DIC, AYC, LMR, and PMR (WGHS study); SR, NZ, JG, UP, and CK (WHI study); MKu, MKi, JL, and CL (Whitehall study); LPL, NHK, MJ, MKä, OTR, and TL (YFS study). RS, KLY, AEJ, TWW, AM, DH, NLHC, JSN, TSA, LW, TW, FR, MdH, and TOK cleaned and quality checked the association and interaction results from the participating studies. RS, QQ, DH, TSA, LX, AM, TW, and TOK performed the meta-analyses. TWW performed the power computations. AC, MAC, AEJ, and TOK collected the supplementary information from the participating studies. MdH, MC, and RJFL provided look-up information from the GWAS meta-analyses of physical activity and sedentary behavior. AEJ performed the look-up in the NHGRI-EBI GWAS Catalog. AC and MG performed the analyses for variance explained by common variants in the inactive and active groups. MFF, KN, AEJ, KLY, and TOK reviewed the literature for the identified loci. MG performed approximate conditional analyses to identify secondary signals in the novel loci. JDE and ADJ carried out the lookups for Expression Quantitative Trait loci. JEH and RJK performed the analyses of enrichment with functional genomic elements. GRA, IB, MB, IBB, CSF, TF, IMH, RJFL, MIM,

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Figures

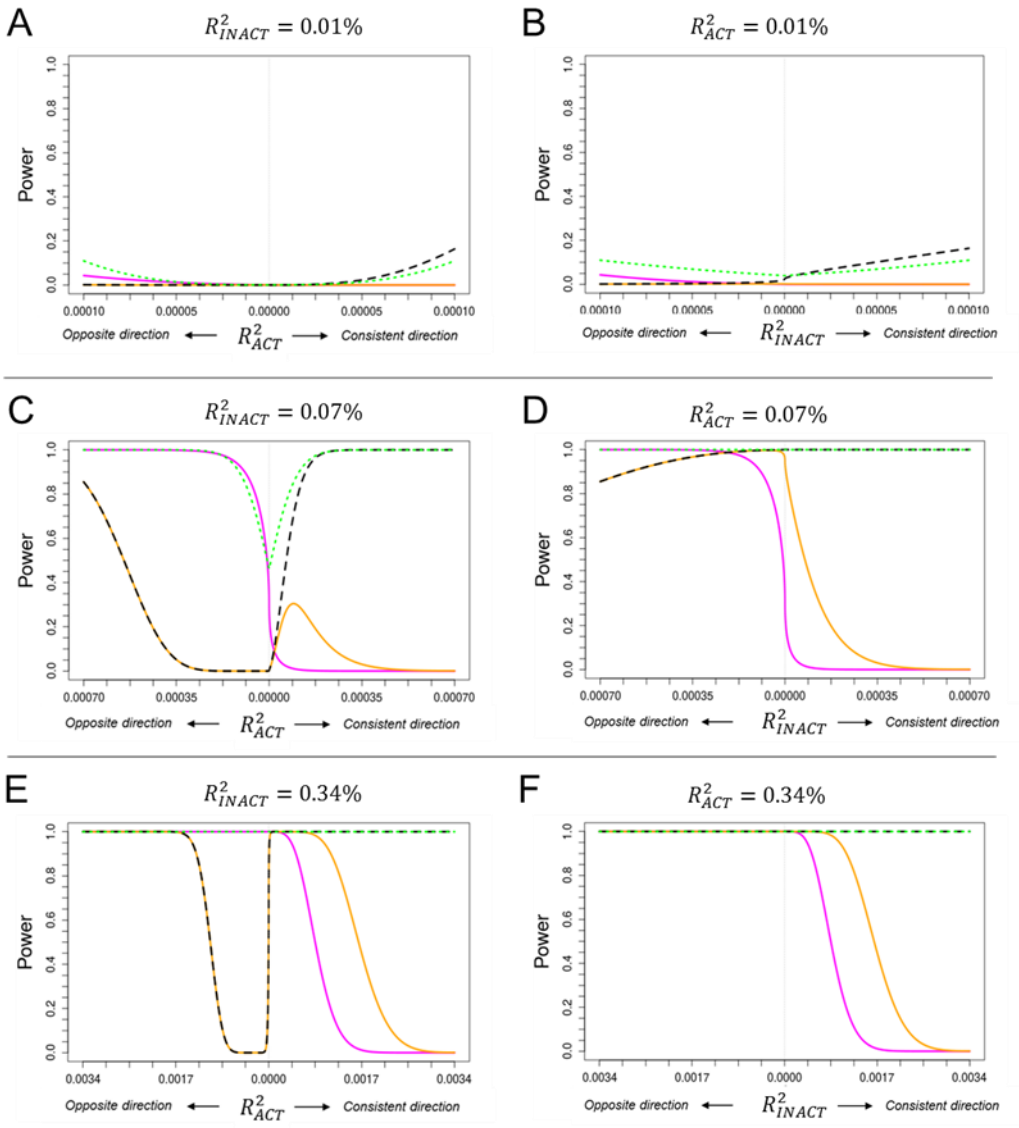

Figure 1. Power to identify PA-adjusted main, joint or GxPA interaction effects in 200,000 individuals (45,000 inactive, 155,000 active). The plots compare power to identify genome-wide significant main effects ($P_{adjPA}<5x10^{-8}$, dashed black), joint effects ($P_{JOINT}<5x10^{-8}$, dotted green) or GxPA interaction effects ($P_{INT}<5x10^{-8}$, solid magenta) as well as the power to identify Bonferroni-corrected interaction effects (P_{INT}<0.05/number of loci, solid orange) for the SNPs that reached a genome-wide significant PA-adjusted main effect association ($P_{adjPA}<5x10^{-8}$). The power computations were based on analytical power formulae provided elsewhere [50] and were conducted a-priori based on various types of known realistic BMI effect sizes [51]. A, C, E: Assuming an effect in inactive individuals similar to a small (R^2_{INACT}=0.01%, comparable to the known BMI effect of the *NUDT3* region), medium (R^2_{INACT}=0.07%, comparable to the known BMI effect of the *BDNF* region) and large (R^2_{INACT}=0.34%, comparable to the known BMI effect of the *FTO* region) realistic effect on BMI and for various effects in physically active individuals (varied on the x axis); B,D,F: Assuming an effect in physically active individuals similar to the small, medium and large realistic effects of the *NUDT3 , BDNF and FTO* regions on BMI and for various effects in inactive individuals (varied on x axis).

Tables

Table 1. Novel loci achieving genome-wide significance ($P<5x10^{-8}$) in meta-analyses for PA-adjusted SNP main effect (P_{adjPA}) or the joint test of SNP main effect and SNP-PA interaction (P_{joint}).

Trait	Marker	Nearest Gene	Chr	Pos (hg19)	Trait increasing/ decreasing allele	Trait increasing allele's frequency	Analysis	N_{adjPA}	$Beta_{adjPA}$	SE_{adjPA}	P_{adjPA}	P_{int}	P_{joint}
Novel loci achieving genome-wide significance in European-ancestry meta-analyses													
BMI	rs1720825	*MRAS*	3	138,108,083	A/G	0.20	Overall	178833	0.026	0.0047	**2.98E-08**	1.62E-01	**3.67E-08**
							Women	102854	0.0281	0.006	2.84E-06	7.27E-02	3.35E-06
							Men	47544	0.024	0.0069	4.91E-04	9.95E-01	1.30E-02
BMI	rs1934100	*ELAVL2*	9	23,234,308	A/T	0.68	Overall	140811	0.0179	0.0049	2.43E-04	3.99E-02	2.15E-04
							Women	85142	0.0048	0.006	4.18E-01	9.89E-01	7.37E-01
							Men	41958	0.0377	0.0074	3.18E-07	8.84E-04	**3.70E-08**
WC_{adjBMI}	rs7176527	*ZSCAN2*	15	85,140,794	C/T	0.81	Overall	130413	0.0317	0.0054	**5.98E-09**	1.79E-01	**2.80E-08**
							Women	77349	0.0303	0.007	1.37E-05	9.36E-01	1.28E-04
							Men	52918	0.0342	0.0084	4.55E-05	3.23E-02	7.50E-06
WHR_{adjBMI}	rs4650943	*PAPPA2*	1	176,414,781	A/G	0.53	Overall	113963	0.0267	0.0048	**2.34E-08**	1.77E-01	5.76E-08
							Women	69016	0.0301	0.006	4.66E-07	7.79E-03	1.57E-07
							Men	44430	0.0212	0.0073	3.55E-03	2.73E-01	5.64E-03
WHR_{adjBMI}	rs2300481	*MEIS1*	2	66,782,467	T/C	0.39	Overall	110881	0.0267	0.0048	**2.41E-08**	5.80E-01	**3.93E-08**
							Women	66519	0.0288	0.0059	1.19E-06	4.71E-01	1.47E-06
							Men	43845	0.0258	0.0073	4.14E-04	1.00E+00	2.82E-03
WHR_{adjBMI}	rs167025	*ARHGEF28*	5	73,433,308	A/G	0.33	Overall	117603	0.0179	0.0048	2.13E-04	8.01E-01	4.64E-04
							Women	70494	0.0023	0.006	7.01E-01	4.50E-01	7.32E-01
							Men	46591	0.0427	0.0074	**6.24E-09**	1.34E-01	**3.73E-09**
WHR_{adjBMI}	rs3094013	*HCP5*	6	31,434,366	G/A	0.87	Overall	149338	0.0269	0.0061	1.06E-05	4.98E-01	6.93E-05
							Women	84538	0.0104	0.0078	1.82E-01	4.50E-01	3.78E-01
							Men	64138	0.0494	0.009	**4.51E-08**	8.91E-01	7.87E-07
WHR_{adjBMI}	rs6976930	*BAZ1B*	7	72,885,810	G/A	0.81	Overall	145913	0.0294	0.0051	**1.03E-08**	5.28E-01	**1.87E-08**

							Women	83184	0.0326	0.0066	7.70E-07	7.00E-01	2.02E-06
							Men	62149	0.0254	0.0075	7.69E-04	5.93E-01	3.10E-03
							Overall	147123	0.0224	0.004	**1.79E-08**	8.76E-02	**1.44E-08**
WHR_{adjBMI}	rs10786152	*PLCE1*	10	95,893,514	A/G	0.52	Women	83884	0.0192	0.0051	1.56E-04	5.81E-02	1.41E-04
							Men	62722	0.0255	0.0058	1.32E-05	6.38E-01	5.89E-05
							Overall	117417	0.031	0.0074	2.70E-05	4.26E-01	1.13E-04
WHR_{adjBMI}	rs889512	*CTRB2*	16	75,242,012	C/G	0.88	Women	70315	0.0506	0.0091	**2.87E-08**	9.96E-02	1.09E-07
							Men	46440	-0.0022	0.0114	8.50E-01	5.06E-01	7.80E-01
Novel loci achieving genome-wide significance in all-ancestry meta-analyses													
							Overall	151282	0.0356	0.0062	**1.07E-08**	1.21E-01	3.28E-07
BMI	rs754635	*CCK*	3	42,305,131	G/C	0.87	Women	91241	0.026	0.0079	9.66E-04	1.25E-01	8.69E-04
							Men	62741	0.0486	0.0093	1.61E-07	2.98E-01	3.68E-06

Chr: chromosome; Pos(hg19): position based on human assembly 19; N_{adjPA}, $Beta_{adjPA}$, SE_{adjPA}, or P_{adjPA}: sample size, effect size, standard error, or P value, respectively, in the physical activity adjusted SNP main effect model; PA: physical activity; WC_{adjBMI}: BMI-adjusted waist circumference; WHR_{adjBMI}: BMI-adjusted waist-hip ratio; P_{int}: P value for SNP-PA interaction; P_{joint}: P value for the joint test of SNP main effect and SNP-PA interaction.

Box 1 Genes of biological interest within 500 kb of lead SNPs associated with BMI

CCK (rs754635): The lead SNP is located in intron 1 of the *CCK* gene that encodes cholecystokinin, a gastrointestinal peptide that stimulates the digestion of fat and protein in the small intestine by inhibiting gastric emptying, inducing the release of pancreatic enzymes, increasing production of hepatic bile, and causing contraction of the gallbladder. Cholecystokinin induces satiety and reduces the amount of food consumed when administered prior to a meal [52, 53]. In a candidate gene study, four common variants in *CCK* were associated with increased meal size [54], but the variants are not in LD with rs754635 (r^2<0.1). A GWAS of BMI in 62,246 individuals of East Asian ancestry showed a suggestive association (P=2x10^{-7}) for the rs4377469 SNP in high LD with our lead SNP (r^2=0.7) [55].

ELAVL2 (rs1934100): The lead SNP showed an association with BMI only in men (**Table 1**). The only nearby gene *ELAVL2* (455 kb away) is a conserved neuron-specific RNA-binding protein involved in stabilization or enhanced translation of specific mRNAs with AU-rich elements in the 3'-untranslated region [56]. While *ELAVL2* is implicated in neuronal differentiation [56], potential mechanisms linking this function to obesity remain unclear.

MRAS (rs1720825): The lead SNP is an intronic variant in *MRAS*. The *MRAS* rs1199333 SNP, in high LD with rs1720825 (r^2=0.85), has shown suggestive association with typical sporadic amyotrophic lateral sclerosis in a Chinese Han population (P=4x10^{-6}, **Supplementary Table 14**). Other *MRAS* SNPs have been associated with risk of coronary artery disease [57] but they are not in LD with rs1720825 (r^2<0.06). *MRAS* encodes a member of the membrane-associated Ras small GTPase protein family that function as signal transducers in multiple processes of cell growth and differentiation and are involved in energy expenditure, adipogenesis, muscle differentiation, insulin signaling and glucose metabolism [58-60]. Mice with *Mras* knockout develop a severe obesity phenotype [61]. The SNP rs1199334, in high LD with our lead SNP rs1720825 (r^2=0.90), has been identified as the SNP most strongly associated with the *cis*-expression of centrosomal protein 70kDa (*CEP70*) in subcutaneous adipose tissue (P=2x10^{-7}) (**Supplementary Table 15**). *CEP70* encodes a centrosomal protein that is critical for the regulation of mitotic spindle assembly, playing an essential role in cell cycle progression [62].

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Box 2 Genes of biological interest within 500 kb of lead SNPs associated with WC_{adjBMI} or WHR_{adjBMI}

***ZSCAN2 (rs7176527)*:** Twenty two genes lie within 500kb of the WC_{adjBMI}-associated lead SNP (**Supplementary Fig. 3**). The nearest gene, *ZSCAN2,* contains several copies of a zinc finger motif commonly found in transcriptional regulatory proteins. The rs7176527 SNP is in LD (r^2>0.80) with five SNPs (rs3762168, rs2762169, rs12594450, rs72630460, and rs16974951) that are enhancers in multiple tissues in the data from Roadmap Epigenomics Consortium [22]. The rs7176527 SNP is a *cis*-eQTL for the putative transcriptional regulator *SCAND2* [63] in the intestine, prefrontal cortex, and lymphocytes (**Supplementary Table 15**).

***PAPPA2 (rs4650943)*:** Seven genes lie within 500kb of the lead SNP (**Supplementary Fig. 3**). The nearest gene, *PAPPA2*, is 18 kb upstream of rs4650943 and codes for a protease that locally regulates insulin-like growth factor availability through cleavage of IGF binding protein 5, most commonly found in bone tissue. In murine models, the PAPP-A2 protein has been shown to influence overall body size and bone growth, but not glucose metabolism or adiposity [64-66].

***MEIS1 (rs2300481)*:** The only gene within 500 kb of the lead SNP is *MEIS1* encoding a homeobox protein that plays an important role in normal organismal growth and development. Two variants in high LD with the lead SNP (r^2=0.95) have been identified for association with PR interval of the heart (**Supplementary Table 14**). Another variant, in low LD with rs2300481 (r^2=0.25), has been associated with restless leg syndrome [67] – a sleeping disorder that may cause weight gain [68].

ARHGEF28 (rs167025): The lead SNP showed an association with WHR_{adjBMI} in men only (**Table 1**). There are two protein-coding genes within 500kb of rs167025. The nearest gene is *ARHGEF28*, 195 kb downstream, encoding Rho guanine nucleotide exchange factor 28. This exchange factor has been shown to destabilize low molecular weight neurofilament mRNAs in patients with amyotrophic lateral sclerosis, leading to degeneration and death of motor neurons controlling voluntary muscle movement [69, 70]. The *ENC1* gene, 490 kb away, encodes Ectoderm-neural cortex protein 1, an actin-binding protein required for adipocyte differentiation [71]

HCP5 (rs3094013): The lead SNP showed an association with WHR_{adjBMI} in men only (**Table 1**). The rs3094013 SNP is located in the MHC complex on chromosome 6, and the region within 500kb contains 124 genes (**Supplementary Fig. 3**). The known WHR_{adjBMI}-increasing allele rs3099844, in strong LD with our lead SNP (r^2≥0.8), has previously been associated with increased HDL-cholesterol levels [72]. Candidate gene studies suggest that rs1800629 in *tumor necrosis factor* (*TNF*), which is 109 kb upstream and in moderate LD (r^2=0.64) with the lead SNP, may interact with physical activity to decrease serum CRP levels [73, 74]. We did not, however, find an interaction between rs1800629 and physical activity on WHR_{adjBMI} (P=0.3).

BAZ1B (rs6976930): There are 31 genes within 500kb the lead SNP rs6976930 (**Supplementary Fig. 3**) which is in high LD (r^2>0.8) with GWAS hits associated with protein C levels, triglycerides, serum urate levels, lipid metabolism, metabolic syndrome, and gamma-glutamyl transferase levels (**Supplementary Table 14**). The rs6976930 SNP shows an eQTL association with *MLXIPL* expression in omental ($P=7x10^{-22}$) and subcutaneous adipose tissue ($P=4x10^{-14}$). *MLXIPL* is 122 kb downstream of rs6976930 and codes for a transcription factor that binds carbohydrate response motifs, increasing transcription of genes involved in glycolysis, lipogenesis, and triglyceride synthesis [75, 76].

PLCE1 (rs10786152): There are 8 genes within 500 kb of the lead SNP (**Supplementary Fig. 3**). The lead SNP lies within the intron of *PLCE1* encoding a phospholipase involved in cellular growth and differentiation and gene expression among many other biological processes involving phospholipids [77]. Variants in this gene have been shown to cause nephrotic syndrome, type 3 [78]. Nearby variants rs9663362 and rs932764 (r^2=1.0 and 0.85, respectively) have been previously associated with systolic and diastolic blood pressure (**Supplementary Table 14**).

CTRB2 (rs889512): The lead SNP showed an association with WHR_{adjBMI} in women only (**Table 1**). There are 17 genes within 500 kb (**Supplementary Fig. 3**). The nearby rs4888378 SNP has been associated with carotid intima-media thickness in women but not in men, and *BCAR1* (*breast cancer anti-estrogen resistance protein 1*) has been implicated as the causal gene [79]. There rs488378 SNP is not, however, in LD with our lead SNP

(r^2<0.1). The SNP rs7202877, in moderate LD with rs889512 (r^2=0.6), is a risk variant for type 1 diabetes (**Supplementary Table 14**). The data from Roadmap Epigenomics Consortium [22] suggest that five variants in strong LD (r^2>0.8) with our lead SNP rest in known regulatory regions, including rs9936550 within an active enhancer region and rs72802352 in a DNAse hypersensitive region for human skeletal muscle cells and myoblasts; and rs147630228 and rs111869668 within active enhancer regions for the pancreas. Additionally, rs111869668 rests within binding motifs for CEBPB and CEBPD (CCAAT enhancer-binding protein-Beta and Delta) which are enhancer proteins involved in adipogenesis [80, 81].

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