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Section: Original Research

Article Title: Gene-By-Activity Interactions on Obesity Traits of Six Year Old New Zealand European Children: A Children of SCOPE Study

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Gene-by-activity interactions on obesity traits of six year old New Zealand European children: a Children of SCOPE study.

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Abstract

Purpose: The decline of physical activity in children is considered an important determinant to explain the rising rates of obesity. However, this risk may be augmented in children who are genetically susceptible to increased weight gain. We hypothesised that a sedentary lifestyle and moderate activity will interact with genetic loci, resulting in differential effects in relation to obesity risk. **Methods:** We recruited 643 European children born to participants in the New Zealand based Screening for Pregnancy Endpoints (SCOPE) study. Seventy gene variants were evaluated by the Sequenom assay. Interaction analyses were performed between the genetic variants and activity type derived from actigraphy, in relation to Percentage Body Fat (PBF). **Results:** We found a statistically significant association between increased proportions of sedentary activity with increased PBF scores (p=0.012). The *OLFM4-9568856* (p=0.01) and *GNPDA2-rs10938397* (p=0.044) gene variants showed genotype differences with proportions of sedentary activity. Similarly, the *OLFM4-9568856* (p=0.021), *CLOCK-rs4864548* (p=0.029) and *LEPR-1045895* (p=0.047) showed genotype differences with proportions of moderate activity. We found evidence for unadjusted gene-by-activity interactions of the *SPACA3/SPRASA-rs16967845, PFKP-rs6602024* and *SH2B1-rs7498665* on PBF scores. **Conclusions:** These findings indicate a differential effect of physical activity in relation to obesity risk, suggesting that children genetically predisposed to increased weight gain may benefit from higher levels of moderate activity.

Keywords: genetics, sedentary behaviour, moderate activity, BMI z-scores, Percentage Body Fat, childhood obesity

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Introduction

Global shifts surrounding dietary and exercise practices are considered the primary attributable factors in the widespread increase of obesity (22). The transition to an 'obesogenic' environment has encouraged an increased intake of high caloric food and sedentary behaviours by decreasing opportunities to expend energy (18). Notably, children are becoming more obese facilitated by the changing nature of habitual physical activity norms and the perception of a normal body image ideals (18). Often, obesity persists into adulthood and is associated with increased risk of obesity and its related comorbidities (22). Significant technological advancements are concomitant with increased sedentary behaviours and have been associated with reduced physical activity in children (32). The physical activity-obesity paradigm is further compounded by the mechanism in which activity contributes to the maintenance of a healthy body weight (reverse-causality). Obesity is considered to be the direct consequence of energy imbalance resulting from greater food intake and reduced energy expenditure (17). Decreased physical activity would contribute to reduced total energy expenditure leading to detrimental health outcomes. However, studies have suggested that the absence of physical activity in obese children may be directly related to diminished motor skills and low self-esteem issues (5, 29).

Despite the global transition to an 'obesogenic' environment, obesity development is often more pronounced in genetically predisposed children (46). Genome-wide association studies have identified numerous loci associated with differences in anthropometric measures of obesity including Body Mass Index (BMI) and Percentage Body Fat (PBF) (26, 27, 41, 47). Despite these objective associations, the true impact of genetic predisposition with obesity traits is influenced by a given environmental exposure (gene-by-environmental interactions) (21). Recent studies have shown significant gene-by-physical activity interactions in relation to reduced adult obesity risk (2, 7, 24, 33). It has been suggested that individuals meeting

appropriate physical activity recommendations may negate the burdensome effect imposed by the susceptible gene variants on body fat estimates (24). However, the interactive effect of physical activity has not been thoroughly explored in children. Here we test the interaction of 70 gene variants, selected on the basis of prior association with obesity traits and varying types of activity (sedentary and moderate) in relation to BMI z-scores and PBF using the children of Screening for Pregnancy Endpoints (Children of SCOPE) cohort.

We hypothesise that in children genetically susceptible to increased weight gain, this effect is further amplified when exposed to a sedentary lifestyle.

Methods

Study population

The Children of SCOPE is an Auckland led prospective cohort study for the prediction of obesity in New Zealand children. Children were born over a three year period from April 2005 to March 2008 and are offspring of nulliparous pregnant women (*n*=2065) who were participants in the landmark SCOPE study (scopestudy.net). Of these participants, 4%, have been excluded due to loss in follow-up (*n*=23), fetal/neonatal death (*n*=27) and live births with major congenital abnormalities (*n*=34). The remaining 1981 (96%) children comprised the eligible study population for the follow-up study, and 1208 (62%) were successfully recruited to participate in the Auckland Children of SCOPE study. Children were approximately 6 years of age with prospectively collected pregnancy data from 15 to 20 weeks of gestation through to birth, which included maternal weight, height and infant birth weight centiles. Ethnicity of these children was determined through self-reported parental ethnicity collected in the original SCOPE cohort. Based on the ethnic frequencies, only New Zealand European children were considered for eligibility in this genetic part of the study. Informed written consent was obtained from all women whose children participated in this study. Recruitment was approved by the Northern X Regional Ethics committee (NTX/10/10/106).

Outcome measures

The child's weight and height were measured at the Children of SCOPE visit by trained nurses following a standardised protocol. BMI (weight/height^2) was the standard method used to assess obesity status in the Children of SCOPE study. BMI z-scores were created according to age and gender, using the UK 1990 (UK90) BMI growth reference population curve (9). Percentage Body Fat was measured using the Bioelectrical Impedance analysis (BIA) method using the SBF7 (ImpediMed Ltd, QLD, Australia). Fat free mass (FFM) was extracted using the single-frequency 50 kHz data from the SBF7. Resistance, reactance and impedance were recorded, and FFM was calculated as follows:

FFM=(0.65*(height^2/impedance)+0.68*Age(years)+0.15) (38). PBF was calculated using (weight-FFM)/weight*100).

Physical activity assessment

Data was collected for a seven day period by using GT3X Actigraph's (Actigraph Ltd, Pensacola, Florida, USA). The reliability of the Actigraph GT3X accelerometer for measuring habitual levels of physical activity in adults and children were previously validated by (1, 34). For each participant, an Actigraph was set to start recording at 9am one week prior to the appointment for a face to face assessment. The monitor was delivered to the family several days prior to the recording start date with instructions for the proper use of the equipment. Participants wore the monitor firmly around the waist using the adjustable belt provided. They were instructed to take the monitor off, if they were expecting to get wet such as swimming or showering. Parents also provided a diary which included the time the child went to bed each night, woke up each morning, any time that the monitor was removed and the reason, and method of travel to and from school each day.

Data were downloaded using the Actigraph software and exported to Excel files, which were subsequently imported into SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) as 1-min epochs. Epochs of sleep were defined using the validated Sadeh actigraph scoring algorithm (37). Nocturnal sleep/wake onset times were assessed using the times provided in the diary as the starting point. All algorithm assessed times were validated by ensuring that they matched the graphed data for each subject for each day. Where the initial check of the time was not considered to be correct, these were independently assessed by a second person. Any discrepancies where the original and independent check did not agree were again assessed by a third person. Two of the three assessments were required to agree for the time to be used. If there was no agreement between the three independent checks, then the time was not used for further analysis.

The main cause of a requirement to change the algorithm-derived time was due to parental reported times from the diary being inaccurate, causing the algorithm to be unable to start from an appropriate point. These finalised sleep onset and wake times were then used to determine physical activity duration (wake time to sleep onset) for each day, where both times were available.

Variables derived for analysis from the Sadeh sleep-scoring algorithm are as follows: Sleep end time was defined as approximately five consecutive minutes of sleep prior to reported wake time. Sleep onset time was defined as approximately the first three consecutive minutes of sleep after the reported bedtime. Physical activity duration was defined as the elapsed time between wake time and sleep onset. The activity variables derived from actigraphy estimated the total physical activity counts, mean activity counts, and minutes of sedentary/light (<3 metabolic equivalent tasks (METs)), moderate (>3 <6 METs), and vigorous activity (>6 METs) during waking hours. Analysis of actigraphy data required a complete collection of data throughout the night for three or more days.

Sample preparation, SNP selection and genotyping

Genomic DNA was isolated from saliva and buffy coats, according to the manufacturer's instruction using the Oragene DNA purification (DNA Genotek) and the QIAamp DNA Mini kits (Qiagen #51304), respectively, and were stored at -80°C.

Samples were analysed for 70 gene variants selected on the basis of prior association with obesity (**Supplementary Table 1**), and include a number of variants from GWAS and candidate genes from the literature. Due to the limited number of non-European children and allele frequency differences between various ethnic groups, only New Zealand European children were eligible to participate in this study.

Information regarding genotypes and allele frequencies in the European population were obtained using the 1000GENOMES:phase_3:CEU data in Ensembl (www.ensembl.org). Genes that harbour multiple genetic variants were assessed for linkage disequilibrium (LD) scores using LD plots obtained from 1000GENOMES:phase_3:CEU (www.ensembl.org). A pairwise LD (r^r) score over 0.8 was considered to be in high disequilibrium in which only one variant was selected for analysis (45). A total of seven genes had several polymorphisms localised within them (**Supplementary Table 2**) and were subsequently tested for pairwise LD scores. All variants selected for this study had a LD score below 0.8 or had no CEU information and were subsequently retained for association testing.

Genotyping was performed using the Sequenom iPlex MassARRAY platform which uses a matrix assisted laser desorption/ionisation-time of flight (MALDI-TOF) primer extension assay, according to the manufacturer's instructions (Sequenom, New Zealand). All plates contained samples for testing and non-template controls. Quality control measures included a non-template control to ensure the absence of cross contamination and primer cross reactivity and correlation of the minor allele frequency (MAF) with a reference population in 1000GENOMES:phase_3:CEU (**Supplementary Table 1**). A small sample subset (n=384)

was checked for quality control using TaqMan pre-designed assay (Applied Biosystems) for *LEPR-rs1137100* to confirm accuracy of genotyping.

Statistical analyses

The Hardy-Weinberg equilibrium (HWE) test was performed across each genomic marker to assess the genotype distribution across the population. The gene variant was considered to be in HWE if the *p*-value was above 0.05. Univariable linear regression was used to test the association between proportions of sedentary behaviours and moderate activity with BMI z-scores and PBF. A standard linear regression analysis was used to assess the association between proportions of activity type and genotype. Multivariate linear regression analysis was used to model the interaction between gene variants and sedentary activity in relation to BMI z-scores and PBF. Interactions were assessed by including a product term (average activity (sedentary and moderate activity) x genotype) and were adjusted for age, sex, activity type and genotype. Coefficients with $P \leq 0.05$ in all analysis were considered to indicate a nominally significant association.

Significant interactions were stratified according to genotypes to ensure the trajectory of BMI z-scores and PBF, relative to sedentary and moderate activity, was not influenced by residual outliers. Any influential outliers detected were assessed for validity and subsequently removed if found to be of uncertain variability and re-analysed. *P*-values were corrected for multiple testing using the False Discovery Rate (FDR) test as described by Benjamini and Hochberg (1995) (4). Adjusted *P*-values (*Q*-values) were calculated for the total number of tests using the null hypothesis fraction estimated by the ranking method. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of study population

Of the 962 European children, eligible for this study, 319 children did not have adequate activity data (≥3 days recorded data), failed to wear an actigraph, had technical problems precluding use of the data or where the assessment of time of sleep onset and wake times was not agreed. The baseline characteristics of the eligible study population comprising of New Zealand European (n=962) children stratified by availability of activity information are shown in **Table 1**. While there are some statistical differences detected between gender and weight, between the two groups we believe there was no reason to suspect any bias between those children who completed the study with the outcome variables (BMI z-scores and PBF) used in this study. Using the International Obesity Taskforce (IOTF) BMI thresholds defining paediatric obesity (10), we show that approximately 14% (n=92) and 2% (n=11) of our cohort of New Zealand European children were overweight and obese respectively. Furthermore, 99% (n=636) of our children met the standard WHO recommendations of 60min of moderate-to-vigorous physical activity daily (mean (s.d): 2.22 (0.595) (**Supplementary Figure 1**).

Association of physical activity with obesity traits

Univariable models that associate changes in BMI z-scores and PBF in response to proportions of sedentary and moderate activity are shown in **Figure 1**. A significant association was observed between increased proportions of sedentary activity with greater PBF scores (p=0.012, β=0.12[0.023~0.22] (**Figure 1A**)). An inverse trend of borderline significance was also found between increased proportions of moderate activity with decreased PBF scores (p=0.069, β=-0.10[-0.21~0.0076]) (**Figure 1B**).

However, we found significant contradictory associations between increased proportions of sedentary (p=0.003, β=-0.020[-0.033~-0.0068]) and moderate activity

(p=0.001, β=0.024[0.0098~0.039]) with differences in BMI z-scores (**Figure 1C and Figure 1D**). To determine the accuracy of BMI as a marker of obesity, we performed a follow-up regression analysis on body fat ((PBF/100)*Weight of child) and components of body composition (Weight of child–body fat) with proportions of sedentary and moderate activity (**Supplementary Figure 2-5**). The inverse relationship observed between physical activity and BMI z-scores may be driven by significant associations established with lean mass (sedentary: p=<0.001, β=-0.078[-0.11~-0.051] moderate: p=<0.001, β=0.079[0.049~0.11]), but not with body fat (sedentary: p=0.518, moderate: p=0.900). Therefore, the remainder of this study will be confined towards gene-by-physical activity interactions in relation to PBF scores in six year old New Zealand European children.

Genetic association with physical activity

We evaluated the relationship between 70 gene variants and proportions of physical activity in relation to PBF scores in the Children of SCOPE cohort. Most genomic markers were in accordance with HWE except for *ADRB2-rs1042713* (p<0.001), *CLOCK-rs1801260* (p=0.02), *CLOCK-rs4864548* (p=0.02), *HOXC10-7302703* (p=0.04) and *SH2B1-rs7498665* (p=0.009). Genotyping results obtained from Sequenom showed no evidence of genotyping error. We had no family history in the dataset, handling of samples followed a rigorous protocol and scatterplots obtained from Sequenom showed robust genotyping. The minor allele frequencies (MAF) for *ADRB2-rs1042713* (0.441), *CLOCK-rs1801260* (0.273), *CLOCK-rs4864548* (0.385), *HOXC10-7302703* (0.176) and *SH2B1-rs7498665* (0.355) were comparable to the 1000GENOMES:phase_3:CEU population frequency of 0.348, 0.253, 0.409, 0.182 and 0.364 respectively (http://www.ensembl.org/index.html). Disequilibrium can result from a true association, such that genetic variants showing a departure of HWE, at any

given significance threshold can occur by chance (43). Therefore, for the purpose of this study, we have not eliminated these variants from our subsequent association analysis.

Regression analysis was performed using proportions of sedentary and moderate activity to test whether genetic variations influence physical activity behaviours. The *OLFM4-rs9568856* (p=0.010) and *GNPDA2-rs10938397* (p=0.044) gene variants showed uncorrected genotype associations with increased sedentary activity behaviour (**Table 2**). Similarly, significant uncorrected associations was also found with *OLFM4-rs9568856* (p=0.021), *CLOCK-rs4864548* (p=0.029) and *LEPR-rs1045895* (p=0.047) with decreased proportions of moderate activity. However, these associations did not remain significant after correction for multiple comparisons. The complete list of associations with proportions of sedentary and moderate activity is presented in **Supplementary Table 3 and Supplementary Table 4**.

Gene-by-physical activity interactions in relation to PBF scores

We tested for genotypic interactions of 70 genes and the proportion of activity in relation to PBF scores of six year old European children. The *SPACA3*/*SPRASA-rs16967845* (p=0.023), *PFKP-rs6602024* (p=0.041) and *SH2B1-rs7498665* (p=0.041) variants exhibited uncorrected significant interactions in relation to PBF scores (**Figure 2**). However, significant gene-by-moderate activity interactions were also evident between the *SPACA3/SPRASA-rs16967845* (p=0.035), *PFKP-rs6602024* (p=0.027) and *SH2B1-rs7498665* (p=0.029) variants, suggesting a differential effect of activity type on the association of susceptible obesity loci with PBF scores (**Figure 3**). No gene-by-physical activity interactions remained significant after adjustments for multiple comparisons.

Discussion

Physical activity has long been considered an important determinant in the prevention of excess weight gain in children (29, 30, 48). However, global shifts towards an 'obesogenic'

environment has exposed children to both a calorie rich environment and increased sedentary behaviours with reduced opportunities to expend energy (18, 42). This is further complicated by the interaction between genetic predisposition and lifestyle factors to explain the variance of obesity (2). Indeed, numerous studies have found that increased levels of physical activity can attenuate the detrimental effect conveyed by susceptible genetic loci on obesity traits (2, 20). However the opposite holds true, with the genetic burden being higher in physically inactive individuals (3). In the present study, we investigated whether intensity of activity type (sedentary and moderate) has a differential effect on obesity-associated loci in relation to PBF of 6 year old New Zealand European children.

Association of physical activity with obesity traits

This study found evidence of association between increased proportions of sedentary behaviours and greater PBF scores in 6 year old European children. A borderline inverse association was also detected between increased proportions of moderate activity and PBF scores. These results show the expected relationship between varying levels of habitual physical activity and differential obesity risk.

However, a contradictory association was observed between increased proportions of sedentary and moderate activity with BMI z-scores. BMI is a commonly used index to assess body fatness for diagnostic purposes in clinical practices (13). Yet the failure of BMI to provide accurate estimates of body composition, limits its effectiveness as a marker of obesity. In particular, BMI may be misclassifying individuals as having unacceptable body fat due to elevated muscle mass and bone density (35, 51). Indeed, a follow-up regression analysis of body fat and components of body composition with proportions of physical activity, revealed that the inconsistent relationship with BMI z-scores were driven by significant associations with muscle and skeletal mass but not body fat. It is entirely plausible children participating in

increased developmentally appropriate moderate activity could result in alterations in skeletal muscle mass, which is a considered a primary component when using BMI to estimate obesity status.

Genetic association with physical activity

The propensity towards being physically active is largely dependent on shared aspects of the environment including social and parental influences, education and their recreational surroundings (12). Yet, genetic differences associated with physical activity suggest that children may be predisposed towards variability in activity levels when exposed to certain environments (12, 25). This study found 'uncorrected' putative genotype associations between *OLFM4* and *GNPDA2* with increased proportions of sedentary activity. By contrast, the *OLFM4*, *CLOCK* and *LEPR* gene variants were associated with decreased proportions of moderate activity. Only *OLFM4* showed overlapping, yet inverse association, with physical activity type in this cohort of New Zealand European children. Many of these genes identified here (*GNPDA2, CLOCK, LEPR*) are expressed in the hypothalamus, suggesting important biological roles in the regulation of appetite, eating behaviours and neuronal effects on energy balance (15, 19, 44). The hypothalamus acts as the system-mediated regulator of converging nutritional cues and energy expenditure expressed by hormonal signals from the periphery. Variations of *GNPDA2* have been reported to confer susceptibility to obesity in several studies; yet the molecular mechanism has not been elucidated (19, 23). Genetic studies of *CLOCK* have suggested the synchrony between circadian and metabolic processes plays an important role in the regulation of energy balance and bodyweight control (8). Differences in *LEPR* may mediate the effectiveness of metabolic action by enhancing body fat storage capacity and reduced satiety, via the the leptin-melanocortin neurotransmission pathway (50). The *OLFM4*, first associated with BMI in children, may modify immune activity in response to the gut

microbiota load in the gastrointestinal tract (6). Taken together, we speculate that genes involved in the cognitive processing of food-related behaviours may impact physical activity levels through the modulation of adequate nutrient absorption, emphasising the importance of a homeostatic relationship between energy intake and expenditure.

Gene-by-physical activity interactions on PBF scores

Numerous studies have explored the effects of physical activity and its impact on susceptible genetic association in relation to obesity traits (3, 14, 20, 49). Here, we suggest that the association between three gene variants (*SPACA3/SPRASA-rs16967845, PFKP-rs6602024* and *SH2B1-rs7498665*) and risk of obesity (reflected by mean effect of PBF scores) may be modified by both sedentary and moderate activity behaviours.

Our study suggest the susceptible association between an increased proportion of sedentary behaviours and greater PBF scores is only observable in children harbouring the heterozygote (A/G) of the *SPACA*3/*SPRASA* locus and the minor genotypes of the *PFKP* (A/A) and *SH2B1* (G/G) loci. By contrast, when exposed to increased proportions of moderate activity, children possessing the same genotypes showed markedly lower PBF scores. These findings suggest that children can have different genetic susceptibilities to the effects of activity type in relation to obesity traits, at least in part, by offsetting sedentary behaviour.

All putative interactions found in this study comprised of genes involved with energy intake as opposed to expenditure. It is widely regarded that the rising rates of childhood obesity is the result of both increased energy consumption accompanied by reduced physical activity (18). Yet, numerous epidemiological studies suggest that habitual physical activity in children may not be a key determinant of energy imbalance (reviewed by Wilks *et al.* (48)). Instead, physical activity is considered a mediator of weight gain which is primarily determined by energy intake (48). The underlying cause of positive energy balance can be considered an

apparent bias of the homeostatic mechanisms that favour increased body weight through improved energy intake over expenditure (40). This would imply that there are stringent mechanisms in place to control weight loss but not weight gain, such that physical activity may not be sufficient to compensate for the unregulated energy intake due to the increased exposure of other energy-promoting environmental factors.

Both *PFKP* and *SH2B1* are strong candidate genes of obesity that encompasses biological roles that may predispose towards increased energy intake. Genetic variations in *PFKP* (a critical enzyme required for glucose metabolism) could alter rates of glycolysis, shifting the balance of metabolism towards glucose assimilation in cells (39). Similarly, disruption in *SH2B1* expression is known to impair leptin sensitivity resulting in reduced satiety response and morbid obesity (11, 36). However, the mechanistic attributes of a candidate gene *SPACA3*/*SPRASA* in relation to obesity development is relatively unknown. A preliminary study by our laboratory has found, that the knockout *SPACA3*/*SPRASA* mice were associated with obesity (8 weeks after weaning) compared to their wild type counterparts (Prendergast *et al*., unpublished data), hence their inclusion as a novel candidate gene. A follow-up pilot study showed the increased weight gain in these mice (KO/KO) may be attributed to aberrations in feeding behaviours leading to reduced satiety signals and hyperphagia (Prendergast *et al*., unpublished data). In addition, *SPACA3*/*SPRASA* knockouts were also associated with subfertility (increased time before conception and reduced litter sizes), suggesting that this gene may be involved with obesity and lower reproductive fitness (Prendergast *et al*., unpublished data). This subfertility phenotype may also explain the absence of the minor genotypes (A/A) of the *SPACA3*/*SPRASA* locus in our cohort of New Zealand European children. Our results suggest that genes involved with nutritional aspects of obesity are mediated by increased energy intake and are further amplified by sedentary behaviours. Higher physical activity may counteract the detrimental effects conveyed by these susceptibility loci which may be

advantageous in the prevention of weight gain. However, there are genes, where increased proportions of physical activity would have no differential effect. This suggests not all children predisposed to increased weight gain will benefit the same from a given level of activity. Understanding the genetic basis of obesity and its relationship with varying levels of activity, has the potential to identify groups of individuals that may benefit from regular exercise, instead of approaches that target 'one size fits all'.

Limitations

We acknowledge a number of limitations in this study. No associations remained after adjusting for multiple comparisons. However, we anticipated this as we deliberately chose to screen a large number of gene variants, expecting to identify some causal variants at the expense of losing significance after correction. This study was designed to validate previously identified associations; therefore multiple testing adjustment methods (even FDR) are likely to be overly conservative, as there were no post-hoc comparisons (all statistical tests were defined *a priori*). The low frequency of *SPACA3*/*SPRASA* (*n*=30), *PFKP* (*n*=10) and *SH2B1* (*n*=65) genotypes, requires larger sample sizes to accurately determine whether a real interaction has occurred between physical activity and genetic variation in relation to obesity traits.

It is widely accepted that obesity is a consequence of energy imbalance associated with a high-caloric dietary intake and lifestyle adopted preferences. This study only investigated one feature of the energy balance equation. Increased sedentary behaviours in conjunction with reduced physical activity levels in children are becoming prevalent in the current 'obesogenic' environment and are considered a risk factor for obesity. We hypothesise that the increased PBF scores in these children are facilitated by increased energy intake, which is mediated, in part, by a sedentary lifestyle. Yet without accounting for total caloric intake we may be imprecisely estimating the association of genetic variations and physical activity levels in

relation to obesity traits. While it has been suggested that physical activity has an important role in maintaining a healthy nutritional status (28), other studies have shown dietary habits may diverge with different activity levels (31). Therefore, children who are more physically active are not always inclined to eat healthier diets than their less active peers. Future studies should take into account both dietary and physical activity behaviours and how this may influence the genetic predisposition of obesity.

We have restricted our study to children of European ancestry. While current trends suggest obesity is rising in New Zealand among all children aged 2-14, there is a disproportionate increase in New Zealand Māori and Pacific Island children (16). Therefore, trans-ancestral comparison studies are important in defining whether genetic susceptibility variants are involved in the disproportionate prevalence of obesity across different ethnic groups, even when they live in the same environment.

Conclusion

This study may suggest that varying levels of physical activity could potentially have differential effects of obesity-associated genetic factors in relation to childhood obesity. It seems increasing rates of a sedentary lifestyle can modify the genetic susceptibility to obesity with the genetic burden having a greater manifestation in physically inactive children. Encouraging, susceptible children to partake in increased physical activity could counteract the detrimental effects of a genetic predisposition on childhood obesity. Further studies are warranted to replicate associations detected in this study with other population cohorts of different ancestry, larger sample-sets and detailed lifestyle information, especially levels of energy intake associated with dietary pathways.

Disclosure Statement

All authors have nothing to disclose.

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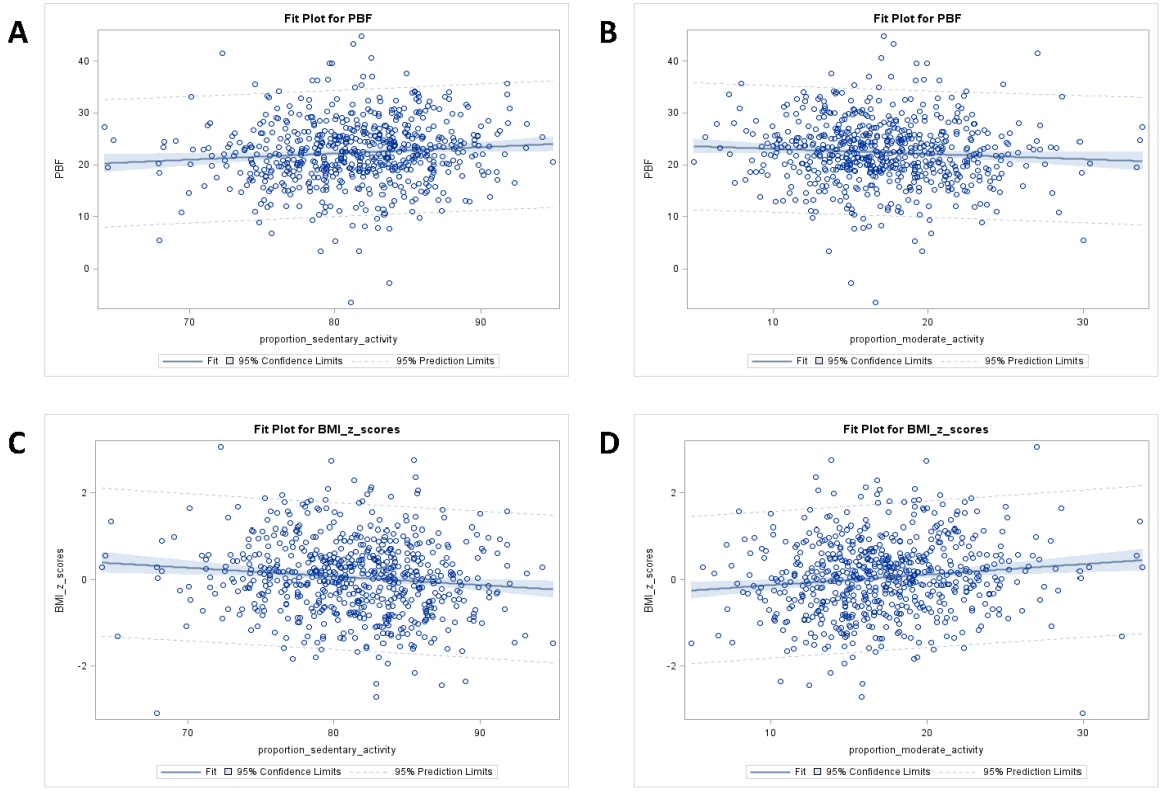

Figure 1: Linear models of proportions of physical activity (sedentary and moderate) (%) against obesity traits in 6 year old New Zealand European children in Children of SCOPE. A) Proportions of sedentary activity against PBF scores (p=0.012). B) Proportions of moderate activity against PBF scores (p=0.069). C) Proportions of sedentary activity against BMI z-scores scores (p=0.003). D) Proportions of moderate activity against BMI z-scores scores (p=0.001).

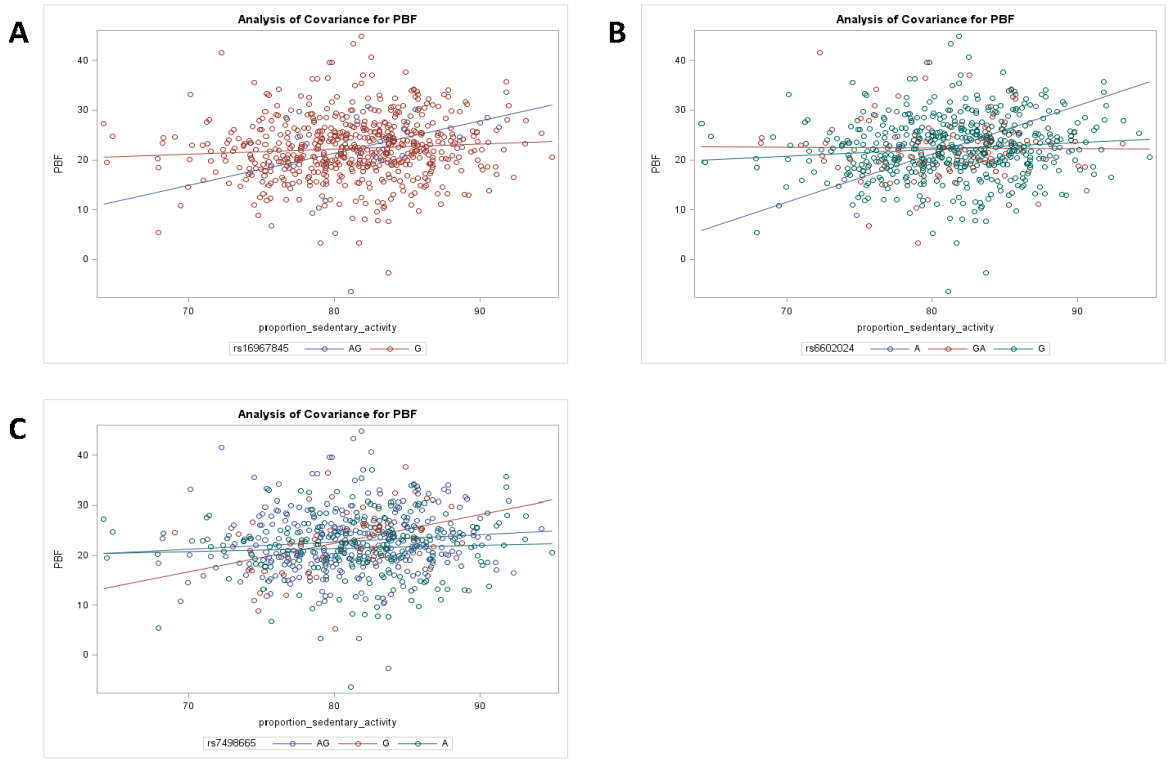

Figure 2: Stratified genotype models of (A) the SPACA3/SPRASA-rs16967845 (uncorrected p=0.023) (B) PFKP-rs6602024 (uncorrected p=0.041) and (C) SH2B1-rs7498665 (uncorrected p=0.041) and proportions of sedentary activity (%) in relation to PBF scores of 6 year old New Zealand European children in Children of SCOPE. The interactive effect of increased sedentary activity on greater PBF scores is occurring in children harbouring the heterozygotes (A/G) of the SPRASA locus and minor homozygotes of the PFKP (A/A) and SH2B1(G/G) loci.

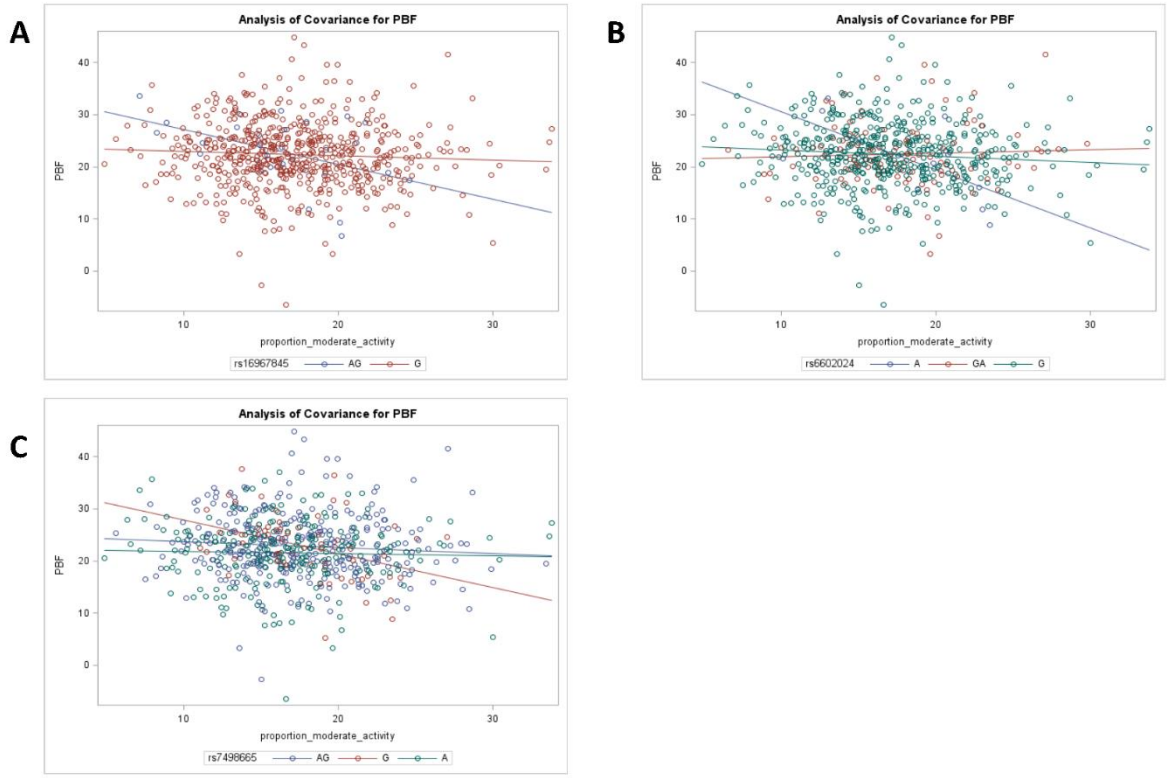

Figure 3: Stratified genotype models of (A) the SPACA3/SPRASA-rs16967845 (uncorrected p=0.035) (B) PFKP-rs6602024 (uncorrected p=0.027) and (C) SH2B1-rs7498665 (uncorrected p=0.029) and proportions of moderate activity (%) in relation to PBF scores of 6 year old New Zealand European children in Children of SCOPE. The interactive effect of increased sedentary activity on decreased PBF scores is occurring in children harbouring the heterozygotes (A/G) of the SPRASA locus and minor homozygotes of the PFKP (A/A) and SH2B1(G/G) loci.

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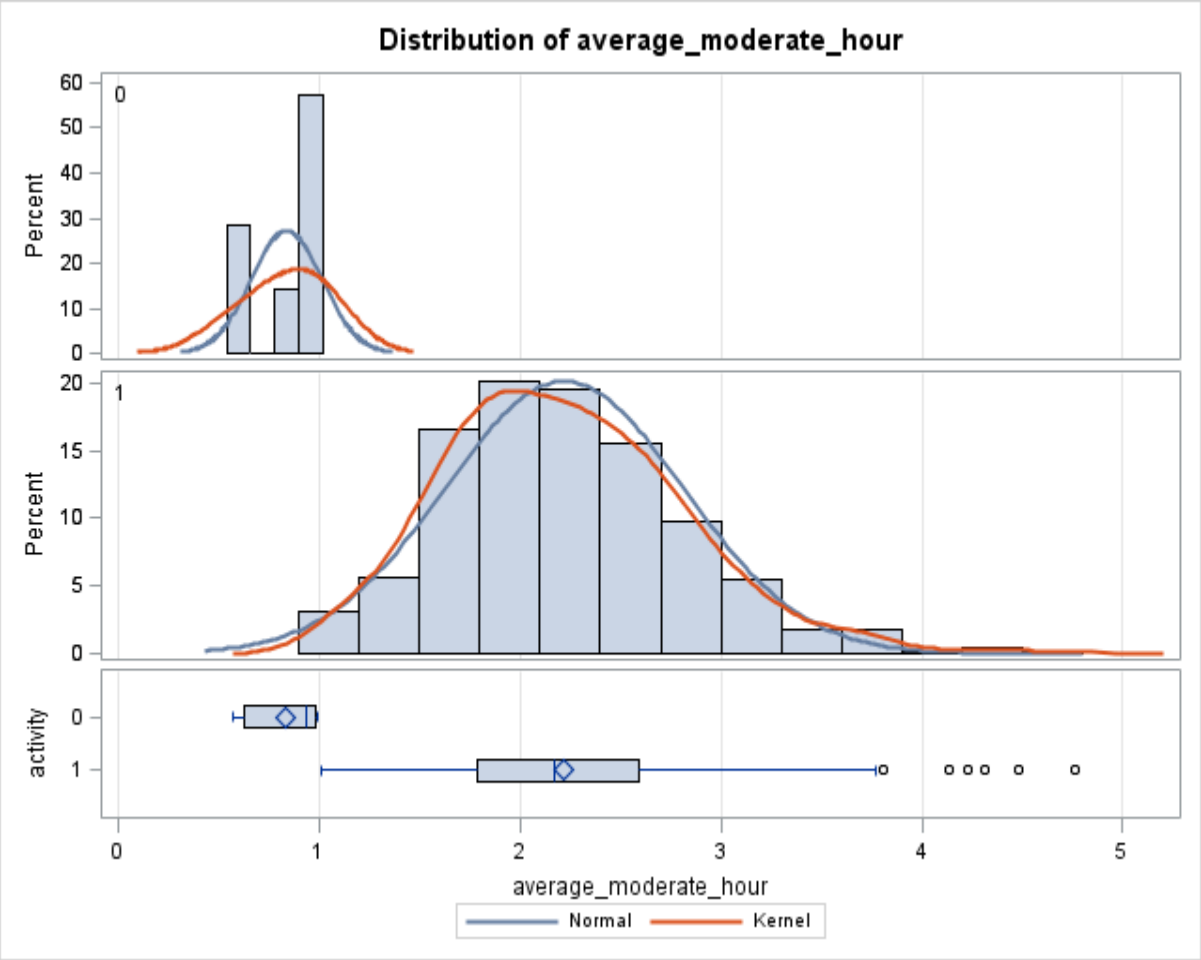
Table 1: Baseline characteristics of six year old New Zealand European children, stratified by the availability of activity information. * *P-values* indicate significant differences between the eligible study population and children with missing or inadequate activity data.

Cohort of New Zealand European children who participated in Children of SCOPE (*n*=962)			
Characteristics (s.d)	**Children who had activity data**	**Children who had no activity data**	***p-value***
Number	643	319	-
Male	341 (0.530)	147 (0.461)	0.042
Female	302 (0.470)	172 (0.539)	
Child's age of assessment (years)	5.98 (0.178)	6.04 (0.198)	<0.001
Height (cm)	117.7 (4.67)	118.3 (4.96)	0.054
Weight (kg)	21.78 (2.79)	22.17 (3.04)	0.048
BMI z-scores	0.055 (0.867)	0.116 (0.937)	0.317
PBF (%)	22.35 (6.23)	22.47 (6.01)	0.775
Mother's SEI*	50.50 (15.09)	50.84 (13.99)	0.734
Father's SEI*	54.24 (13.89)	53.67 (13.85)	0.607
Average SEI*	52.34 (11.27)	52.29 (11.33)	0.958
Average Proportion of sedentary activity (%)	10.40 (1.08)	-	-
Average Proportion of moderate activity (%)	2.20 (0.610)	-	-

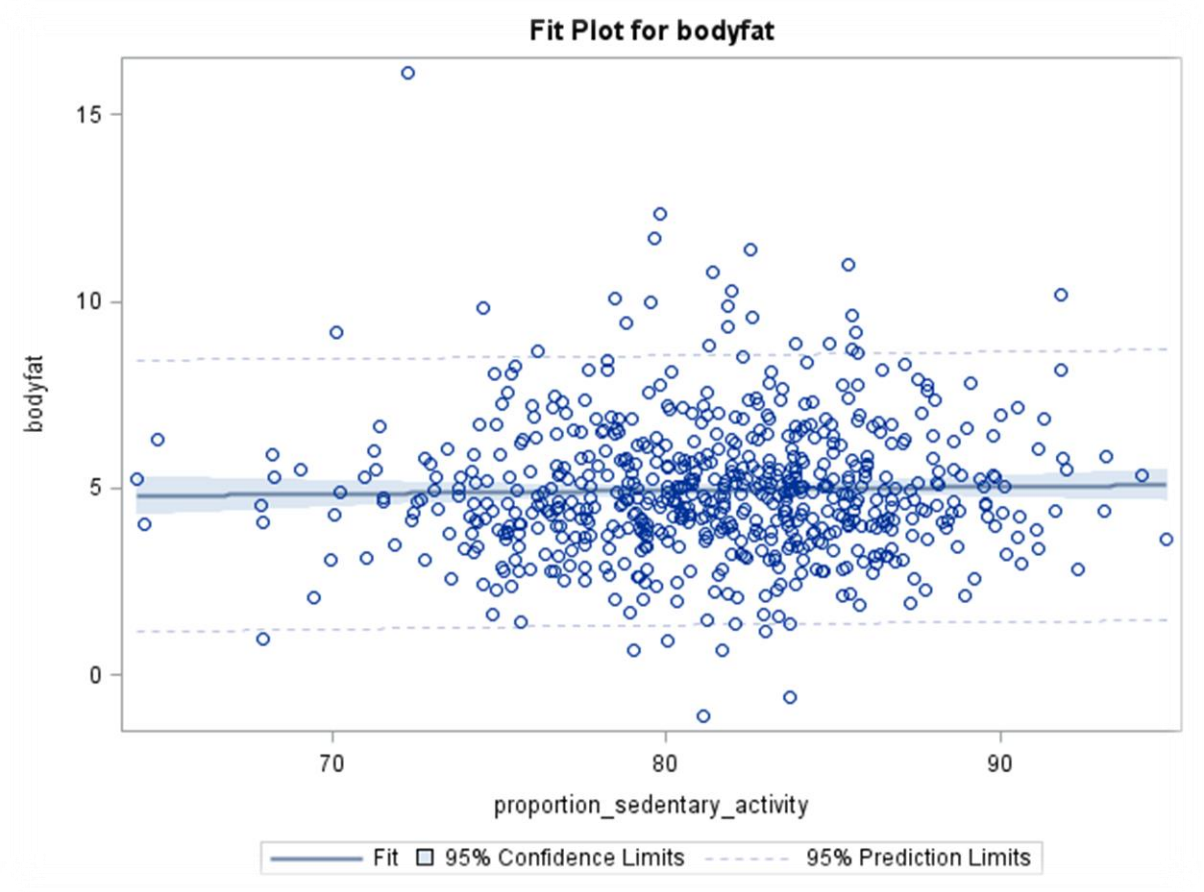
*SEI: Socioeconomic index (10-90) is a composite based-measure of socioeconomic status derived on equal weighting of education level and income associated with each occupation. Final scores were scaled to range from 10 (low socioeconomic status) to 90 (high socioeconomic status). While it is known socioeconomic status is associated with obesity outcomes, this association is unlikely to be causal. As can be seen in **Table 1**, there was no difference in those children with and without activity data in terms of SES, or measures of adiposity, thus we believe that the results of the analysis are generalizable across our cohort.

Table 2: Significant uncorrected associations (*p<0.05*) of genotype models for *OLFM4* (*p*=0.010) and *GNPDA2* (*p*=0.044) variants with proportions of sedentary activity and *OLFM4* (*p*=0.021), *CLOCK* (*p*=0.029) and *LEPR* (*p*=0.047) with proportions of moderate activity of six year old New Zealand European children in Children of SCOPE. Results are expressed as effect size in percentages (95% Confidence Intervals). After adjusting for multiple comparisons, no significant associations remained.

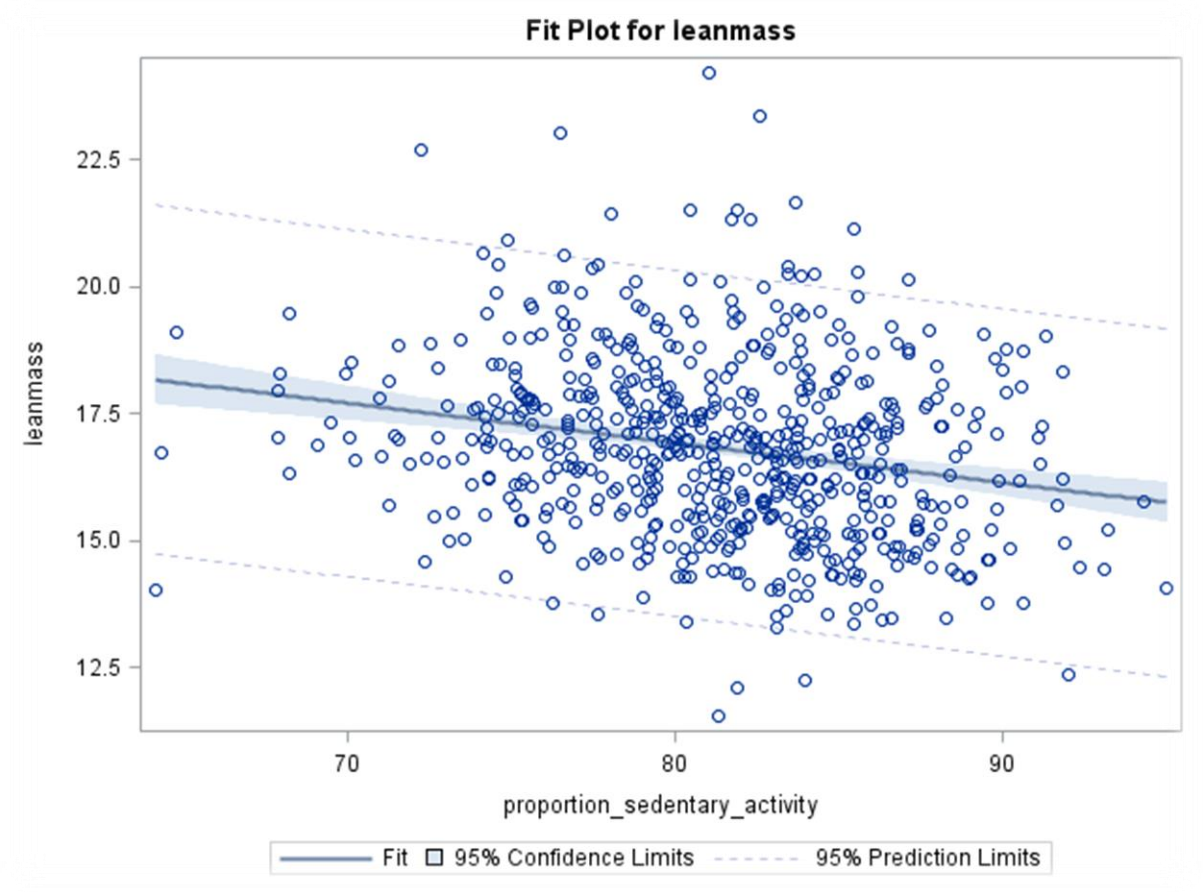
Model	Activity	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	Sedentary	13	*OLFM4*	rs9568856	G/G	477	-	-	0.010	0.714
					G/A	144	-0.79[-1.72~0.14]	0.097		
					A/A	8	4.33[0.84~7.81]	0.015		
Genotypic	Sedentary	4	*GNPDA2*	rs10938397	A/A	193	-	-	0.044	0.822
					A/G	304	1.07[0.17~1.99]	0.020		
					G/G	134	1.10[0.0016~2.20]	0.050		
Genotypic	Moderate	13	*OLFM4*	rs9568856	G/G	477	-	-	0.021	0.828
					G/A	144	0.66[-0.20~1.51]	0.131		
					A/A	8	-3.66[-6.84~-0.47]	0.025		
Genotypic	Moderate	4	*CLOCK*	rs4864548	G/G	250	-	-	0.029	0.828
					G/A	268	-1.07[-1.85~-0.28]	0.0078		
					A/A	106	-0.59[-1.62~0.45]	0.368		
Genotypic	Moderate	1	*LEPR*	rs1045895	G/G	241	-	-	0.047	0.828
					G/A	286	-0.86[-1.64~-0.076]	0.032		
					A/A	105	0.13[-0.92~1.17]	0.812		



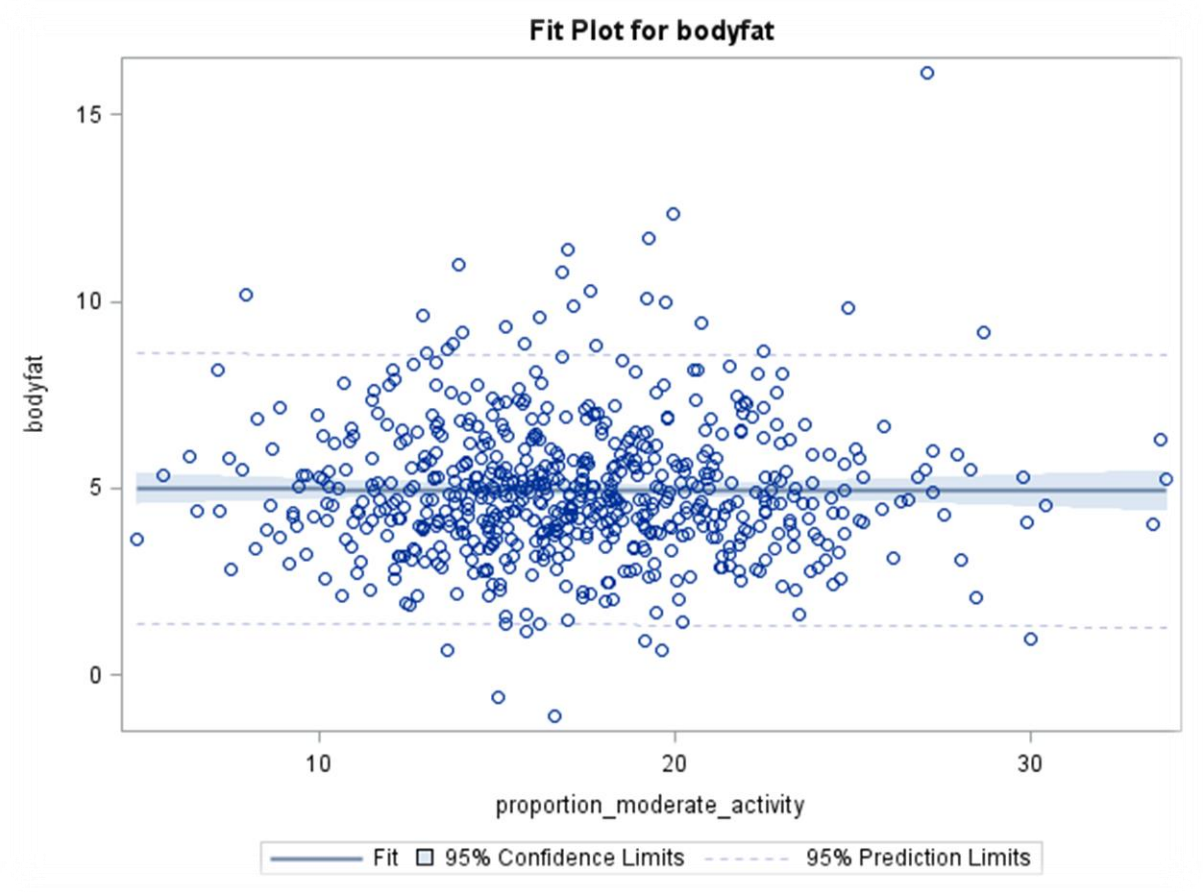
Supplementary Figure 1: Distribution of average moderate activity (per hr) stratified by WHO recommended guidelines of developmentally appropriate moderate activity for children aged 5-17. Ninety nine percent (n=638) of our children met the daily standard recommendation of 60min of moderate-to-vigorous activity (mean (s.d): 2.22 (0.595).



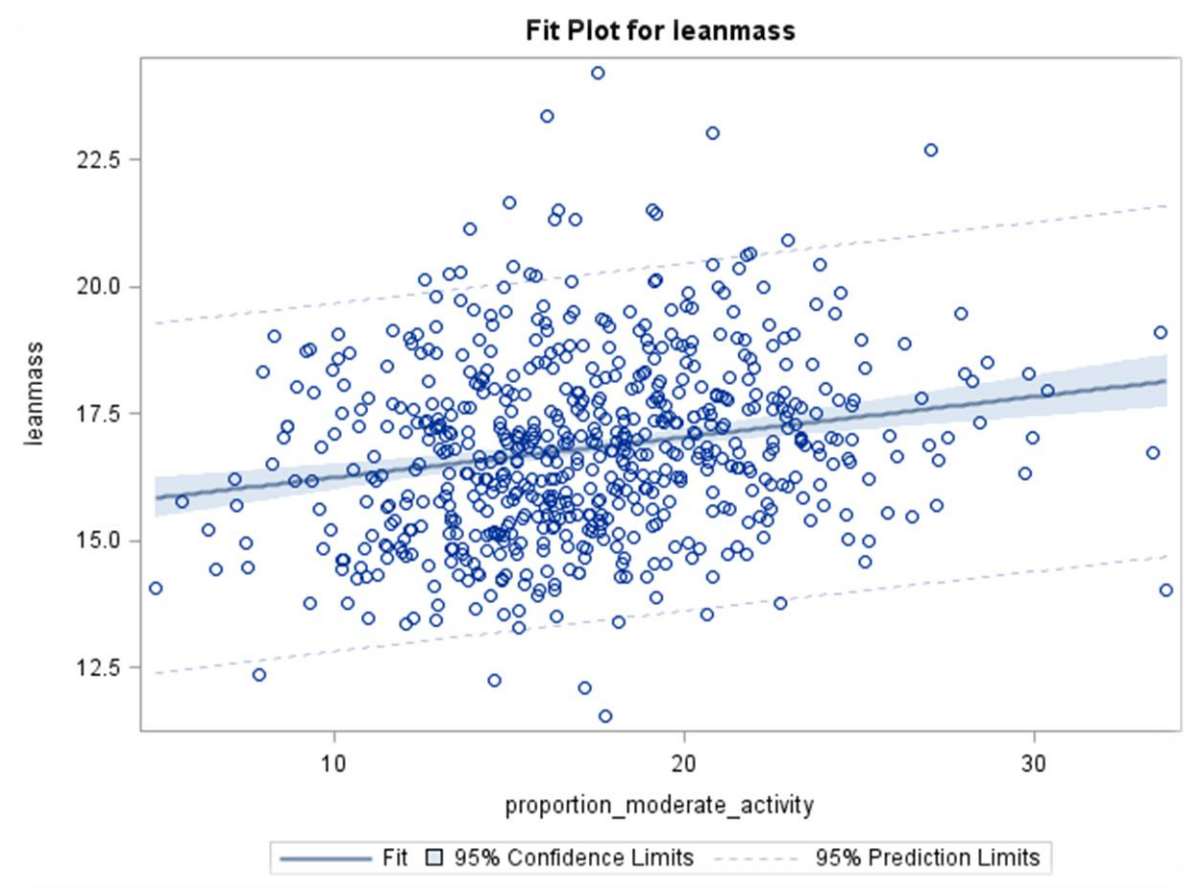
Supplementary Figure 2: Linear regression of proportion of sedentary activity against body fat in 6 year old European children of the Children of SCOPE cohort (p=0.518, β=-0.0095[-0.019~0.039]).



Supplementary Figure 3: Linear regression of proportion of sedentary activity against lean mass in 6 year old European children of the Children of SCOPE cohort (p=<0.0001, β=-0.078[-0.11~-0.051]).



Supplementary Figure 4: Linear regression of proportion of moderate activity against body fat in 6 year old European children of the Children of SCOPE cohort (p=0.900, β=-0.0020[-0.034~0.030]).



Supplementary Figure 5: Linear regression of proportion of moderate activity against lean mass in 6 year old European children of the Children of SCOPE cohort (p=<0.0001, β=0.079[0.049~0.11]).

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Supplementary Table1: Complete list of gene variants used to assess association with BMI z-scores and PBF in European children in Children of SCOPE. Twenty-seven gene variants selected for this study were from GWAS and are considered strong candidate genes of obesity. The remaining gene variants were selected on prior knowledge and suspected roles they may have had in obesity development. These include candidate genes involved in appetite regulation, energy metabolism fetal development and circadian rhythm. CEU_minor allele frequencies (MAF) were obtained from 1000GENOMES:phase_3: CEU in Ensembl (www.ensembl.org). Children of SCOPE (CoS) New Zealand European were calculated using our data. We have tried to represent a good coverage of relevant gene variants across the genome to provide novel insights into associations with obesity traits in New Zealand children.

CHR	GENE	rs number	Selection criteria	CEU_MAF	CoS-MAF
1	SEC16B	rs10913469	GWAS	0.242	0.212
1	TNNI3K	rs1514175	GWAS	0.470	0.399
1	NEGR1	rs2815752	GWAS	0.364	0.380
1	FAAH	rs324420	Candidate	0.207	0.207
1	LEPR	rs1137101	Candidate	0.485	0.456
1	LEPR	rs1045895	Candidate	0.399	0.392
2	INSIG2	rs7566605	Pre-GWAS	0.242	0.332
2	TMEM18	rs6548238	GWAS	0.167	0.147
2	POMC	rs1009388	Appetite	0.212	0.293
2	ADCY3	rs753529	Candidate	0.465	0.431
2	NPAS2	rs1811399	Sleep	0.222	0.236
2	MCM6	rs4988235	Dietary	0.263	0.297
2	POMC	rs1042571	Appetite	0.212	0.202
2	NPAS2	rs11123857	Sleep	0.258	0.260
2	NPAS2	rs2305160	Sleep	0.303	0.315
3	ADIPOQ	rs1501299	Candidate	0.313	0.243
3	ADIPOQ	rs266729	Candidate	0.303	0.263
3	ADAMT-S9	rs4607103	GWAS	0.217	0.239
3	FASN	rs4246444	Candidate	0.253	0.336
3	PPARγ	rs1801282	Diabetes	0.096	0.109
3	ETV5	rs7647305	GWAS	0.227	0.243
3	PPARγ	rs3856806	Diabetes	0.015	0.131
3	TMCC1	rs2811337	GWAS	0.131	0.173
3	GHRELIN	rs696217	Appetite	0.086	0.087
3	CCNL1/LEKR1	rs900400	Birthweight	0.414	0.390

CHR	GENE	rs number	Selection criteria	CEU_MAF	CoS-MAF
3	ADCY5	rs9883204	Birthweight	0.237	0.261
4	CLOCK	rs1801260	Sleep	0.253	0.273
4	GNPDA2	rs10938397	GWAS	0.424	0.453
4	CLOCK	rs4864548	Sleep	0.409	0.385
5	ADRB2	rs1042713	Energy	0.348	0.441
5	ROBO1	rs1455832	Candidate	0.318	0.284
5	PCSK1	rs6235	Candidate	0.308	0.256
5	TSLP	rs3806933	Immune	0.429	0.429
6	TFAP2B	rs987237	GWAS	0.167	0.168
6	IGF2R	rs8191754	Birthweight	0.172	0.139
6	ENPP1/PC-1	rs1044498	Candidate	0.131	0.150
6	RSPO3	rs11154383	GWAS	0.288	0.315
7	NYP	rs16139	Appetite	0.040	0.033
8	MSRA	rs545854	GWAS	0.167	0.174
8	FABP4	rs1054135	Candidate	0.116	0.109
10	PFKP	rs6602024	GWAS	0.101	0.103
11	UCP2	rs659366	Candidate	0.364	0.351
11	KCNJ11	rs5219	Diabetes	0.384	0.350
11	ARNTL	rs3816358	Sleep	0.101	0.103
11	ARNTL	rs11022775	Sleep	0.091	0.070
11	ARNTL	rs969485	Sleep	0.253	0.328
11	BDNF	rs6265	GWAS	0.197	0.191
11	LRP5	rs634008	Candidate	0.429	0.459
11	IGF2	rs3741205	Birthweight	0.278	0.238
12	TIMELESS	rs4630333	Sleep	0.389	0.312
12	FAIM2	rs7138803	GWAS	0.323	0.361
12	HOXC10	rs7302703	GWAS	0.182	0.176
12	ITPR2	rs1049376	GWAS	0.232	0.259
13	OLFM4	rs9568856	GWAS	0.126	0.127
13	MTIF3	rs4771122	GWAS	0.247	0.214
15	MAP2K5	rs2241423	GWAS	0.202	0.237
16	SH2B1	rs7498665	GWAS	0.364	0.355

CHR	GENE	rs number	Selection criteria	CEU_MAF	CoS-MAF
16	FTO	rs9939609	GWAS	0.444	0.386
16	AGRP	rs5030980	Candidate	0.035	0.044
16	MMP2	rs243865	Candidate	0.253	0.273
16	GPRC5B	rs12444979	GWAS	0.157	0.150
17	HOXB5	rs9299	GWAS	0.364	0.360
17	NR1D1	rs2071427	Candidate	0.303	0.265
17	SREBF-1	rs2297508	Candidate	0.303	0.350
17	PEMT	rs936108	GWAS	0.475	0.454
17	SPACA3/SPRASA	rs16967845	Candidate	0.030	0.024
17	STAT3	rs8069645	Candidate	0.258	0.254
18	NPC1	rs1805081	GWAS	0.480	0.438
18	MC4R	rs17782313	GWAS	0.258	0.220
19	KCTD15	rs29941	GWAS	0.308	0.330

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Table S2: Pairwise LD (r^r) scores of genes that have multiple polymorphisms. Pairwise LD scores were obtained from 1000GENOMES:phase_3: CEU in Ensembl (www.ensembl.org).

Gene	SNP combination	r^2 scores
LEPR	rs1137101/rs1045895	0.097
POMC	rs1009388/rs1042571	0.47
NPAS	rs1511399/rs11123857/rs2305160	No CEU data
ADIPOQ	rs1501299/rs266729	0.16
PPARγ	rs1801282/rs3856806	0.32
CLOCK	rs1801260/rs4864548	0.23
ARNTL	rs3816358/rs11022775/rs969485	No CEU data

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Supplementary Table 3: Genotype models testing the association between proportions of sedentary behaviours and 70 gene variants of 6 year old New Zealand European children in Children of SCOPE.

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	13	OLFM4	rs9568856	G/G G/A A/A	477 144 8	- -0.788[-1.72~0.142] 4.33[0.839~7.81]	- 0.0967 0.0151	0.0102	0.7140
Genotypic	4	GNPAD2	rs10938397	A/A A/G G/G	193 304 134	- 1.07[0.167~1.99] 1.10[0.00156~2.20]	- 0.0203 0.0497	0.0441	0.8215
Genotypic	16	SH2B1	rs7498665	A/A A/G G/G	249 321 65	- -0.850[-1.68~-0.0233] -1.17[-2.53~0.197]	- 0.0439 0.0934	0.0755	0.8215
Genotypic	1	LEPR	rs1137101	A/A A/G G/G	194 297 139	- -0.737[-1.64~0.169] 0.319[-0.771~1.41]	- 0.1105 0.5654	0.0791	0.8215
Genotypic	1	LEPR	rs1045895	G/G G/A A/A	241 286 105	- 0.899[0.0429~1.76] 0.0388[-1.11~1.18]	- 0.0396 0.9470	0.0844	0.8215
Genotypic	4	CLOCK	rs4864548	G/G G/A A/A	250 268 106	- 0.948[0.0861~1.81] 0.649[-0.488~1.79]	- 0.0312 0.2629	0.0937	0.8215
Genotypic	11	ARNTL	rs11022775	C/C C/T T/T	542 84 2	- -0.671[-1.82~0.482] 5.93[-1.03~12.90]	- 0.2534 0.0946	0.1236	0.8215

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	1	SEC16B	rs10913469	T/T T/C C/C	388 222 23	- -0.261[-1.09~0.564] -2.13[-4.23~-0.0225]	- 0.5437 0.0476	0.1325	0.8215
Genotypic	2	TMEM18	rs6548238	C/C C/T T/T	458 160 13	- 0.884[-0.0179~1.79] 0.964[-1.80~3.73]	- 0.0547 0.4931	0.1375	0.8215
Genotypic	6	RSPO3	rs11154383	A/A A/G G/G	299 265 66	- -0.479[-1.31~0.351] -1.18[-2.51~0.161]	- 0.2574 0.0848	0.1822	0.8215
Genotypic	13	MTIF3	rs4771122	A/A A/G G/G	386 215 27	- 0.558[-0.279~1.40] 1.48[-0.483~3.43]	- 0.1907 0.1395	0.1843	0.8215
Genotypic	6	TFAP2B	rs987237	A/A A/G G/G	439 179 17	- -0.648[-1.52~0.222] 1.18[-1.25~3.60]	- 0.1440 0.3409	0.1858	0.8215
Genotypic	2	ADCY3	rs753529	A/A A/G G/G	203 314 116	- 0.668[-0.215~1.55] -0.108[-1.25~1.03]	- 0.1377 0.8534	0.2017	0.8215
Genotypic	6	IGF2R	rs8191754	C/C C/G G/G	468 151 12	- 0.146[-0.773~1.07] 2.54[-0.338~5.41]	- 0.7555 0.0834	0.2198	0.8215
Genotypic	11	ARNTL	rs3816358	G/G G/T T/T	505 117 6	- -0.700[-1.71~0.309] 1.94[-2.10~5.98]	- 0.1737 0.3459	0.2387	0.8215

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	16	FTO	rs9939609	T/T T/A A/A	239 297 95	- -0.390[-1.24~0.464] 0.543[-0.648~1.73]	- 0.3701 0.3706	0.2645	0.8215
Genotypic	1	NEGR1	rs2815752	T/T T/C C/C	238 306 87	- -0.638[-1.49~0.210] -0.744[-1.97~0.486]	- 0.1402 0.2352	0.2696	0.8215
Genotypic	11	IGF2	rs3741205	T/T T/G G/G	355 236 30	- 0.638[-0.185~1.46] -0.250[-2.11~1.61]	- 0.1283 0.7923	0.2717	0.8215
Genotypic	17	SPACA3/SPRASA	rs16967845	G/G G/A A/A	601 30 -	- 1.03[-0.809~2.87] -	- 0.2721 -	0.2721	0.8215
Genotypic	17	PEMT	rs936108	A/A A/G G/G	189 312 131	- 0.721[-0.184~1.63] 0.266[-0.851~1.38]	- 0.1182 0.6406	0.2750	0.8215
Genotypic	18	NPC1	rs1805081	A/A A/G G/G	195 317 117	- -0.601[-1.50~0.294] -0.842[-1.99~0.308]	- 0.1878 0.1509	0.2763	0.8215
Genotypic	19	KCTD15	rs29941	C/C C/T T/T	287 269 73	- -0.518[-1.35~0.318] -0.896[-2.19~0.394]	- 0.2241 0.1729	0.2797	0.8215
Genotypic	5	PCSK1	rs6235	G/G G/C C/C	353 234 45	- 0.392[-0.435~1.22] 1.15[-0.404~2.70]	- 0.3520 0.1468	0.2848	0.8215

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	3	CCNL1/LEKR1	rs900400	T/T T/C C/C	230 300 93	- -0.574[-1.44~0.289] -0.827[-2.04~0.384]	- 0.1919 0.1804	0.2876	0.8215
Genotypic	11	UCP2	rs659366	C/C C/T T/T	270 278 82	- 0.487[-0.353~1.33] 0.886[-0.354~2.13]	- 0.2551 0.1612	0.2934	0.8215
Genotypic	11	ARNTL1	rs969485	A/A A/G G/G	316 242 61	- 0.00257[-0.837~0.842] 1.03[-0.342~2.41]	- 0.9952 0.1405	0.3115	0.8387
Genotypic	1	FAAH	rs324420	C/C C/A A/A	396 204 28	- -0.00469[-0.852~0.843] -1.41[-3.38~0.509]	- 0.9913 0.1491	0.3454	0.8955
Genotypic	11	KCNJ11	rs5219	C/C C/T T/T	260 299 71	- -0.267[-1.10~0.569] 0.626[-0.693~1.95]	- 0.5307 0.3526	0.3924	0.9604
Genotypic	8	MSRA	rs545854	G/G G/C C/C	432 179 20	- 0.357[-0.517~1.23] 1.35[-0.897~3.60]	- 0.4224 0.2383	0.3979	0.9604
Genotypic	3	ADIOPQ	rs1501299	C/C C/A A/A	365 222 42	- 0.513[-0.325~1.35] -0.208[-1.82~1.40]	- 0.2297 0.7989	0.4284	0.9634
Genotypic	5	ROBO1	rs1455832	T/T T/C C/C	317 260 47	- -0.0369[-0.861~0.787] -0.946[-2.48~0.593]	- 0.9299 0.2280	0.4728	0.9634

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	12	FAIM2	rs7138803	G/G G/A A/A	259 284 85	- 0.322[-0.524~1.17] 0.718[-0.513~1.95]	- 0.4548 0.2523	0.4865	0.9634
Genotypic	5	ADRB2	rs1042713	G/G G/A A/A	242 223 167	- 0.220[-0.692~1.13] -0.374[-1.36~0.614]	- 0.6363 0.4576	0.5089	0.9634
Genotypic	10	PFKP	rs6602024	G/G G/A A/A	513 111 10	- -0.364[-1.39~0.665] -1.54[-4.68~1.60]	- 0.4870 0.3362	0.5130	0.9634
Genotypic	3	ADIOPQ	rs266729	C/C C/G G/G	345 244 45	- -0.193[-1.02~0.630] -0.900[-2.46~0.660]	- 0.6449 0.2576	0.5142	0.9634
Genotypic	2	NPAS2	rs2305160	C/C C/T T/T	298 256 68	- 0.0851[-0.753~0.923] 0.738[-0.583~2.06]	- 0.8419 0.2733	0.5440	0.9634
Genotypic	2	NPAS2	rs11123857	A/A A/G G/G	342 250 39	- -0.270[-1.09~0.545] 0.601[-1.05~2.26]	- 0.5154 0.4762	0.5558	0.9634
Genotypic	3	PPARγ	rs3856806	C/C C/T T/T	476 147 9	- -0.300[-1.23~0.627] 1.40[-1.90~4.71]	- 0.5250 0.4054	0.5566	0.9634
Genotypic	17	STAT3	rs8069645	A/A A/G G/G	341 253 33	- -0.0821[-0.890~0.736] 0.867[-0.929~2.66]	- 0.8438 0.3434	0.5918	0.9634

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	2	INSIG2	rs7566605	G/G G/C C/C	279 285 67	- -0.322[-1.15~0.509] -0.601[-1.94~0.740]	- 0.4461 0.3794	0.5957	0.9634
Genotypic	16	AGRP	rs5030980	G/G G/A A/A	577 51 2	- -0.174[-1.61~1.26] -3.33[-10.30~3.65]	- 0.8121 0.3487	0.6288	0.9634
Genotypic	2	POMC	rs1042571	C/C C/T T/T	400 204 25	- 0.325[-0.522~1.17] 0.680[-1.35~2.71]	- 0.5110 0.4515	0.6449	0.9634
Genotypic	17	HOXB5	rs9299	A/A A/G G/G	258 289 82	- 0.274[-0.570~1.12] 0.547[-0.702~1.80]	- 0.5242 0.3904	0.6494	0.9634
Genotypic	17	SREBF-1	rs2297508	C/C C/G G/G	267 281 79	- -0.397[-1.24~0.446] -0.224[-1.49~1.04]	- 0.3556 0.7280	0.6521	0.9634
Genotypic	3	ADAMT-S9	rs4607103	C/C C/T T/T	357 240 30	- 0.366[-0.457~1.19] -0.106[-1.98~1.77]	- 0.3826 0.9119	0.6585	0.9634
Genotypic	12	HOXC10	rs7302703	G/G G/A A/A	420 198 12	- -0.000365[-0.845~0.848] -1.28[-4.16~1.60]	- 0.9993 0.3839	0.6820	0.9634
Genotypic	3	ADCY5	rs9883204	C/C C/T T/T	342 241 43	- -0.0122[-0.838~0.814] 0.683[-0.907~2.27]	- 0.9769 0.3991	0.6846	0.9634

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	1	TNNI3K	rs1514175	C/C C/T T/T	233 289 106	- 0.134[-0.734~1.00] 0.511[-0.644~1.67]	- 0.7616 0.3856	0.6847	0.9634
Genotypic	16	GPRC5B	rs12444979	C/C C/T T/T	460 151 19	- 0.400[-0.523~1.32] 0.193[-2.11~2.50]	- 0.3956 0.8691	0.6947	0.9634
Genotypic	3	TMCC1	rs2811337	C/C C/G G/G	430 182 18	- -0.114[-0.984~0.756] 0.896[-1.47~3.26]	- 0.7967 0.4575	0.7158	0.9634
Genotypic	3	GHRELIN	rs696217	G/G G/T T/T	528 95 7	- -0.0136[-1.11~1.08] -1.55[-5.29~2.20]	- 0.9806 0.4180	0.7201	0.9634
Genotypic	16	MMP2	rs243865	C/C C/T T/T	330 261 42	- 0.247[-0.569~1.06] 0.543[-1.07~2.16]	- 0.5529 0.5086	0.7238	0.9634
Genotypic	17	NR1D1	rs2071427	G/G G/A A/A	343 241 47	- -0.0453[-0.873~0.783] 0.561[-0.971~2.09]	- 0.9145 0.4720	0.7433	0.9634
Genotypic	8	FABP4	rs1054135	G/G G/A A/A	504 117 10	- 0.151[-0.859~1.16] -1.08[-4.22~2.06]	- 0.7692 0.4997	0.7527	0.9634
Genotypic	4	CLOCK	rs1801260	T/T T/C C/C	346 228 59	- -0.311[-1.14~0.523] -0.0703[-1.45~1.31]	- 0.4644 0.9201	0.7627	0.9634

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	3	FASN	rs426444	T/T T/A A/A	284 267 78	- 0.293[-0.547~1.13] 0.226[-1.03~1.49]	- 0.4938 0.7249	0.7836	0.9634
Genotypic	3	PPARγ	rs1801282	C/C C/G G/G	504 115 11	- 0.351[-0.666~1.37] 0.193[-2.81~3.19]	- 0.4982 0.8995	0.7921	0.9634
Genotypic	11	BDNF	rs6265	G/G G/A A/A	417 192 25	- 0.284[-0.574~1.14] -0.0245[-2.05~2.00]	- 0.5158 0.9811	0.8045	0.9634
Genotypic	15	MAP2K5	rs2241423	G/G G/A A/A	364 235 32	- 0.0637[-0.760~0.887] 0.596[-1.22~2.41]	- 0.8793 0.5196	0.8120	0.9634
Genotypic	12	ITPR2	rs1049376	A/A A/G G/G	348 236 45	- -0.183[-1.01~0.648] -0.407[-1.99~1.15]	- 0.6660 0.6085	0.8307	0.9640
Genotypic	6	ENNP1/PC-1	rs1044498	A/A A/C C/C	461 153 18	- 0.202[-0.717~1.12] -0.402[-2.77~1.97]	- 0.6658 0.7387	0.8483	0.9640
Genotypic	3	ETV5	rs7647305	C/C C/T T/T	356 239 33	- -0.165[-0.989~0.660] 0.256[-1.54~2.05]	- 0.6947 0.7798	0.8683	0.9640
Genotypic	11	LRP5	rs634008	T/T T/C C/C	190 304 138	- 0.204[-0.707~1.12] 0.000512[-1.10~1.10]	- 0.6600 0.9993	0.8777	0.9640

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	12	TIMELESS	rs4630333	G/G G/A A/A	247 222 51	- -0.140[-1.05~0.768] -0.341[-1.85~1.17]	- 0.7616 0.6573	0.8909	0.9640
Genotypic	2	MCM6	rs4988235	T/T T/C C/C	311 266 55	- 0.195[-0.626~1.02] 0.0788[-1.36~1.52]	- 0.6413 0.9144	0.8970	0.9640
Genotypic	5	TSLP	rs3806933	C/C C/T T/T	200 319 111	- -0.0816[-0.971~0.808] -0.250[-1.42~0.918]	- 0.8572 0.6742	0.9152	0.9640
Genotypic	2	NPAS2	rs1811399	T/T T/G G/G	369 226 36	- 0.0456[-0.786~0.877] -0.304[-2.02~1.42]	- 0.9144 0.7286	0.9274	0.9640
Genotypic	7	NYP	rs16139	A/A A/G G/G	589 39 1	- 0.210[-1.42~1.84] -1.17[-11.03~8.70]	- 0.8006 0.8166	0.9423	0.9640
Genotypic	18	MC4R	rs17782313	T/T T/C C/C	385 213 32	- 0.0181[-0.824~0.861] -0.282[-2.10~1.53]	- 0.9664 0.7600	0.9502	0.9640
Genotypic	2	POMC	rs1009388	C/C C/G G/G	319 254 58	- 0.0225[-0.804~0.849] 0.175[-1.23~1.58]	- 0.9573 0.8064	0.9703	0.9703

"Gene-By-Activity Interactions on Obesity Traits of Six Year Old New Zealand European Children: A Children of SCOPE Study" by Krishnan M et al.
Pediatric Exercise Science

Supplementary Table 4: Genotype models testing the association between proportions of moderate activity and 70 gene variants of 6 year old New Zealand European children in Children of SCOPE.

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	13	OLFM4	rs9568856	G/G G/A A/A	477 144 8	- 0.655[-0.195[1.51] -3.66[-6.84~-0.471]	- 0.1305 0.0245	0.0205	0.8275
Genotypic	4	CLOCK	rs4864548	G/G G/A A/A	250 268 106	- -1.07[-1.85~-0.282] -0.585[-1.62~0.452]	- 0.0078 0.3683	0.0290	0.8275
Genotypic	1	LEPR	rs1045895	G/G G/A A/A	241 286 105	- -0.857[-1.64~-0.0763] 0.126[-0.918~1.17]	- 0.0315 0.8124	0.0474	0.8275
Genotypic	16	SH2B1	rs7498665	A/A A/G G/G	249 321 65	- 0.877[0.123[1.63] 0.992[-0.252~2.24]	- 0.0277 0.1178	0.0527	0.8275
Genotypic	1	LEPR	rs1137101	A/A A/G G/G	194 297 139	- 0.603[-0.223~1.43] -0.443[-1.44~0.551]	- 0.1520 0.3815	0.0658	0.8275
Genotypic	4	GNPAD2	rs10938397	A/A A/G G/G	193 304 134	- -0.888[-1.71~-0.0649] -0.890[-1.90~0.115]	- 0.0345 0.0826	0.0788	0.8275
Genotypic	13	MTIF3	rs4771122	A/A A/G G/G	386 215 27	- -0.535[-1.30~0.228] -1.62[-3.41~0.163]	- 0.1689 0.0749	0.1099	0.8275

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	2	TMEM18	rs6548238	C/C C/T T/T	458 160 13	- -0.842[-1.66~0.0198] -0.823[-3.34~1.70]	- 0.0448 0.5214	0.1192	0.8275
Genotypic	6	TFAP2B	rs987237	A/A A/G G/G	439 179 17	- 0.643[-0.150~1.45] -1.21[-3.42~1.01]	- 0.1116 0.2848	0.1306	0.8275
Genotypic	11	ARNTL	rs11022775	C/C C/T T/T	542 84 2	- 0.365[-0.687~1.42] -5.60[-11.96~0.757]	- 0.4957 0.0841	0.1737	0.8275
Genotypic	6	RSPO3	rs11154383	A/A A/G G/G	299 265 66	- 0.525[-0.232~1.28] 0.997[-0.223~2.22]	- 0.1739 0.1090	0.1792	0.8275
Genotypic	11	IGF2	rs3741205	T/T T/G G/G	355 236 30	- -0.618[-1.37~0.132] 0.422[-1.28~2.12]	- 0.1063 0.6259	0.1994	0.8275
Genotypic	6	IGF2R	rs8191754	C/C C/G G/G	468 151 12	- -0.0195[-0.859~0.820] -2.38[-5.00~0.239]	- 0.9636 0.0748	0.2032	0.8275
Genotypic	1	SEC16B	rs10913469	T/T T/C C/C	388 222 23	- 0.193[-0.560~0.947] 1.69[-0.227~3.62]	- 0.6149 0.0838	0.2166	0.8275
Genotypic	19	KCTD15	rs29941	C/C C/T T/T	287 269 73	- 0.537[-0.224~1.30] 0.834[-0.342~2.01]	- 0.1665 0.1644	0.2310	0.8275

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	5	PCSK1	rs6235	G/G G/C C/C	353 234 45	- -0.337[-1.09~0.418] -1.12[-2.54~0.295]	- 0.3816 0.1206	0.2564	0.8275
Genotypic	17	SPACA3/SPRASA	rs16967845	G/G G/A A/A	601 30 -	- -0.959[-2.64~0.718] -	- 0.2618 -	0.2618	0.8275
Genotypic	11	UCP2	rs659366	C/C C/T T/T	270 278 82	- -0.426[-1.19~0.340] -0.877[-2.00~0.254]	- 0.2752 0.1285	0.2622	0.8275
Genotypic	2	ADCY3	rs753529	A/A A/G G/G	203 314 116	- -0.574[-1.38~0.233] 0.0394[-1.00~1.08]	- 0.1629 0.9409	0.2682	0.8275
Genotypic	3	CCNL1/LEKR1	rs900400	T/T T/C C/C	230 300 93	- 0.486[-0.302~1.27] 0.805[-0.300~1.91]	- 0.2267 0.1529	0.2833	0.8275
Genotypic	11	ARNTL	rs3816358	G/G G/T T/T	505 117 6	- 0.615[-0.307~1.54] -1.52[-5.21~2.17]	- 0.1907 0.4192	0.2909	0.8275
Genotypic	18	NPC1	rs1805081	A/A A/G G/G	195 317 117	- 0.497[-0.320~1.31] 0.782[-0.268~1.83]	- 0.2329 0.1440	0.2941	0.8275
Genotypic	3	ADIOPQ	rs1501299	C/C C/A A/A	365 222 42	- -0.593[-1.36~0.171] -0.0335[-1.50~1.43]	- 0.1280 0.9641	0.3033	0.8275

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	3	ADIOPQ	rs266729	C/C C/G G/G	345 244 45	- 0.195[-0.555~0.945] 1.11[-0.316~2.53]	- 0.6102 0.1272	0.3071	0.8275
Genotypic	8	MSRA	rs545854	G/G G/C C/C	432 179 20	- -0.335[-1.13~0.462] -1.41[-3.47~0.639]	- 0.4092 0.1768	0.3195	0.8275
Genotypic	16	FTO	rs9939609	T/T T/A A/A	239 297 95	- 0.447[-0.332~1.23] -0.262[-1.35~0.825]	- 0.2606 0.6357	0.3213	0.8275
Genotypic	17	PEMT	rs936108	A/A A/G G/G	189 312 131	- -0.567[-1.39~0.260] -0.0541[-1.07~0.965]	- 0.1786 0.9170	0.3241	0.8275
Genotypic	11	ARNTL1	rs969485	A/A A/G G/G	316 242 61	- 0.143[-0.622~0.909] -0.825[-2.08~0.429]	- 0.7133 0.1964	0.3310	0.8275
Genotypic	1	NEGR1	rs2815752	T/T T/C C/C	238 306 87	- 0.478[-0.297~1.25] 0.631[-0.492~1.75]	- 0.2266 0.2701	0.3800	0.9064
Genotypic	5	ROBO1	rs1455832	T/T T/C C/C	317 260 47	- 0.0165[-0.735~0.768] 0.928[-0.476~2.33]	- 0.9656 0.1949	0.4151	0.9064
Genotypic	2	NPAS2	rs2305160	C/C C/T T/T	298 256 68	- 0.00831[-0.756~0.772] -0.760[-1.97~0.444]	- 0.9830 0.2115	0.4282	0.9064

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	10	PFKP	rs6602024	G/G G/A A/A	513 111 10	- 0.407[-0.531~1.35] 1.33[-1.53~4.20]	- 0.3945 0.3607	0.4783	0.9064
Genotypic	12	HOXC10	rs7302703	G/G G/A A/A	420 198 12	- 0.0184[-0.756~0.792] 1.60[-1.03~4.23]	- 0.9628 0.2325	0.4890	0.9064
Genotypic	16	GPRC5B	rs12444979	C/C C/T T/T	460 151 19	- -0.508[-1.35~0.334] -0.161[-2.26~1.94]	- 0.2362 0.8807	0.4952	0.9064
Genotypic	11	KCNJ11	rs5219	C/C C/T T/T	260 299 71	- 0.0520[-0.710~0.814] -0.648[-1.85~0.555]	- 0.8935 0.2905	0.4987	0.9064
Genotypic	12	FAIM2	rs7138803	G/G G/A A/A	259 284 85	- -0.221[-0.993~0.552] -0.657[-1.78~0.467]	- 0.5750 0.2514	0.5113	0.9064
Genotypic	5	ADRB2	rs1042713	G/G G/A A/A	242 223 167	- -0.317[-1.15~0.515] 0.187[-0.715~1.09]	- 0.4544 0.6843	0.5389	0.9064
Genotypic	3	ADCY5	rs9883204	C/C C/T T/T	342 241 43	- 0.0278[-0.726~0.782] -0.739[-2.19~0.712]	- 0.9424 0.3175	0.5809	0.9064
Genotypic	2	NPAS2	rs11123857	A/A A/G G/G	342 250 39	- 0.201[-0.542~0.945] -0.564[-2.07~0.946]	- 0.5952 0.4633	0.5984	0.9064

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	3	PPARγ	rs3856806	C/C C/T T/T	476 147 9	- 0.227[-0.619~1.07] -1.27[-4.29~1.75]	- 0.5983 0.4083	0.5994	0.9064
Genotypic	17	NR1D1	rs2071427	G/G G/A A/A	343 241 47	- 0.167[-0.589~0.922] -0.527[-1.92~0.871]	- 0.6652 0.4597	0.6304	0.9064
Genotypic	1	FAAH	rs324420	C/C C/A A/A	396 204 28	- 0.0118[-0.762~0.786] 0.846[-0.911~2.60]	- 0.9761 0.3447	0.6356	0.9064
Genotypic	17	STAT3	rs8069645	A/A A/G G/G	341 253 33	- -0.0281[-0.774~0.718] -0.787[-2.43~0.853]	- 0.9411 0.3465	0.6379	0.9064
Genotypic	3	GHRELIN	rs696217	G/G G/T T/T	528 95 7	- 0.125[-0.877~1.13] 1.57[-1.85~4.99]	- 0.8068 0.3665	0.6512	0.9064
Genotypic	15	MAP2K5	rs2241423	G/G G/A A/A	364 235 32	- -0.0645[-0.816~0.687] -0.776[-2.43~0.880]	- 0.8662 0.3580	0.6552	0.9064
Genotypic	3	FASN	rs426444	T/T T/A A/A	284 267 78	- -0.357[-1.12~0.408] -0.209[-1.36~0.939]	- 0.3597 0.7205	0.6558	0.9064
Genotypic	17	SREBF-1	rs2297508	C/C C/G G/G	267 281 79	- 0.351[-0.418~1.12] 0.0903[-1.06~1.24]	- 0.3701 0.8777	0.6602	0.9064

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	16	MMP2	rs243865	C/C C/T T/T	330 261 42	- -0.329[-1.07~0.415] -0.301[-1.77~1.17]	- 0.3852 0.6880	0.6704	0.9064
Genotypic	2	INSIG2	rs7566605	G/G G/C C/C	279 285 67	- 0.306[-0.452~1.06] 0.383[-0.840~1.61]	- 0.4284 0.5386	0.6781	0.9064
Genotypic	8	FABP4	rs1054135	G/G G/A A/A	504 117 10	- -0.0417[-0.963~0.880] 1.26[-1.61~4.13]	- 0.9293 0.3888	0.6828	0.9064
Genotypic	1	TNNI3K	rs1514175	C/C C/T T/T	233 289 106	- -0.0963[-0.888~0.696] -0.461[-1.51~0.593]	- 0.8113 0.3908	0.6859	0.9064
Genotypic	3	ETV5	rs7647305	C/C C/T T/T	356 239 33	- 0.210[-0.543~0.962] -0.451[-2.09~1.19]	- 0.5846 0.5890	0.6960	0.9064
Genotypic	2	POMC	rs1042571	C/C C/T T/T	400 204 25	- -0.265[-1.04~0.508] -0.572[-2.43~1.28]	- 0.5012 0.5443	0.6978	0.9064
Genotypic	3	TMCC1	rs2811337	C/C C/G G/G	430 182 18	- 0.122[-0.672~0.916] -0.828[-2.99~1.33]	- 0.7628 0.4519	0.6992	0.9064
Genotypic	4	CLOCK	rs1801260	T/T T/C C/C	346 228 59	- 0.269[-0.492~1.03] 0.0316[-1.22~1.29]	- 0.4875 0.9606	0.7799	0.9525

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	11	BDNF	rs6265	G/G G/A A/A	417 192 25	- -0.251[-1.03~0.532] 0.211[-1.64~2.06]	- 0.5288 0.8224	0.7811	0.9525
Genotypic	6	ENNP1/PC-1	rs1044498	A/A A/C C/C	461 153 18	- -0.240[-1.08~0.599] 0.389[-1.77~2.55]	- 0.5748 0.7239	0.7856	0.9525
Genotypic	2	MCM6	rs4988235	T/T T/C C/C	311 266 55	- -0.244[-0.993~0.506] -0.0880[-1.40~1.23]	- 0.5239 0.8954	0.8155	0.9525
Genotypic	3	PPARγ	rs1801282	C/C C/G G/G	504 115 11	- -0.285[-1.21~0.643] -0.262[-3.00~2.48]	- 0.5462 0.8511	0.8241	0.9525
Genotypic	17	HOXB5	rs9299	A/A A/G G/G	258 289 82	- -0.224[-0.994~0.546] -0.247[1.39~0.893]	- 0.5677 6.6711	0.8259	0.9525
Genotypic	16	AGRP	rs5030980	G/G G/A A/A	577 51 2	- 0.181[-1.13~1.49] 1.76[-4.60~8.12]	- 0.7865 0.5873	0.8338	0.9525
Genotypic	11	LRP5	rs634008	T/T T/C C/C	190 304 138	- -0.150[-0.981~0.682] 0.110[-0.896~1.12]	- 0.7243 0.8296	0.8458	0.9525
Genotypic	18	MC4R	rs17782313	T/T T/C C/C	385 213 32	- 0.0282[-0.740~0.800] 0.463[-1.19~2.12]	- 0.9425 0.5830	0.8598	0.9525

"Gene-By-Activity Interactions on Obesity Traits of Six Year Old New Zealand European Children: A Children of SCOPE Study" by Krishnan M et al.
Pediatric Exercise Science

Model	CHR	Gene	SNP	Genotype	Frequency	Effect (β) (95% CI)	*p*-value	Genotypic *p* value	Genotypic *q* value
Genotypic	12	TIMELESS	rs4630333	G/G G/A A/A	247 222 51	- 0.0998[-0.728~0.928] 0.363[-1.01~1.74]	- 0.8130 0.6050	0.8709	0.9525
Genotypic	3	ADAMT-S9	rs4607103	C/C C/T T/T	357 240 30	- -0.134[-0.885~0.618] 0.125[-1.59~1.84]	- 0.7271 0.8863	0.9208	0.9587
Genotypic	2	POMC	rs1009388	C/C C/G G/G	319 254 58	- -0.132[-0.887~0.622] -0.189[-1.47~1.09]	- 0.7306 0.7717	0.9223	0.9587
Genotypic	12	ITPR2	rs1049376	A/A A/G G/G	348 236 45	- 0.0896[-0.669~0.848] 0.242[-1.18~1.67]	- 0.8167 0.7392	0.9334	0.9587
Genotypic	5	TSLP	rs3806933	C/C C/T T/T	200 319 111	- -0.0504[-0.862~0.762] 0.128[-0.937~1.19]	- 0.9031 0.8132	0.9393	0.9587
Genotypic	2	NPAS2	rs1811399	T/T T/G G/G	369 226 36	- 0.0931[-0.666~0.852] 0.220[-1.35~1.79]	- 0.8098 0.7831	0.9450	0.9587
Genotypic	7	NYP	rs16139	A/A A/G G/G	589 39 1	- -0.0588[-1.55~1.43] 0.185[-8.82~9.19]	- 0.9381 0.9677	0.9961	0.9961