**Does genetic risk of obesity modify associations between characteristics of the neighbourhood built environment and BMI?**

Genetic risk of obesity modifies associations between neighbourhood environment and BMI

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**ABSTRACT**

**Importance:** There is growing recognition that recent global increases in obesity are the product of a complex interplay between individual genetic and environmental factors. However, in gene-environment studies of obesity, ‘environment’ usually refers to individual behavioural factors that influence energy balance, while more upstream environmental factors are overlooked.

**Objectives:** To investigate interactions between genetic risk of obesity and neighbourhood characteristics likely to be associated with overweight and obesity (proximity to fast food and availability of physical activity facilities) in relation to BMI.

**Design:** Population-based cross-sectional study using objective measures of BMI and food and physical activity environments near home, and polygenic risk scores and individual SNPs associated with BMI.

**Setting:** United Kingdom

**Participants:** 332,174 adults aged 40-70 in the UK Biobank cohort

**Main outcome measures:** Body Mass Index

**Results:** The association between proximity to fast-food and BMI was stronger among those at increased genetic risk of obesity, with evidence of an interaction with polygenic risk scores (P=0.017) and in particular with a SNP linked to *MC4R* (P=0.009), a gene known to regulate food intake. We found no evidence of a gene-environment interaction for availability of physical activity facilities.

**Conclusions:** Individuals at an increased genetic risk of obesity may be more sensitive to exposure to the local fast-food environment.

**BACKGROUND**

Obesity has a heritable component1, but the rapid rise in global obesity prevalence suggests an important role for environmental influences2. However, individuals may have differing physiological or behavioural responses to the increasingly ‘obesogenic’ environment, suggesting that a complex interplay between genetic and non-genetic factors affects weight3,4.

Advances in genotyping technologies have enabled the investigation of gene-environment (GxE) interactions4,5. For obesity outcomes, the ‘environment’ in GxE studies is often operationalised as the lifestyle or behavioural factors that influence energy balance6, rather than more upstream features of the built and natural environment; the settings where behavioural ‘choices’ are made and constrained. Despite long being recognised in social epidemiology as potentially important determinants of weight status, these ‘socio-ecological’ environmental factors have been examined in only a small number of GxE studies7–11.

The residential environment comprises many features that potentially influence energy balance. These include the proximity, density and relative proportions of healthy and unhealthy food retailers12–14, and resources for physical activity (PA), such as leisure centres, swimming pools, gyms and sports fields15–18. Other neighbourhood features linked to energy balance include walkability, access to public transport and local resources such as public parks and greenspace19,20. If the genetic risk of obesity modifies the influence of these neighbourhood exposures, we would expect to observe differential effects of the residential environment on BMI according to level of genetic risk. The influence of the environment may be strongest in people with high genetic risk due to increased sensitivity to external factors21,22, or it may be strongest in people with low genetic risk, who maximise their genetic ‘advantage’ within a healthier environment while those at greater risk express a higher BMI phenotype regardless of environmental factors6.

In this study we use the UK Biobank cohort to examine whether genetic risk of obesity modifies the effect of two residential environment exposures likely to influence BMI: proximity to fast-food and availability of formal PA facilities. We operationalise genetic risk in two ways. First, using polygenic risk scores derived from single nucleotide polymorphisms (SNPs) linked to BMI, and second, using the individual SNPs most strongly linked to BMI and thought to be involved in diet or PA pathways.

**METHODS**

*Data*

We used baseline data from UK Biobank (project 17380)23. Data were potentially available from 502,656 individuals who visited 22 UK Biobank assessment centres across the UK between 2006 and 2010. Individuals aged 40–69 years living within 25 miles of an assessment centre and listed on National Health Service (NHS) patient registers were invited to participate.

Linked to UK Biobank is UKBUMP, a high-resolution spatial database of objectively measured characteristics of the physical environment surrounding each participant’s residential address, derived from multiple national spatial datasets24. Environmental measures include densities of various land uses and proximity to various health-relevant resources. Measures for the current study are available for 96% of the UK Biobank sample.

Genome-wide genetic data are available for 488,363 participants. Genetic data are missing from the remaining 3% of the sample as insufficient DNA was extracted from blood samples for genotyping assays. Procedures used to derive the genetic data and undertake quality assurance are reported in Bycroft et al25. Genetic data were downloaded, decrypted and linked to participant IDs. Data for the relevant SNPs were extracted for use in analysis.

*Outcome*

Body Mass Index (BMI, kg/m2) was calculated from weight and height measurements collected by trained staff using standard procedures23. The variable was normally distributed and analysed as a continuous outcome variable.

*Neighbourhood exposures*

We examined interactions between genetic risk and two neighbourhood characteristics likely to influence BMI: availability of formal PA facilities (number of indoor and outdoor sporting and leisure facilities within a one-kilometre street-network distance of an individual’s home) and fast-food proximity (distance in metres to nearest takeaway/fast-food outlet). Greater neighbourhood availability of PA facilities may influence BMI through increased opportunities for physical activity, while greater distances from home to fast-food outlets may influence BMI by reducing access to fast food26,27. In prior analyses we found both were associated with BMI in the expected direction15. Both exposures were analysed as continuous variables, with higher values of each (more facilities; greater distance to nearest fast-food outlet) representing lower exposure. Due to the positively skewed distribution of these variables, number of PA facilities was capped at 15 (<1% recoded from >15) and distance to nearest fast-food outlet was log transformed (base 10) such that regression coefficients were interpreted as the mean difference in BMI associated with a 10-fold increase in distance to nearest fast-food outlet e.g. 100 metres to one kilometre. In the UKBUMP dataset only fast-food proximity measures are present, and although there is evidence that alternate measures of the food environment (e.g. count of fast-food facilities; relative density of healthy and unhealthy stores) may be superior to proximity measures28, the two have been shown to be correlated in the UK29.

*Genetic risk scores and individual SNPs*

A recent genome-wide association study (GWAS) identified 97 SNPs associated with BMI30. Of these, 77 SNPs were identified in a primary meta-analysis of studies of individuals of European descent, and a further 20 SNPs from secondary meta-analyses of studies of regional, sex-stratified or non-European-descent populations. Of the 97 SNPs, one (rs12016871) was unavailable in UK Biobank. In a study of UK Biobank participants of White British ancestry, Tyrrell et al31 tested interactions between genetic risk and behavioural exposures using a genetic risk score (GRS) derived only from the SNPs identified in the primary meta-analysis. They excluded a further six SNPs on the basis of linkage disequilibrium with other SNPs (rs17001654, rs2075650 and rs9925964) and possible pleiotropy (rs11030104, rs3888190, rs13107325), both of which may produce bias in associations between the genetic risk score and the outcome, and in interaction analyses32. Here we apply those restrictions, but include one additional SNP identified in the GWAS that has become available (rs2033529), giving a total of 70 SNPs. We also constructed an alternative GRS including additional SNPs identified in the secondary meta-analyses, using 90 SNPs in total. Full lists of the SNPs included in each GRS are provided in Supplementary Table 1.

The GRSs were constructed by summing the number of BMI-increasing alleles across the set of 70 or 90 loci, and weighting the allele count at each SNP by its published effect size30. Thirty-eight percent of the sample had a missing genotype for at least one SNP in the 70-SNP GRS (74% missing one; 18% missing two) and 50% were missing genotype data for at least one SNP in the 90-SNP GRS (66% missing one; 23% missing two). To maximise the available sample for analyses, we imputed missing genotypes using the mean allele count for a given SNP within quintiles of BMI. We only imputed data for individuals missing data for a maximum of two SNPs. The remaining 3-6% of the sample with missing genotypes for three or more SNPs were excluded.

From the literature we identified individual SNPs with a well-established link to obesity and the largest published effect sizes (rs1558902 rs6567160 rs13021737, markers of the *FTO*, *MC4R* and *TMEM18* genes respectively)1,30, and three SNPs recently linked to physical activity (rs13078960, rs10938397 and rs7141420, markers of *CADM2*, *GNPDA2* *NRXN3*)33,34. We tested for interactions between the number of BMI-increasing alleles (0, 1 or 2) at each of these loci, and each neighbourhood variable.

*Covariates*

Models were adjusted for potential confounding by age, sex, educational attainment, household income, employment status, area deprivation (Townsend score), urban/non-urban status, and neighbourhood residential density and mutually adjusted for the other neighbourhood exposure. We also corrected for population stratification by adjusting for ten UK Biobank-provided genetic ancestry principal components from a genome-wide PCA of UK Biobank’s genetic data25.

*Statistical analysis & analytic sample*

Accounting for the nested structure of the data (individuals within assessment areas), we used mixed effects models with a random coefficient for the neighbourhood exposure and assuming an unstructured variance/covariance matrix. Models included an interaction term between the neighbourhood exposure and the genetic risk score, with both analysed as continuous variables. BMI difference per unit change in the exposure was estimated for each quintile of genetic risk. The P value for the additive interaction term was interpreted as strength of evidence of effect modification. The marginal predicted values of BMI associated with different levels of each neighbourhood exposure from these models were plotted for the top and bottom quintile of genetic risk, to visualise observed effect heterogeneity according to genetic risk. A complete case analysis was used, restricted to UK Biobank participants of White British ancestry (defined by concordant self-report and PCA results for White British/Caucasian ancestry) for the primary analyses because the smaller GRS was limited to SNPs associated with BMI in analyses of individuals with European ancestry. Sample sizes for the 70-SNP and 90-SNP analyses were 332,174 and 326,698 respectively. Sample sizes for the analysis of GxE interactions with individual SNPs varied according to the extent of missing data at each locus, and are reported in Table 3. Analysis was performed using Stata SE v14.2 (Stata Corp, Texas USA).

*Sensitivity analyses*

As the 90-SNP GRS included SNPs associated with BMI in populations of non-European descent, we undertook a sensitivity analysis which tested for an interaction with the 90-SNP GRS in a sample unrestricted by ethnicity to test generalisability to a more ethnically diverse population.

Finally, although weighting of the polygenic risk scores is appropriate due to the varying degree to which each SNP is associated with BMI, we performed sensitivity analyses using an unweighted version of each GRS. Evidence of a GxE interaction using unweighted scores is expected to be weaker, due to dilution of the effects of the more influential SNPs.

*Ethics*

UK Biobank has ethical approval from the North West Multi-centre Research Ethics Committee (reference 16/NW/0274), the Patient Information Advisory Group (PIAG), and the Community Health Index Advisory Group (CHIAG). Additional ethical approval for the specific study was obtained from the London School of Hygiene and Tropical Medicine’s Research Ethics Committee in September 2016 (reference 11897).

**RESULTS**

The sample was 52.2% female, with a mean age of 56.5 years (range 40-70 years at baseline). Mean BMI was 27.4 kg/m2 (SD=4.7), median distance to nearest fast-food outlet was 1170 metres and median number of PA facilities within one kilometre of home was one. Sample characteristics are summarised in Table 1.

Using the two alternative weighted genetic risk scores, we observed evidence of an interaction between fast-food proximity and genetic risk (P=0.017 for the 70-SNP GRS, P=0.026 for the 90-SNP GRS). The magnitude of the estimated effect between fast-food proximity and BMI was small at all levels of genetic risk, but increased as genetic risk increased. In the highest quintile of genetic risk of obesity, each 10-fold increase in distance to the nearest fast-food store was associated with a 0.204kg/m2 lower mean BMI (95%CI: -0.339,-0.068), which was more than twice the magnitude of association in the lowest risk quintile (β=-0.078; 95%CI: -0.214,0.057) (Table 2; Figures 1 and 2).

There was less evidence that the association between availability of PA facilities and BMI was modified by genetic risk. The magnitude of the association between number of formal PA facilities within 1km of home and BMI was similar at all levels of genetic risk, and while effect estimates did increase slightly with increasing genetic risk, differences between risk groups were small with weak evidence of interaction for the 70-SNP GRS (P=0.206) and 90-SNP GRS (P=0.195). For both environmental exposures, the results obtained from the two different weighted GRSs were substantively identical (Table 2).

Examination of interactions between neighbourhood variables and specific SNPs revealed strong evidence of one interaction: among people with higher risk allele counts at the marker of *MC4R*, which encodes the melanocortin-4 receptor previously shown to be important in the regulation of food intake, living nearer to a fast-food store was more closely associated with higher BMIs than it was among people with fewer risk alleles at this locus (Pinteraction=0.009, Table 3; Figure 3). Some evidence of an interaction between fast-food proximity and rs1558902, the marker of the *FTO* gene (P=0.067), where again the higher risk group showed a stronger association between fast-food proximity and BMI was observed. We also observed some evidence of a GxE interaction between the availability of PA facilities and rs13021737 (in the *TMEM18* gene) (P=0.076). In this case, increased genetic risk attenuated the association between availability of PA facilities and BMI (Figure 3).

In sensitivity analyses, interactions between fast-food proximity and genetic risk were – as expected – weaker when the genetic risk scores were not weighted by the effect sizes of the component SNPs, with mean differences in BMI more similar across levels of genetic risk than we observed using the weighted score (Supplementary Table 1). Expanding the sample to include non-White ethnicities, we observed slightly increased P-values for the interaction terms but otherwise no substantive difference from the primary analysis (Table 4).

**DISCUSSION**

In UK Biobank we found evidence that genetic risk of obesity modifies sensitivity to the neighbourhood food environment, though effects are small. We found that people at higher genetic risk of obesity have higher average BMI the closer they live to a fast-food outlet, whereas for those at low genetic risk of obesity, distance to the nearest fast-food outlet does not appear to be associated with BMI. In contrast, an overall negative association between neighbourhood availability of PA facilities and BMI varies very little across levels of polygenic risk.

The observed gene-environment interaction for fast-food proximity using polygenic risk scores was supported by stronger evidence of an interaction between fast-food proximity and a specific SNP near *MC4R*, a gene known to be involved in regulation of food intake35. Previous research has linked *MC4R* specifically to binge eating36 although this remains contested37. We also observed some evidence of a possible interaction with a SNP marker of *FTO*, a gene with well-established links to obesity. While *FTO* has long been recognised as an obesity-associated locus, and has been implicated in central nervous system regulation of appetite, its exact function remains poorly understood1. In a study of gene-diet interactions, genetic risk scores for BMI were found to be associated with fried food consumption, and, consistent with our results, individual loci in or near both *MC4R* and *FTO* contributed to this38.

Weak evidence for an interaction between genetic risk and the PA environment is consistent with findings from a recent study in adolescents that found that availability of recreation facilities did not contribute to the attenuation by PA of genetic risk of obesity33. While overall genetic risk of obesity did not interact with the PA environment in our study, the weaker association we observed between the availability of PA facilities and BMI in those with more risk alleles at the *TMEM18* locus suggests that some specific SNPs might. Further examination of other SNPs are warranted. Lack of interaction with specific SNPs might be explained by the pathways they influence being less sensitive to environmental exposures. As the functional pathways by which most BMI-associated loci influence BMI remain poorly understood, it is difficult to speculate further.

Stronger evidence for interactions with specific SNPs highlights the lack of specificity of polygenic risk scores. While useful in exploratory studies, grouping all SNPs statistically associated with a complex phenotype such as BMI into a single score, regardless of the function of the genes they represent, may dilute or obscure important interactions. Scores based on known or putative biological mechanisms may prove more valuable, particularly for elucidating causal relationships. We observed almost identical results for both the 70-SNP and 90-SNP genetic risk scores, which suggests that the additional 20 SNPs contribute substantially more to these GxE interactions. Extending analysis to all ethnic groups resulted in similar findings suggesting results are broadly generalisable to a more diverse UK population, and/or that any interaction between the neighbourhood environment and the additional 20 SNPs was negligible in both populations.

We have reported elsewhere that the main association between fast-food proximity and BMI in UK Biobank may be attenuated due to measurement error in the exposure15. Others have recently improved on the measure and found stronger associations in a regional sub-sample39. Also, proximity measures of the fast-food environment may produce smaller effect sizes than count or density measures28 and that measures of relative densities of healthy/unhealthy food stores may better capture food environment exposure40. However, in this study we were limited by the available measures. As main effect sizes are relatively small, even the reasonably strong interaction effects we observed translate to small differences between high and low risk groups. Given the likely measurement error and the distal and complex nature of the relationships under investigation, detecting even weak associations and small differences might point to potentially important processes. Here we examined only two characteristics of neighbourhood environments; others may also interact with genetic risk. For example, GxE interactions have recently been reported for neighbourhood walkability and obesity11, and neighbourhood deprivation and BMI10. Given that unhealthy characteristics of neighbourhoods often cluster together41, the combined effects of multiple ‘obesogenic’ features on those at increased genetic risk of obesity may be substantial.

Our findings provide evidence for a potentially important GxE interaction, but further confirmatory studies are required. Geographical genetic structure in the sample remains a risk, even after adjustment for ancestry components and geography. Such structure may induce spurious associations with polygenic risk scores42. GxE interactions are also sensitive to the scaling of environmental variables, and the power to detect a GxE interaction can depend on the main effect sizes, and distribution and measurement quality of the genetic and environmental variables43. It is important these analyses are replicated in other samples at lower risk of these biases.

It is widely accepted that environmental factors are important in explaining the recent rise in the global prevalence of overweight and obesity. In this study, we find evidence that those at higher genetic risk of obesity may more sensitive to exposure to the residential fast-food environment. Ensuring that neighbourhood residential environments are designed to promote a healthy weight may be particularly important for those with genetic susceptibility for obesity.

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**Table 1. Characteristics of total sample and top and bottom quintile of 70-SNP genetic risk score**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **70-SNP genetic risk score** | | **Total sample** |
|  | Quintile 1  (lowest risk of obesity) | Quintile 5  (highest risk of obesity) |
| Total number of participants | 64965 | 67760 | 332174 |
|  |  |  |  |
| BMI (kg/m2) (mean, SD) | 27.0 (4.5) | 27.8 (4.9) | 27.4 (4.7) |
|  |  |  |  |
| Distance to nearest fast-food outlet (m) (median, IQR) | 1168 (634 - 2294) | 1177 (636 - 2289) | 1170 (630-2302) |
|  |  |  |  |
| Number of PA facilities within 1km of home address (median, IQR) | 1 (0 - 3) | 1 (0 - 3) | 1 (0 - 3) |
|  |  |  |  |
| Age (mean, SD) | 56.5 (8.0) | 56.6 (8.0) | 56.5 (8.0) |
|  |  |  |  |
| Sex (female) | 34080 (52.5%) | 35200 (52.0%) | 173417 (52.2%) |
|  |  |  |  |
| Income |  |  |  |
| Less than 18,000 | 14440 (22.2%%) | 15284 (22.6%) | 73910 (22.3%) |
| 18,000 to 30,999 | 16713 (25.7%) | 17638 (26.0%) | 86200 (26.0%) |
| 31,000 to 51,999 | 17068 (26.3%) | 17890 (26.4%) | 87952 (26.5%) |
| 52,000 to 100,000 | 13342 (20.5%) | 13582 (20.0%) | 67313 (20.3%) |
| Greater than 100,000 | 3402 (5.2%) | 3366 (5.0%) | 16799 (5.1%) |
|  |  |  |  |
| Education |  |  |  |
| College or University degree | 21439 (33.0%) | 22000 (32.5%) | 109165 (32.9%) |
| A levels/AS levels or equivalent | 7604 (11.7%) | 7979 (11.8%) | 38706 (11.7%) |
| O levels/GCSEs or equivalent | 14644 (22.5%) | 15092 (22.3%) | 74353 (22.4%) |
| CSEs or equivalent | 3652 (5.6%) | 3795 (5.6%) | 18541 (5.6%) |
| NVQ or HND or HNC or equivalent | 4388 (6.8%) | 4587 (6.8%) | 22711 (6.8%) |
| Other professional qualifications | 3335 (5.1%) | 3414 (5.0%) | 16824 (5.1%) |
| None of the above | 9903 (15.2%) | 10893 (16.1%) | 51874 (15.6%) |
|  |  |  |  |
| Employment status |  |  |  |
| Paid employment or self-employed | 38689 (59.6%) | 40106 (59.2%) | 197572 (59.5%) |
| Retired | 21405 (33.0%) | 22720 (33.5%) | 110167 (33.2%) |
| Unable to work | 1846 (2.8%) | 1935 (2.9%) | 9372 (2.8%) |
| Unemployed | 827 (1.3%) | 853 (1.3%) | 4197 (1.3%) |
| Home duties/carer/student/other | 2198 (3.4%) | 2146 (3.2%) | 10866 (3.3%) |
|  |  |  |  |
| Urbanicity (% urban dwelling) | 55155 (84.9%) | 57733 (85.2%) | 282046 (84.9%) |
|  |  |  |  |
| Area deprivation† (mean, SD) | -1.6 (2.9) | -1.6 (2.9) | -1.6 (2.9) |
|  |  |  |  |
| Residential density\* (median, IQR) | 1796 (1043 - 2920) | 1795 (1048 - 2910) | 1798 (1044 - 2918) |

† 2001 Townsend index score

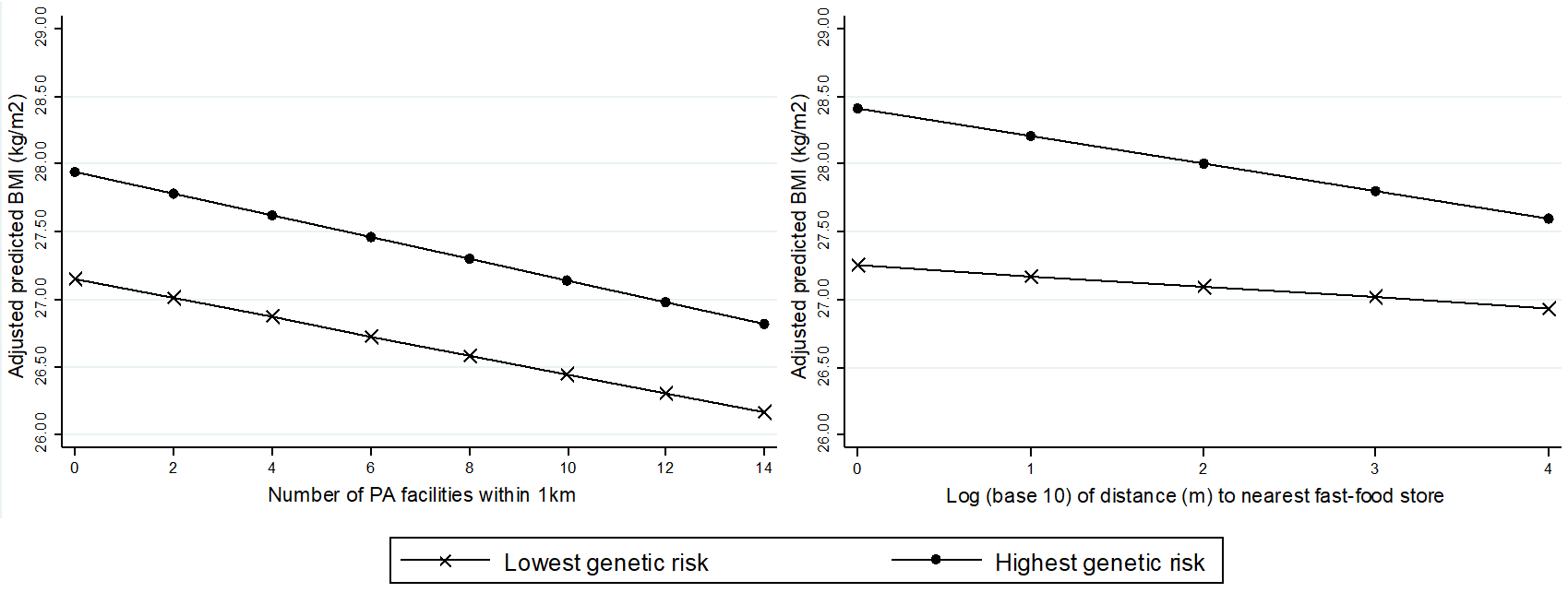
\* Residential address points per 1km street-network buffer**Table 2. Associations between neighbourhood variables and BMI, by quintile of genetic risk based on 70-SNP and 90-SNP risk scores**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | ***70-SNP GRS (n=332,174)*** | | | ***90-SNP GRS (n=326,698)*** | | |
|  | Quintile of genetic risk | Mean BMI difference for unit increase in neighbourhood exposure | P-interaction | Quintile of genetic risk | Mean BMI difference for unit increase in neighbourhood exposure | P-interaction |
| **Fast-food proximitya,b**  (log (base 10) of distance (m) to nearest fast-food outlet) | Q1 | -0.078 (-0.214, 0.057) | 0.017 | Q1 | -0.086 (-0.219, 0.048) | 0.026 |
| Q2 | -0.116 (-0.244, 0.011) | Q2 | -0.121 (-0.246, 0.003) |
| Q3 | -0.140 (-0.266, -0.014) | Q3 | -0.144 (-0.266, -0.021) |
| Q4 | -0.164 (-0.291, -0.037) | Q4 | -0.166 (-0.290, -0.042) |
| Q5 | -0.204 (-0.339, -0.068) | Q5 | -0.203 (-0.336, -0.070) |
| **Availability of PA facilitiesa,c**  (beta represents BMI difference for each additional facility) | Q1 | -0.070 (-0.097, -0.044) | 0.206 | Q1 | -0.071 (-0.098, -0.044) | 0.195 |
| Q2 | -0.073 (-0.099, -0.047) | Q2 | -0.074 (-0.100, -0.048) |
| Q3 | -0.075 (-0.101, -0.049) | Q3 | -0.076 (-0.102, -0.050) |
| Q4 | -0.077 (-0.103, -0.051) | Q4 | -0.078 (-0.104, -0.052) |
| Q5 | -0.080 (-0.107, -0.053) | Q5 | -0.081 (-0.108, -0.054) |

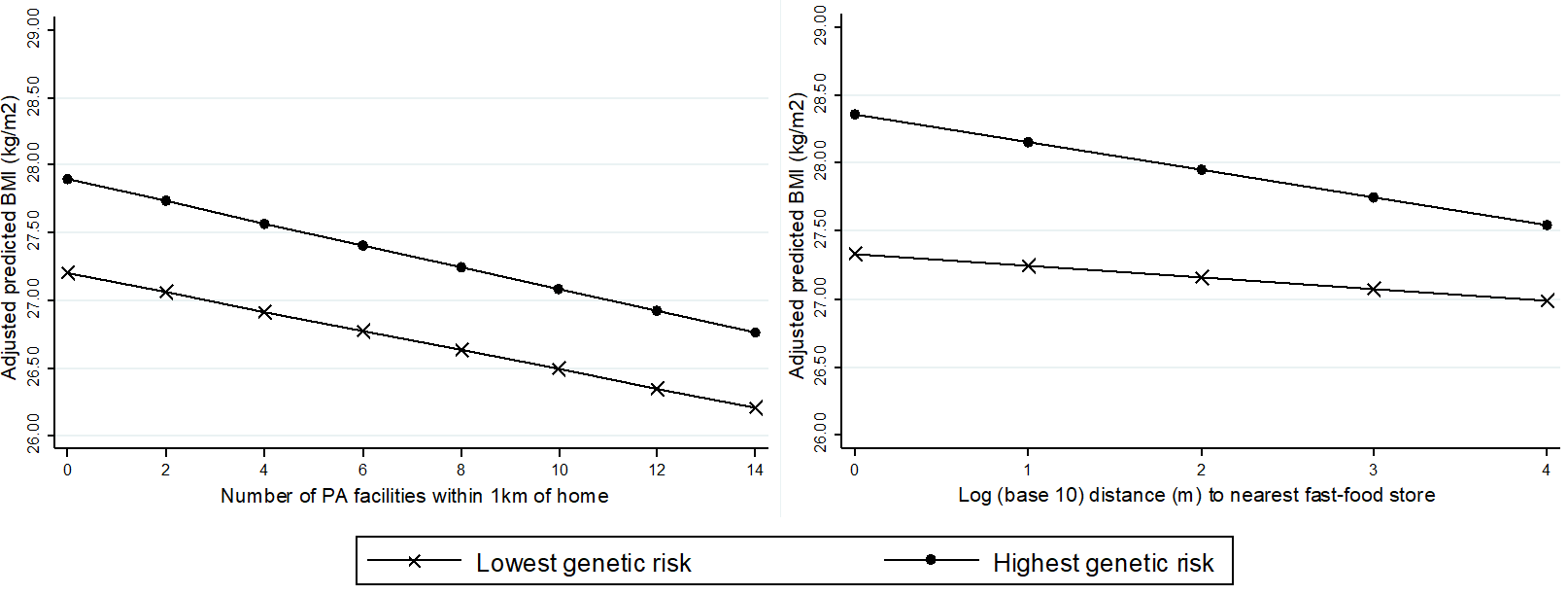
a Regression models were adjusted for age (years), sex (male/female), highest education level attained (Degree; A level or equivalent; O level or equivalent; CSE or equivalent; NVQ/HND/HNC; other professional qualification; none of the above), annual household income (<£18,000; £18,000-£30,999; £31,000-£51,999; £52,000-£100,000; >£100,000), employment status (paid work, retired, unable to work, unemployed, other), area deprivation (Townsend score), urbanicity (urban/non-urban), neighbourhood residential density (count of residential features within a one-km street network buffer of home address, log transformed).

b Also adjusted for availability of PA facilities.

c Also adjusted for fast-food proximity.

****

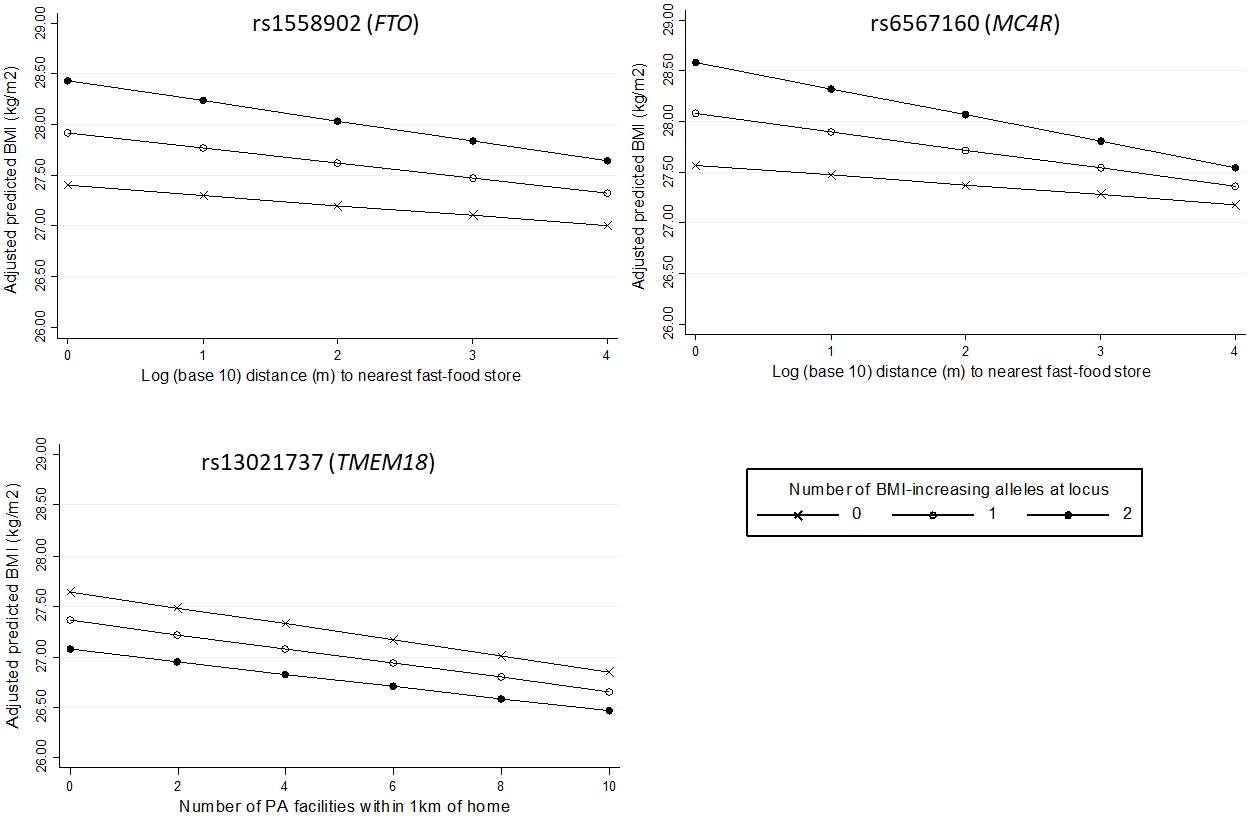
**Figure 1. Association between neighbourhood variables and BMI in the highest and lowest quintiles of genetic risk, based on 70-SNP Genetic Risk Score**

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**Figure 2. Association between neighbourhood variables and BMI in the highest and lowest quintiles of genetic risk, based on 90-SNP Genetic Risk Score**

**Table 3. Association between neighbourhood variables and BMI, testing interaction with number of risk alleles at selected loci**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **rs1558902 *(FTO)*** | | | |
|  | P-interaction | Homozygous low risk  (0 risk alleles) | Heterozygous  (1 risk allele) | Homozygous high risk  (2 risk alleles) |
| **Fast-food proximity (km)** | 0.067 | -0.099 (-0.198, -0.001) | -0.148 (-0.238, -0.059) | -0.197 (-0.305, -0.088) |
| **PA facilities** | 0.933 | -0.077 (-0.104, -0.050) | -0.077 (-0.103, -0.051) | -0.076 (-0.104, -0.049) |
|  | **rs6567160 *(MC4R)*** | | | |
|  | P-interaction | Homozygous low risk  (0 risk alleles) | Heterozygous  (1 risk allele) | Homozygous high risk  (2 risk alleles) |
| **Fast-food proximity** | 0.009 | -0.096 (-0.188, -0.003) | -0.177 (-0.271, -0.083) | -0.258 (-0.386, -0.130) |
| **PA facilities** | 0.606 | -0.078 (-0.104, -0.051) | -0.075 (-0.102, -0.049) | -0.073 (-0.103, -0.043) |
|  | **rs13021737 *(TMEM18)*** | | | |
|  | P-interaction | Homozygous low risk  (0 risk alleles) | Heterozygous  (1 risk allele) | Homozygous high risk  (2 risk alleles) |
| **Fast-food proximity** | 0.993 | -0.135 (-0.226, -0.043) | -0.135 (-0.234, -0.036) | -0.135 (-0.279, 0.008) |
| **PA facilities** | 0.076 | -0.080 (-0.106, -0.053) | -0.071 (-0.098, -0.043) | -0.061 (-0.093, -0.030) |
|  | **rs13078960 *(CADM2)*** | | | |
|  | P-interaction | Homozygous low risk  (0 risk alleles) | Heterozygous  (1 risk allele) | Homozygous high risk  (2 risk alleles) |
| **Fast-food proximity** | 0.114 | -0.159 (-0.252, -0.066) | -0.108 (-0.205, -0.010) | -0.056 (-0.192, 0.081) |
| **PA facilities** | 0.419 | -0.076 (-0.102, -0.049) | -0.079 (-0.106, -0.053) | -0.083 (-0.114, -0.053) |
|  | **rs10938397 *(GNPDA2)*** | | | |
|  | P-interaction | Homozygous low risk  (0 risk alleles) | Heterozygous  (1 risk allele) | Homozygous high risk  (2 risk alleles) |
| **Fast-food proximity** | 0.328 | -0.115 (-0.215, -0.015) | -0.141 (-0.230, -0.052) | -0.167 (-0.274, -0.061) |
| **PA facilities** | 0.694 | -0.076 (-0.102, -0.049) | -0.077 (-0.103, -0.051) | -0.079 (-0.106, -0.051) |
|  | **rs7141420 *(NRXN3)*** | | | |
|  | P-interaction | Homozygous low risk  (0 risk alleles) | Heterozygous  (1 risk allele) | Homozygous high risk  (2 risk alleles) |
| **Fast-food proximity** | 0.520 | -0.152 (-0.257, -0.048) | -0.135 (-0.227, -0.043) | -0.118 (-0.224, -0.012) |
| **PA facilities** | 0.125 | -0.071 (-0.097, -0.044) | -0.077 (-0.102, -0.051) | -0.083 (-0.110, -0.056) |

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**Figure 3. Association between neighbourhood variables and BMI according to number of risk alleles at individual SNPs where P-for-interaction<0.10 (rs1558902 & rs6567160 for fast-food proximity; rs13021737 for availability of PA facilities)**

**Table 4. Results of sensitivity analyses using an expanded sample including observations from UK Biobank participants of non-White ethnicities**

|  |  |  |  |
| --- | --- | --- | --- |
|  | ***90-SNP weighted imputed GRS (N=373,691)*** | | |
|  | Quintile of genetic risk | Mean BMI difference for unit increase in neighbourhood exposure | P-interaction |
| **Fast-food proximity** | Q1 | -0.089 (-0.211, 0.033) | 0.041 |
| (log (base 10) of distance (m) to nearest fast-food outlet) | Q2 | -0.120 (-0.234, -0.007) |
|  | Q3 | -0.139 (-0.251, -0.027) |
|  | Q4 | -0.159 (-0.272, -0.045) |
|  | Q5 | -0.191 (-0.312, -0.069) |
| **Availability of PA facilities** | Q1 | -0.068 (-0.095, -0.041) | 0.220 |
| (number of formal PA facilities within 1km of home address) | Q2 | -0.071 (-0.097, -0.045) |
|  | Q3 | -0.073 (-0.099, -0.047) |
|  | Q4 | -0.074 (-0.100, -0.048) |
|  | Q5 | -0.077 (-0.104, -0.050) |

**Supplementary Table 1. SNPs included in each polygenic risk score**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | Chr | Position | Gene | BMI-increasing allele | Effect size  (β coefficient per effect allele, SD units of BMI) | Included in 70-SNP risk score | Included in 90-SNP risk score | Reason for exclusion30,31 |
| rs1558902 | 16 | 52,361,075 | FTO | A | 0.0818 | Yes | Yes |  |
| rs17024393 | 1 | 109,956,211 | GNAT2 | C | 0.0658 | Yes | Yes |  |
| rs13021737 | 2 | 622,348 | TMEM18 | G | 0.0601 | Yes | Yes |  |
| rs6567160 | 18 | 55,980,115 | MC4R | C | 0.0556 | Yes | Yes |  |
| rs11847697 | 14 | 29,584,863 | PRKD1 | T | 0.0492 | Yes | Yes |  |
| rs16851483 | 3 | 142,758,126 | RASA2 | T | 0.0483 | Yes | Yes |  |
| rs543874 | 1 | 176,156,103 | SEC16B | G | 0.0482 | Yes | Yes |  |
| rs13107325 | 4 | 103,407,732 | SLC39A8 | T | 0.0477 | No | No | Possible pleiotropy |
| rs1516725 | 3 | 187,306,698 | ETV5 | C | 0.0451 | Yes | Yes |  |
| rs2207139 | 6 | 50,953,449 | TFAP2B | G | 0.0447 | Yes | Yes |  |
| rs11030104 | 11 | 27,641,093 | BDNF | A | 0.0414 | No | No | Possible pleiotropy |
| rs12446632 | 16 | 19,842,890 | GPRC5B | G | 0.0403 | Yes | Yes |  |
| rs10938397 | 4 | 44,877,284 | GNPDA2 | G | 0.0402 | Yes | Yes |  |
| rs7899106 | 10 | 87,400,884 | GRID1 | G | 0.0395 | Yes | Yes |  |
| rs2287019 | 19 | 50,894,012 | QPCTL | C | 0.0360 | Yes | Yes |  |
| rs11727676 | 4 | 145,878,514 | HHIP | T | 0.0358 | Yes | Yes |  |
| rs16907751 | 8 | 81,538,012 | ZBTB10 | C | 0.0350 | No | Yes | Identified in secondary meta-analyses only |
| rs3101336 | 1 | 72,523,773 | NEGR1 | C | 0.0334 | Yes | Yes |  |
| rs12429545 | 13 | 53,000,207 | OLFM4 | A | 0.0334 | Yes | Yes |  |
| rs2245368 | 7 | 76,446,079 | DTX2P1 | C | 0.0317 | Yes | Yes |  |
| rs7138803 | 12 | 48,533,735 | BCDIN3D | A | 0.0315 | Yes | Yes |  |
| rs16951275 | 15 | 65,864,222 | MAP2K5 | T | 0.0311 | Yes | Yes |  |
| rs3888190 | 16 | 28,796,987 | ATP2A1 | A | 0.0309 | No | No | Possible pleiotropy |
| rs11191560 | 10 | 104,859,028 | NT5C2 | C | 0.0308 | Yes | Yes |  |
| rs10182181 | 2 | 25,003,800 | ADCY3 | G | 0.0307 | Yes | Yes |  |
| rs11057405 | 12 | 121,347,850 | CLIP1 | G | 0.0307 | Yes | Yes |  |
| rs17001654 | 4 | 77,348,592 | SCARB2 | G | 0.0306 | No | No | Linkage disequilibrium |
| rs12016871 | 13 | 26,915,782 | MTIF3 | T | 0.0298 | No | No | Unavailable in UK Biobank |
| rs13078960 | 3 | 85,890,280 | CADM2 | G | 0.0297 | Yes | Yes |  |
| rs3810291 | 19 | 52,260,843 | ZC3H4 | A | 0.0283 | Yes | Yes |  |
| rs13191362 | 6 | 162,953,340 | PARK2 | A | 0.0277 | Yes | Yes |  |
| rs3817334 | 11 | 47,607,569 | MTCH2 | T | 0.0262 | Yes | Yes |  |
| rs2112347 | 5 | 75,050,998 | POC5 | T | 0.0261 | Yes | Yes |  |
| rs2075650 | 19 | 50,087,459 | TOMM40 | A | 0.0258 | No | No | Linkage disequilibrium |
| rs17094222 | 10 | 102,385,430 | HIF1AN | C | 0.0249 | Yes | Yes |  |
| rs10968576 | 9 | 28,404,339 | LINGO2 | G | 0.0249 | Yes | Yes |  |
| rs2121279 | 2 | 142,759,755 | LRP1B | T | 0.0245 | Yes | Yes |  |
| rs12566985 | 1 | 74,774,781 | FPGT | G | 0.0242 | Yes | Yes |  |
| rs7141420 | 14 | 78,969,207 | NRXN3 | T | 0.0235 | Yes | Yes |  |
| rs7903146 | 10 | 114,748,339 | TCF7L2 | C | 0.0234 | Yes | Yes |  |
| rs13201877 | 6 | 137,717,234 | IFNGR1 | G | 0.0233 | No | Yes | Identified in secondary meta-analyses only |
| rs10132280 | 14 | 24,998,019 | STXBP6 | C | 0.0230 | Yes | Yes |  |
| rs1016287 | 2 | 59,159,129 | LINC01122 | T | 0.0229 | Yes | Yes |  |
| rs657452 | 1 | 49,362,434 | AGBL4 | A | 0.0227 | Yes | Yes |  |
| rs758747 | 16 | 3,567,359 | NLRC3 | T | 0.0225 | Yes | Yes |  |
| rs17405819 | 8 | 76,969,139 | HNF4G | T | 0.0224 | Yes | Yes |  |
| rs205262 | 6 | 34,671,142 | C6orf106 | G | 0.0221 | Yes | Yes |  |
| rs7599312 | 2 | 213,121,476 | ERBB4 | G | 0.0220 | Yes | Yes |  |
| rs11165643 | 1 | 96,696,685 | PTBP2 | T | 0.0218 | Yes | Yes |  |
| rs12286929 | 11 | 114,527,614 | CADM1 | G | 0.0217 | Yes | Yes |  |
| rs7243357 | 18 | 55,034,299 | GRP | T | 0.0217 | Yes | Yes |  |
| rs12401738 | 1 | 78,219,349 | FUBP1 | A | 0.0211 | Yes | Yes |  |
| rs17203016 | 2 | 207,963,763 | CREB1 | G | 0.0210 | No | Yes | Identified in secondary meta-analyses only |
| rs4256980 | 11 | 8,630,515 | TRIM66 | G | 0.0209 | Yes | Yes |  |
| rs11126666 | 2 | 26,782,315 | KCNK3 | A | 0.0207 | Yes | Yes |  |
| rs12885454 | 14 | 28,806,589 | PRKD1 | C | 0.0207 | Yes | Yes |  |
| rs2650492 | 16 | 28,240,912 | SBK1 | A | 0.0207 | Yes | Yes |  |
| rs1167827 | 7 | 75,001,105 | HIP1 | G | 0.0202 | Yes | Yes |  |
| rs9914578 | 17 | 1,951,886 | SMG6 | G | 0.0201 | No | Yes | Identified in secondary meta-analyses only |
| rs2365389 | 3 | 61,211,502 | FHIT | C | 0.0200 | Yes | Yes |  |
| rs2176598 | 11 | 43,820,854 | HSD17B12 | T | 0.0198 | Yes | Yes |  |
| rs1460676 | 2 | 164,275,935 | FIGN | C | 0.0197 | No | Yes | Identified in secondary meta-analyses only |
| rs2820292 | 1 | 200,050,910 | NAV1 | C | 0.0195 | Yes | Yes |  |
| rs17724992 | 19 | 18,315,825 | PGPEP1 | A | 0.0194 | Yes | Yes |  |
| rs9925964 | 16 | 31,037,396 | KAT8 | A | 0.0192 | No | No | Linkage disequilibrium |
| rs1000940 | 17 | 5,223,976 | RABEP1 | G | 0.0192 | Yes | Yes |  |
| rs2033732 | 8 | 85,242,264 | RALYL | C | 0.0192 | Yes | Yes |  |
| rs9641123 | 7 | 93,035,668 | CALCR | C | 0.0191 | No | Yes | Identified in secondary meta-analyses only |
| rs2033529 | 6 | 40,456,631 | TDRG1 | G | 0.0190 | Yes | Yes |  |
| rs9400239 | 6 | 109,084,356 | FOXO3 | C | 0.0188 | Yes | Yes |  |
| rs3849570 | 3 | 81,874,802 | GBE1 | A | 0.0188 | Yes | Yes |  |
| rs1928295 | 9 | 119,418,304 | TLR4 | T | 0.0188 | Yes | Yes |  |
| rs6091540 | 20 | 50,521,269 | ZFP64 | C | 0.0188 | No | Yes | Identified in secondary meta-analyses only |
| rs9374842 | 6 | 120,227,364 | LOC285762 | T | 0.0187 | No | Yes | Identified in secondary meta-analyses only |
| rs6804842 | 3 | 25,081,441 | RARB | G | 0.0185 | Yes | Yes |  |
| rs29941 | 19 | 39,001,372 | KCTD15 | G | 0.0182 | Yes | Yes |  |
| rs12940622 | 17 | 76,230,166 | RPTOR | G | 0.0182 | Yes | Yes |  |
| rs7164727 | 15 | 70,881,044 | LOC100287559 | T | 0.0180 | No | Yes | Identified in secondary meta-analyses only |
| rs4740619 | 9 | 15,624,326 | C9orf93 | T | 0.0179 | Yes | Yes |  |
| rs1528435 | 2 | 181,259,207 | UBE2E3 | T | 0.0178 | Yes | Yes |  |
| rs11583200 | 1 | 50,332,407 | ELAVL4 | C | 0.0177 | Yes | Yes |  |
| rs3736485 | 15 | 49,535,902 | DMXL2 | A | 0.0176 | Yes | Yes |  |
| rs1441264 | 13 | 78,478,920 | MIR548A2 | A | 0.0175 | No | Yes | Identified in secondary meta-analyses only |
| rs6477694 | 9 | 110,972,163 | EPB41L4B | C | 0.0174 | Yes | Yes |  |
| rs10733682 | 9 | 128,500,735 | LMX1B | A | 0.0174 | Yes | Yes |  |
| rs11688816 | 2 | 62,906,552 | EHBP1 | G | 0.0172 | Yes | Yes |  |
| rs9540493 | 13 | 65,103,705 | MIR548X2 | A | 0.0172 | No | Yes | Identified in secondary meta-analyses only |
| rs2080454 | 16 | 47,620,091 | CBLN1 | C | 0.0168 | No | Yes | Identified in secondary meta-analyses only |
| rs1808579 | 18 | 19,358,886 | C18orf8 | C | 0.0167 | Yes | Yes |  |
| rs977747 | 1 | 47,457,264 | TAL1 | T | 0.0167 | No | Yes | Identified in secondary meta-analyses only |
| rs6465468 | 7 | 95,007,450 | ASB4 | T | 0.0166 | No | Yes | Identified in secondary meta-analyses only |
| rs2836754 | 21 | 39,213,610 | ETS2 | C | 0.0164 | No | Yes | Identified in secondary meta-analyses only |
| rs7239883 | 18 | 38,401,669 | LOC284260 | G | 0.0164 | No | Yes | Identified in secondary meta-analyses only |
| rs7715256 | 5 | 153,518,086 | GALNT10 | G | 0.0163 | No | Yes | Identified in secondary meta-analyses only |
| rs4787491 | 16 | 29,922,838 | INO80E | G | 0.0159 | No | Yes | Identified in secondary meta-analyses only |
| rs492400 | 2 | 219,057,996 | USP37 | C | 0.0158 | No | Yes | Identified in secondary meta-analyses only |
| rs2176040 | 2 | 226,801,046 | LOC646736 | A | 0.0141 | No | Yes | Identified in secondary meta-analyses only |

Note: This table is derived from Locke et al (2015), with additional information from Tyrrell et al (2017).

**Supplementary Table 2. Results of sensitivity analyses using unweighted genetic risk scores**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | ***70-SNP unweighted imputed GRS (n=332,174)*** | | | | ***90-SNP unweighted imputed GRS (n=326,698)*** | | |
|  | Quintile of genetic risk | | Mean BMI difference for unit increase in neighbourhood exposure | P-interaction | Quintile of genetic risk | | Mean BMI difference for unit increase in neighbourhood exposure | P-interaction |
| **Fast-food proximity** | Q1 | | -0.099 (-0.234, 0.036) | 0.091 | Q1 | | -0.107 (-0.240, 0.026) | 0.151 |
|  | Q2 | | -0.127 (-0.254, 0.000) | Q2 | | -0.130 (-0.255, -0.006) |
|  | Q3 | | -0.142 (-0.268, -0.016) | Q3 | | -0.144 (-0.267, -0.021) |
|  | Q4 | | -0.157 (-0.285, -0.030) | Q4 | | -0.159 (-0.283, -0.035) |
|  | Q5 | | -0.185 (-0.321, -0.049) | Q5 | | -0.183 (-0.316, -0.049) |
| **PA facilities** | Q1 | | -0.070 (-0.096, -0.043) | 0.126 | Q1 | | -0.070 (-0.097, -0.043) | 0.117 |
|  | Q2 | | -0.073 (-0.099, -0.047) | Q2 | | -0.073 (-0.100, -0.047) |
|  | Q3 | | -0.075 (-0.101, -0.050) | Q3 | | -0.076 (-0.102, -0.050) |
|  | Q4 | | -0.077 (-0.103, -0.051) | Q4 | | -0.078 (-0.104, -0.052) |
|  | Q5 | | -0.081 (-0.108, -0.054) | Q5 | | -0.082 (-0.109, -0.055) |