nature human behaviour

SUPPLEMENTARY INFORMATION

https://doi.org/10.1038/s41562-019-0757-5

In the format provided by the authors and unedited.

Genetic correlates of social stratification in Great Britain

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GENETIC CORRELATES OF SOCIAL STRATIFICATION IN GREAT BRITAIN (ABDELLAOUI ET AL, 2019)

SUPPLEMENTARY MATERIAL

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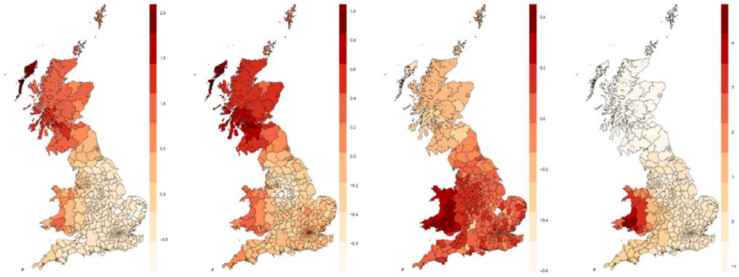
General Summary & Frequently Asked Questions

General Summary

We conducted a study on the geographic distributions of human DNA differences in Great Britain. Human DNA variation is not randomly distributed across geographic regions. Regional differences in human DNA have been long known to reflect ancestry differences from the distant past (see Figure), where different parts of Britain were settled by people from different parts of Europe. These regional ancestry differences were maintained because, for most of human history, people tended to spend their life in the same region and have children with people from the same region. In addition to DNA differences that reflect distant ancestry, there are also DNA differences that have been associated with heritable human characteristics. We investigated the extent to which DNA variants that have previously been found to influence heritable human characteristics also show regional differences. We looked at genetic variation associated with physical health, mental health, substance use, personality, BMI, reproduction, height, and educational attainment.



The largest patterns of genetic variation reflecting (distant) ancestry differences

More than the half of the traits we investigated showed regional differences at a genetic level. This is mostly the case for genetic variants that are associated with educational attainment, i.e., how many years a person spends in education. Genetic variants identified in other studies to be associated with higher educational attainment are more common in richer areas. Genetic variants associated with lower educational attainment are more common in regions that faced economic challenges, such as coal mining regions. It is not exactly clear yet why these genetic variants are associated with educational attainment. It may be through underlying traits such as cognitive ability, industriousness, and persistence. Part of the associations however reflects that genetic variants associated with higher educational attainment are more common in children born to parents with greater levels of education, who tend to have more resources to provide better learning environments for their children. The regional differences in genes associated with educational attainment are not due to the ancestry differences from the distant past. These geographical differences are more in line with recent selective migration of people within Great Britain.

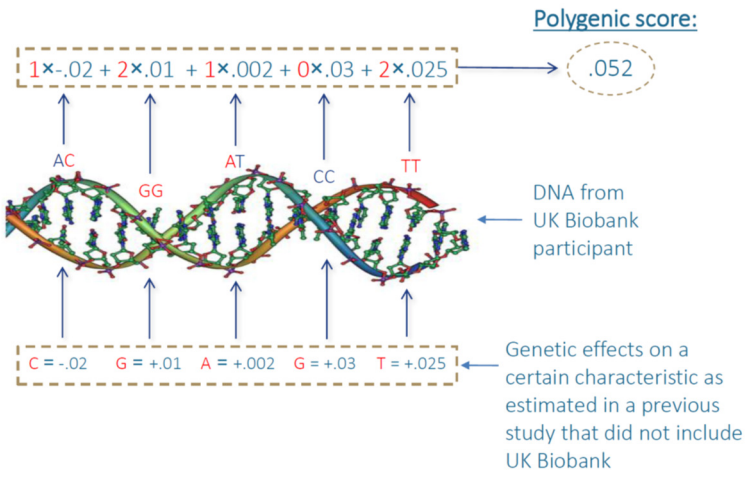
At the beginning of the Industrial Revolution, laborers and farmers left rural areas to work in regions with many industrial jobs, such as coal mining regions. As the coal industry declined in the 20th century, these areas have become among the poorest regions in Great Britain with high unemployment rates. We find that, today, people who migrate *out* of coal mining regions to other areas in Great Britain, on average, carry more genetic variants associated with higher educational attainment than is typical for people who live in Great Britain. In other words, people seem more likely to leave poorer regions if they have a higher genetic predisposition for educational attainment. These migration flows are associated with a visible increase in regional differences in genetic variants associated with educational attainment and economic success. If these demographic processes continue, the inequalities we observe may grow larger over time. Besides lower economic outcomes, people living in these poorer regions also have greater risk for health problems like obesity and diabetes. The regional differences in health outcomes are more in line with regional differences in genes associated with educational attainment than with genes associated with the health outcomes themselves. This suggests that there are important *environmental* influences that cause people from regions with lower education levels to have worse health outcomes.

WHY DID WE DO THIS STUDY?

Understanding what drives the geographic distribution of DNA is important for multiple reasons. Education, wealth, and health are unevenly distributed within countries. We have known for many decades that *individual* differences in these outcomes are partly caused by environmental influences and partly by genetic influences, but it is not well understood why there are *regional* differences in these outcomes. By looking at the geographic distribution of genetic variants that are associated with socio-economic and health outcomes and comparing it to the actual regional differences in these outcomes, we can try to better understand the roots of these regional differences. In addition, geographic clustering of genetic variants can violate assumptions of several study designs that are widely used in physical and mental health research. Therefore, understanding the geographic distribution of genetic variants is vital in improving genetically informed health research. The UK Biobank provided a unique data resource that could address these questions in a way that has not been possible previously.

HOW WAS THE STUDY CONDUCTED?

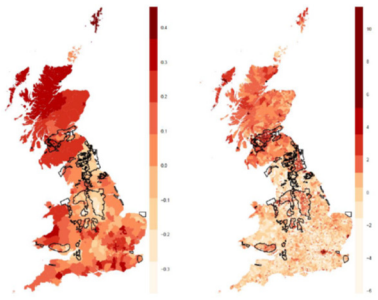
The participants of this study come from UK Biobank: approximately 450,000 participants of European descent that were recruited throughout Great Britain. We used about 1.2 million genetic variants to compute **polygenic scores** for these British participants for a wide range of characteristics. A polygenic score is an estimate of someone's genetic predisposition for a certain characteristic. We know from previous studies that there are many genetic variants that influence socio-economic and health outcomes. These studies have estimated the separate effects of millions of genetic variants on these outcomes. We used genetic effects estimated in these previous studies to compute the polygenic scores for UK Biobank participants. This was done by simply summing all the effects of all the individual genetic variants carried by a participant (see Figure). We computed polygenic scores for 33 socio-economic and physical and mental health outcomes and looked at whether the polygenic scores showed regional differences after controlling for the older genetic ancestry differences.



Note that these polygenic scores reflect only a fraction of all genetic influences and that all these characteristics are also influenced by environmental factors. We would therefore not recommend that people use the currently available polygenic scores for risk prediction at an individual level. However, these scores can be very useful to understand larger patterns within populations in scientific research. The polygenic score used in this study explains about 4% of the British* individual differences in educational attainment. This is just a fraction of the total genetic influence, which has been estimated to explain between 20% and 40% of individual differences in educational attainment. Despite the relatively small amount of variance captured by the polygenic scores, we are able to detect small differences across regions because of the exceptionally large size of the UK Biobank dataset.

**This polygenic score was computed using estimated genetic effects on educational attainment obtained from non-British European populations.*

WHAT ARE THE MAIN FINDINGS?



Educational Attainment Polygenic Score

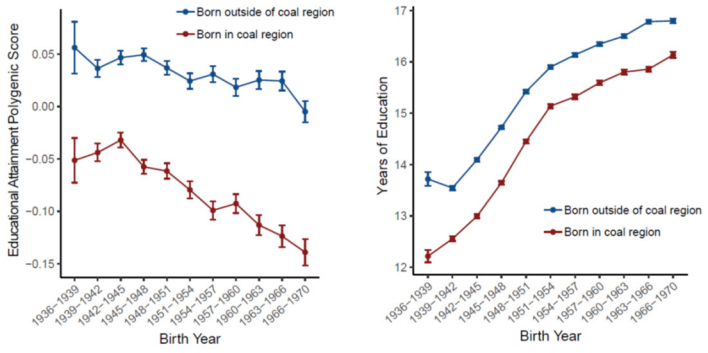
Townsend Index (measure of economic differences)

black lines = coal mining regions

Our research shows that people have polygenic scores that are more similar to their neighbors´ polygenic scores than to the polygenic scores of people who live far away. This is especially true of polygenic scores for educational attainment. The geographic distribution of polygenic scores for educational attainment resembles the geographic distribution of economic differences. Economically challenged regions, such as coal mining regions, show lower average polygenic scores for educational attainment. However, people that were born in these regions and migrate away show higher polygenic scores, on average, than the rest of Great Britain. This pattern of selective migration is exacerbating regional differences in genes associated with educational attainment and is disrupting the geographic distributions of the older genetic ancestry differences. The regional differences of educational attainment polygenic scores are in line with regional measures of educational success, wealth, and health outcomes, such as obesity and diabetes. While *individual* differences in health outcomes are expected to be in line with genes that are associated with health outcomes, the *regional* differences in health outcomes are much more in line with regional differences in genes associated with educational attainment than with genes associated with the health outcomes themselves. This suggests that the *regional* differences in health are likely to be due to environmental circumstances that cause people from the economically challenged regions with lower average education levels to have more health problems.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Complex behavioural outcomes such as educational attainment and socio-economic status are only partly influenced by our genes. The environment also plays an important role in explaining individual differences in these traits. It is very likely that social and other environmental influences play an important role in regional differences as well, especially when it comes to regional differences in health. The importance of the environment can be seen from our observation that, on average, the polygenic scores for educational attainment decrease over time (left Figure), while the actual education increases over time (right Figure) due to an improving educational system. The decrease in polygenic scores, which has been found in previous studies and in other countries as well, may be related to people with a higher polygenic score having fewer children. An alternative explanation to this decline is that people who have survived long enough to participate in this research at an older age are also more likely to carry more genes associated with a higher education. We see a faster decline of average polygenic scores within the coal mining regions (left Figure), which could be related to the migration of individuals with higher polygenic scores out of these regions. It is possible that the differences in genes associated with educational attainment between economically disadvantaged and economically more prosperous regions could continue to grow over generations. Furthering this pattern, increasing geographic clustering might lead people's polygenic scores to increasingly resemble the polygenic scores of the partners that they have children with.

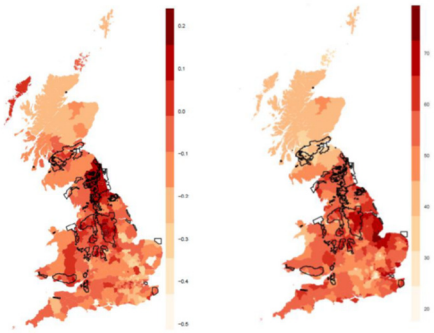


Even though the genetic effects we measure explain only a fraction of individual differences, researchers and social policymakers may want to keep these genetic effects in mind: regional genetic differences seem to be growing due to migration and could potentially exacerbate regional differences in health or socio-economic success. It is also apparent from our study that environmental effects must be taken into account, as they are likely to be harming especially the regions where genetic variants that are associated with lower educational attainment cluster. Giving specific policy advice based on the findings of our study alone however is beyond the scope of the study and beyond the authors' expertise.

How large are these regional genetic differences?

We can see the regional differences in genetics growing, but there are a number of factors that make it complicated to quantify how big these differences are. First, even though the recruitment strategy of UK Biobank was designed to cover the complete spectrum of socioeconomic strata and an urban–rural mix, the dataset is not entirely representative of Great Britain. The UK Biobank participants are healthier and more educated on average than the general population. Secondly, even if we were able to quantify the genetic differences more precisely, it remains difficult to interpret what those differences mean in terms of their impact, because of the uncertainty of the strength of the genetic effects on educational attainment and its related health outcomes. On the one hand, the polygenic scores used in this study capture about 4% of individual differences in educational attainment. This is only a fraction of the total genetic influences on educational attainment, which are estimated to account for at least 20% of individual differences (estimates vary between studies). This would lead to an *underestimation* of the strength of the genetic effects on educational attainment. On the other hand, recent studies have shown that there are factors that lead to an *overestimation* of the relationship between the polygenic scores and educational attainment. For instance, educational attainment is also influenced by the environment that parents provide for their children, and that environment is more likely to be resourceful if the parents have a higher education. Therefore, the environment of the children is correlated with the genes of the parents and the genes they inherited from their parents. When estimating the relationship between the children's polygenic scores and their educational outcomes, the effects their parents' genes have on their environment are also included in these estimates, which means that genetic effects will be overestimated. A recent study has indeed shown that polygenic scores can predict educational attainment better in biological offspring than in adopted offspring.

Are there other measures that are in line with these regional genetic differences?



Overall Health

Brexit
(Leave Votes)

black lines = coal mining regions

We have looked at a wide range of regional measures obtained from publicly available data sources and found that most of those measures are in line with the regional genetic differences we described above. The regional measures we looked at include economic outcomes (e.g., educational attainment, employment, income, electricity consumption), nutrition & health (e.g., obesity & diabetes rates, children's BMI & height, physical exercise, fast food outlets, and fruit/vegetable consumption), and major ideologies (political preference and religion). Selective migration has led not only to geographic clustering of genetic variants, but also geographic clustering of social and economic needs, which in turn can coincide with collective attitudes towards how communities or countries should be organized and governed. Therefore regional differences in things like election results (e.g., Brexit Leave votes) are not only in line with regional differences in socio-economic

status, which had been establishes in previous studies, but also with genetic variants that are associated with educational attainment. It is important for studies on the relationship between genes and behavioral outcomes to realize that these kinds of relationships exist on a regional level, since they could potentially lead to spurious evidence of genetics “causing” these outcomes.

RGWAS & GENETIC CORRELATION RESULTS

Regional GWASs (RGWASs) were run for 33 regional measures (Supplementary Table 2). The highest SNP-based heritability estimates were observed for regional measures of average EA outcomes as obtained from census data, namely the weighted average of 2011 estimates of the highest qualification of residents >16 years old, obtained from the Office for National Statistics. The genetic signals were very close to those of an individual-level EA3[1] GWAS that excluded British subjects. Most significant SNPs in the regional GWAS were at least nominally significant in the individual level GWAS and their effect sizes correlate .93 (Figure 6A). The genetic correlation between the regional EA GWAS and the individual level EA GWAS was .90, and the genetic correlations with 45 other complex traits were almost identical between the regional and individual level EA GWASs (r = .99, Figure 6B).

The RGWASs on SES-related traits showed, as expected, high genetic correlations with especially SES-related traits (Extended Data Figure 8). Electricity consumption for example has been shown to be strongly associated with regional SES differences, with more deprived regions using less electricity,[2] in line with our genetic correlations. RGWASs on regional measures of childhood height, childhood BMI, adult obesity, and diabetes, show considerably higher genetic correlations with individual-level GWASs on SES-related traits (e.g., EA & income) than with individual-level GWASs on height, BMI, or diabetes (Extended Data Figure 9). This may be due to regional differences in SES-, health-, and nutrition-related lifestyle factors, such as the availability of fast food, physical activity, and fruit/vegetable consumption, which all show similar genetic correlations. The association between unhealthy food outlets, obesity, and regional economic deprivation has been established previously.[3] The regional heritability estimates increase with age for BMI (0.06% for 4-5 year olds, 0.7% for 10-11 year olds, and 3.2% for adult obesity), suggesting that the effects of neighborhood deprivation are larger for adult BMI than for childhood BMI. This is in line with a previous study on the positive association between regional healthy food options and the prevalence of being overweight and obese in children, in which this association was found to be stronger in 10-11 year old children than in 4-5 year old children.[3] For height we see the opposite, namely a decrease of the regional heritability with age, with a heritability of 1.4% for 4-5 year olds and 0.5% for 10-11 year olds. This suggests that living in a deprived neighborhood may affect the height of 4-5 year old children, while not having a detectable impact on their BMI until they are older, at which point the effect of living in an economically deprived neighborhoods on height decreases.

The genetic correlations between the regional GWASs of BMI, obesity, height, and diabetes and the individual-level GWASs of BMI, height, and diabetes are significantly greater than zero (~.15 - ~.30). There are a number of possible explanations for these significant genetic correlations. One possibility is that the regional GWASs pick up the effects of genetic variants that have a direct causal influence on BMI, height, or diabetes. Another explanation is that the RGWAS picks up signals from genetic variants that influence SES/EA, and that the genetic correlations with BMI, height, or diabetes are due to pleiotropic effects of these genetic variants. A third explanation is that the genetic signals from the individual-level GWASs that we use to compute genetic correlations are confounded by signals from genetic variants that influence SES/EA, which influence in which neighborhood the people end up living, which in turn influences their environment and lifestyle and thereby the wide range of related physical and mental health outcomes. This type of confounding may be a source of the many genetic correlations a trait like EA shows with a wide range of health outcomes.

The RGWASs on election outcomes suggest that these can be divided roughly into higher SES and lower SES regions, with Green Party, Liberal Democrats, and Conservative regions containing more alleles associated with higher SES trait values, and the Labour Party, UKIP, “Leave” votes for Brexit,

and non-voters reflecting regions with more alleles associated with lower SES trait values (Extended Data Figure 10). A different pattern was observed for the proportion of religious inhabitants, which showed weaker genetic correlations with the SES related traits (cognition and health) and stronger associations with the two personality dimensions that showed significant geographic clustering in our previous analyses, openness and conscientiousness (more religious regions = lower openness and higher conscientiousness). Risk taking, schizophrenia, and autism also show the highest genetic correlations with being religious (more religious regions = lower genetic risk).

The signals were largely consistent within parties over time (1970 & 2015) with respect to SES, but UKIP and Green Party did not yet exist in 1970 (note that we used birth place for the RGWASs on 1970 election outcomes). The genetic correlations between regional religiousness and the 1970 & 2015 election outcomes suggest that UKIP regions include former Labour Party regions with a more religious genetic profile (lower openness, higher conscientiousness), while the Green Party regions include former Conservative regions with a more non-religious genetic profile (higher openness, lower conscientiousness). Not voting in 1970 showed a weaker genetic correlation with educational attainment and income (r_g's are -.40 and -.38 respectively) than not voting in 2015 (r_g's are -.72 and -.82 respectively) or in 2016 during the Brexit vote (r_g's are -.87 and -.72 respectively), suggesting that regional SES may have played a larger role in whether people voted the more recent elections.

The genetic correlations between the regional outcomes were much stronger than the phenotypic correlations, and in some instances in opposite directions. For the election outcomes for example: Labour Party 2015 & Green Party (negative genetic, positive phenotypic correlation), Conservative Party 2015 & Green Party (positive genetic, negative phenotypic correlation), Conservative Party 2015 & Brexit (negative genetic, positive phenotypic correlation). A possible explanation is that the part of the regional variation that is explained by genetic differences is mostly related to regional socio-economic status (lower SES associated alleles in Labour and Brexit areas, higher SES in Conservative and Green areas), while environmental factors, which are responsible for most of the regional variation, are more characterized by ideology (Labour and Green areas being more left-wing, Conservative and Brexit more right-wing).

POPULATION STRATIFICATION

In genetic association studies, false positives due to population stratification occur when systematic ancestry differences get mistaken for associations due to genetic variants that influence the trait that is being studied.[4] False positives due to population stratification can occur when trait differences are in line with ancestry differences, which could also occur due to non-genetic factors, such as regional differences in environmental exposures. Geographic location is known to strongly correlate with ancestry differences: the closer people live to each other, the more likely it is that they share more ancestors. The main focus of this study is the relationship between geographic location and genome-wide complex trait variation, which is why we had to be particularly rigorous in accounting for population stratification. We summarize below why it is unlikely that our observations are merely a result of ancestry differences or biased polygenic scores.

- The most widely used approach to account for ancestry differences is to quantify ancestry differences with a principal component analysis (PCA) on genome-wide SNP data and then account for the resulting principal components (PCs).[4,5] Instead of using the standard 40 PCs provided by UK Biobank, which capture both non-European and European ancestry differences,[6] we re-computed PCs to more effectively capture population stratification within the more homogeneous group of British participants with European ancestry (see Methods). While genome-wide association studies (GWASs) usually control for 10 to 40 PCs, we controlled for the first 100 PCs in all our analyses. We tested whether the 100 PCs themselves were significantly geographically clustered, which is expected if they capture ancestry differences, and almost all did (72 showed p-value < .0005 and 95 a p-value < .05). When correcting for 25 and 40 PCs, the Moran's I results did not change much as compared to correcting for 100 PCs: only 1 more trait was significantly clustered, type-2 diabetes, and the Moran's I estimates were very similar (see Supplementary Figure 14), indicating that the bulk of the geographically clustered ancestry differences that were part of the polygenic scores were already captured by the top 25 PCs.
- We validated the effectiveness of the 100 PCs in accounting for geographic clustering due to population stratification using polygenic scores that reflect European ancestry differences as captured in an independent European-American dataset: the GERA cohort.[7] First, we conducted GWASs in GERA (N = 51,258) on the first 20 GERA PCs in order to get SNP effects that reflect genome-wide patterns of their European-American ancestry differences. We then used these SNP effects to build polygenic scores in UK Biobank. These all show significant geographic clustering as quantified with Moran's I. After controlling for 100 PCs from UKB all Moran's I's dropped to being not significantly greater than 0 (see Methods and Supplementary Figures 15 and 16).
- The polygenic scores we analyzed were constructed from 1,312,100 autosomal SNPs, regardless of how significantly associated they are with the trait. The ensemble of non-significant SNPs contain a substantial amount of signals due to true causal relationships, and thus meaningful effect sizes, which increase the predictive power of polygenic scores.[8] Increasing the number of non-associated SNPs however may also increase the chances of including more stratified SNPs in the polygenic score. It has been shown for example that lower frequency SNPs are more prone to population stratification than more common SNPs.[9] We built polygenic scores including only more common SNPs, with a MAF > .1, which resulted in very similar results (Supplementary Figure 17). In addition, we created a set of polygenic scores using only independent SNPs (i.e., clumped) that were at least nominally significantly associated with the trait at p < .05. This results in scores that are based on fewer SNPs that are more reliably associated with the trait, but also results in less predictive scores. With this approach, 9 out of 21 previously significant traits are significantly geographically clustered after FDR correction (see Supplementary Figure 18). These geographically clustered clumped scores

also showed similar and significant associations with Townsend (Supplementary Figures 19 & 20), coal mining regions (Supplementary Figure 21) and migration out of coal fields (Supplementary Figures 22), with educational attainment showing the strongest effects.

- We show that the geographically clustered polygenic scores are significantly associated with regional outcomes of economic deprivation and with migration out of the more economically deprived regions in the UK (coal mining regions). The strength of the geographic clustering is in line with the strength of the association with regional outcomes and, more importantly, migration (Supplementary Figure 10). In other words, 1) the traits that show significant geographic clustering are the traits that cluster in specific regions that are characterized by lower SES measures, and 2) we show that the processes that would result in these regional differences are measurable in the current dataset, namely migration out of the lower SES regions by individuals with a higher predisposition for SES-related traits such as higher educational attainment and lower body weight. Although these observations do not directly prove that ancestry differences cannot account for this geographic clustering, it does show that *if* subtle population stratification would be the cause of these regional differences (which is unlikely given our stringent control for ancestry differences), it would have to involve ancestry differences that are in line with genome-wide complex trait variation.
- We included two EA polygenic scores based on two similar-sized GWASs, one excluding UK Biobank participants (N = 217,569), based on the Okbay et al (2016)[10] EA GWAS (EA2), and one excluding all British cohorts (N = 245,621), based on the larger Lee et al (2018)[1] EA GWAS (EA3). The polygenic score based on the GWAS excluding all British cohorts should more robust to residual population stratification, i.e., robust to differences in the polygenic score that are due to ancestry differences within the UK that are correlated with EA outcomes and therefore captured in the EA GWAS effect size estimates. The two polygenic scores show very similar results throughout our article, indicating that the residual stratification, if present, does not play considerable a role in our findings.
- SNPs that are in LD with many SNPs are more likely to tag a causal SNP (i.e., be correlated with a causal SNP), and are thus more likely to have a higher test-statistic in a GWAS. The amount of SNPs that is tagged by a SNP is quantified by its LD Score. LD Score regression is an approach that leverages the relationship between the LD score of a SNP and the GWAS test statistic to distinguish inflation of genome-wide test statistics due to variants that influence the complex trait under study from inflation due to confounding bias such as population stratification.[11] LD Score regression analyses show that the results from our RGWASs all show an inflation of test statistics that is partly due to confounding (likely shared environmental influences) but also contains a considerable inflation due to variants that are associated with complex trait variation that is being captured by the regional measures. LD Score regression was used to compare the parts of the genetic signals that were due to causal variants between our RGWASs and individual-level GWASs from a wide range of other complex traits. Importantly, LD Score regression showed that the signals from our RGWAS on EA contained almost the same signals as an individual-level GWAS on EA that was conducted on non-British datasets (Figures 6B and 6C), which is in line with the geographic clustering of genome-wide alleles that have a causal influence on EA.

ASCERTAINMENT BIAS

The UK Biobank ascertainment strategy was designed to capture sufficient variation in socioeconomic, urban–rural, and ethnic background.[12] The participation rate however was 5.45% and was biased towards older, more healthy, and female residents.[13] The UK Biobank sample does reflect nationally representative data sources to a significant degree, making it likely that our observations would generalize to the population at large. We tested at the MSOA level how EA measurements in UK Biobank compare to nationally representative census data (the same EA census measurements that we used for the EA RGWAS). The average EA per MSOA region as measured in UK Biobank is strongly predictive of MSOA-EA as measured from the nationally representative census data ($p < 10^{-16}$, R^2 = 39%; Supplementary Figure 23). The average polygenic scores per MSOA region, with 100 PCs regressed out, are also highly predictive of MSOA-EA according to nationally representative census data ($p < 10^{-16}$, R^2 = 20%; Supplementary Figure 23. Since UK Biobank has sampled healthier individuals as well as fewer individuals from more economically deprived areas as compared to the British population as a whole,[13] the regional differences that we report may turn out to be stronger in the real population than in the UK Biobank sample. This is the case for at least the EA differences between coal mining regions and the rest of the country (see Supplementary Figure 24), with EA as measured by census data showing larger differences (standardized mean in coal fields = -.39, outside coal field = .19; t(4764.9) = -24.7) than EA as measured in UK Biobank (standardized mean in coal fields = -.20, mean outside coal field = .25; t(3331.6) = -13.9). It is not clear however whether this level of ascertainment bias is the same across the four migration groups we have compared.

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SUPPLEMENTARY TABLES

Supplementary Table 1: Overview of GWASs that provided the effect size estimates that were used to compute polygenic scores

Trait Name	N_{GWAS}	N_{cases}	$N_{controls}$	$N_{effective}$	h^2_{SNP}	LDSC Intercept
Cognition & SES:						
EA2 (no UKB) [10]	217,569	-	-	217,569	.10	1.02
EA3 (no GB)[1]	245,621	-	-	245,621	.10	1.00
Cognitive ability[1]	35,298	-	-	35,298	.13	1.05
Personality:						
Openness[14,15]	76,551	-	-	76,551	.10	.95
Conscientiousness[14,15]	76,551	-	-	76,551	.08	.96
Extraversion[14,15]	76,600	-	-	76,600	.14	.92
Agreeableness[14,15]	76,548	-	-	76,548	.07	.96
Neuroticism[14,15]	76,581	-	-	76,581	.09	.94
Psychiatric Traits:						
Schizophrenia[16]	150,064	36,989	113,075	111,486.6	.18	1.05
Bipolar[17]	63,766	11,974	51,792	38,902.1	.14	1.02
Anorexia[18]	14,477	3,495	10,982	10,605	.22	1.01
Autism[19]	46,350	18,381	27,969	44,366.62	.11	1.01
Alzheimer[20]	54,162	17,008	37,154	46,668.5	.08	1.04
ADHD[21]	55,374	20,183	35,191	51,306.4	.21	1.03
MDD[22]	431,394	116,404	314,990	161,089.68	.08	1.01
Substance Use:						
Alcohol Use[23]	70,493	-	-	70,493	.05	1.02
Drinks per week[24]	226,223	-	-	226,223	.04	.99
Age at smoking Initiation[24]	138,400	-	-	138,400	.03	1.00
Cigarettes per day[24]	143,210	-	-	143,210	.06	.98
Smoking Cessation[24]	143,851	-	-	143,851	.04	.97
Smoking Initiation[24]	249,171	-	-	249,171	.07	.97
Cannabis (ever vs never)[25]	32,330	14,387	17,943	31,938.9	.13	1.00
Caffeine[26]	91,462	-	-	91,462	.04	1.01
CAD & Diabetes:						
Coronary Artery Disease[27]	86,995	22,233	64,762	66,204	.28	.87
Type-2 Diabetes[28]	69,033	12,171	56,862	40,100.7	.18	1.01
Reproduction:						
Age at Menarche[29]	87,802	-	-	87,802	.24	.98
Age at Menopauze[30]	69,360	-	-	69,360	.13	.99
Antropomorphic traits:						
Height[31]	253,280	-	-	253,280	.31	1.33
BMI[32]	322,154	-	-	322,154	.13	.67
Body Fat[33]	100,716	-	-	100,716	.10	.91
Waist Circumference[34]	232,101	-	-	232,101	.13	.76
Hip Circumference[34]	213,038	-	-	213,038	.14	.78
Waist-to-hip-ratio[34]	212,248	-	-	212,248	.10	.84

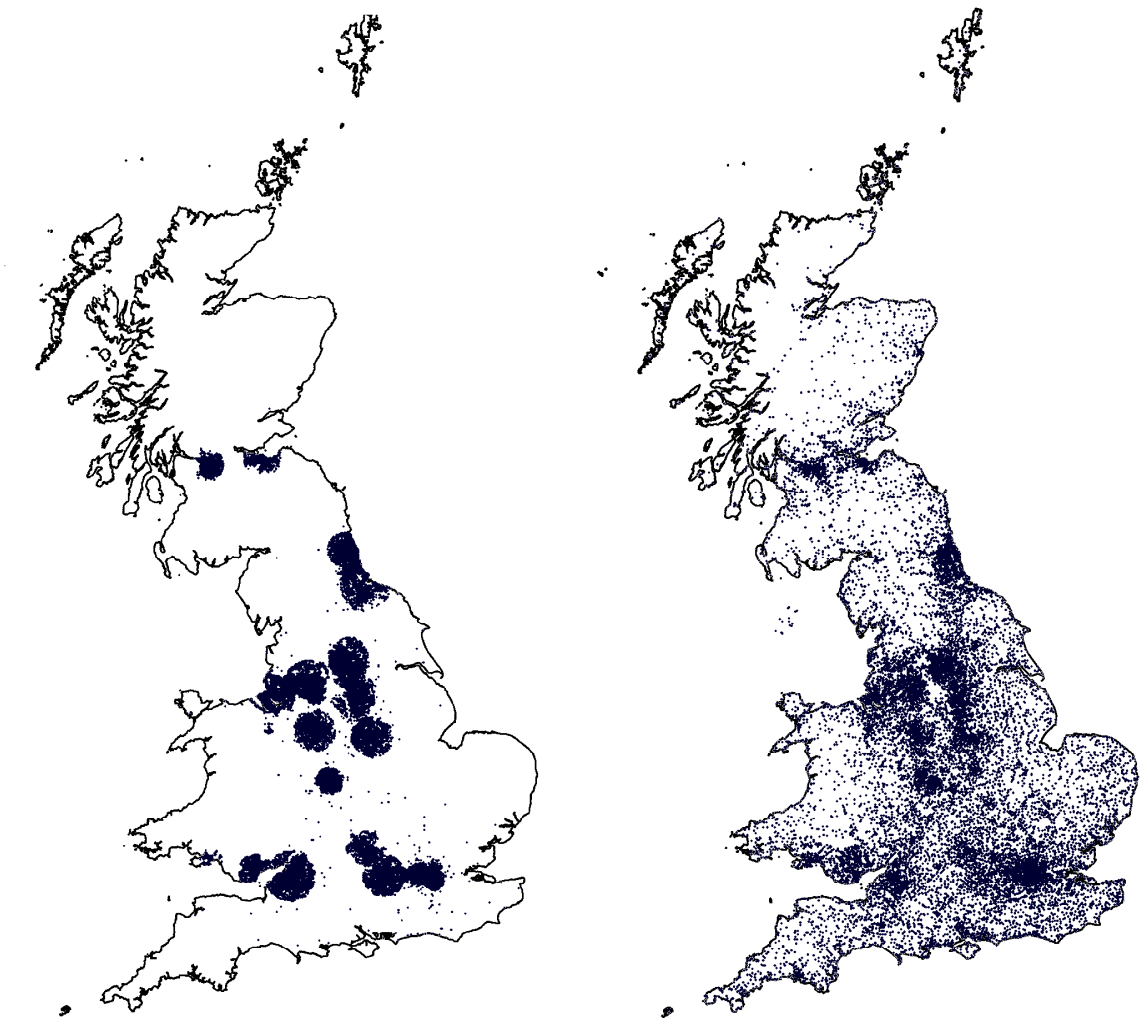
Supplementary Table 2: Sample sizes and LD score regression results for the regional GWASs before and after LDSC-intercept based genomic control.

		Before Genomic Control				After Genomic Control (LDSC intercept=1; ratio=0)	
Regional Phenotype	**N**	**SNP-h2 (SE) %**	**lambda**	**LDSC intercept (SE)**	**ratio**	**SNP-h2 (SE) %**	**lambda**
2011 - Educational attainment (local authorities)	402,552	4.1 (.25)	1.49	1.22 (.01)	.39 (.02)	3.3 (.20)	1.23
2011 - Educational attainment (MSOA)	416,061	7.5 (.29)	1.63	1.14 (.01)	.18 (.01)	6.6 (.25)	1.44
Coal Fields (Birth Place)	422,757	1.5 (.20)	1.56	1.43 (.01)	.77 (.02)	1.0 (.12)	1.07
Coal Fields (Current Address)	449,972	2.1 (.18)	1.43	1.25 (.01)	.55 (.02)	1.7 (.13)	1.14
2015 - Employment	396,108	3.6 (.21)	1.31	1.08 (.01)	.21 (.02)	3.4 (.19)	1.24
2015 - Income	396,108	3.2 (.19)	1.31	1.06 (.01)	.18 (.03)	3.0 (.18)	1.22
2015 - Health deprivation & disability	396,108	3.8 (.22)	1.37	1.14 (.01)	.30 (.02)	3.4 (.19)	1.23
2015 - Crime	396,108	1.5 (.15)	1.15	1.06 (.01)	.31 (.01)	1.4 (.14)	1.11
2015 - Barriers to housing & services	396,108	0.5 (.14)	1.10	1.05 (.01)	.53 (.08)	0.5 (.13)	1.04
2015 - Living environment	396,108	1.6 (.17)	1.25	1.11 (.01)	.47 (.03)	1.4 (.15)	1.11
2010 - Electricity - Avg. Ordinary Domestic Consumption	390,917	2.3 (.18)	1.25	1.07 (.01)	.28 (.03)	2.1 (.16)	1.15
2010 - Electricity - Avg. Economy 7 Consumption	390,917	0.9 (.15)	1.15	1.08 (.01)	.51 (.05)	0.9 (.13)	1.07
2015 - Obesity rates (18+)	382,868	3.2 (.22)	1.43	1.19 (.01)	.42 (.02)	2.7 (.18)	1.19
2015 - Diabetes	382,868	2.8 (.23)	1.43	1.27 (.01)	.54 (.02)	2.2 (.17)	1.15
2015 - BMI (4-5.y.o.)	382,868	0.06 (.13)	1.05	1.04 (.01)	.90 (.16)	0.06 (.12)	1.008
2015 - BMI (10-11 y.o.)	382,868	0.7 (.14)	1.20	1.12 (.01)	.71 (.04)	0.6 (.12)	1.05
2015 - Height (4-5 y.o.)	382,868	1.7 (.21)	1.31	1.19 (.01)	.59 (.03)	1.4 (.16)	1.09
2015 - Height (10-11 y.o.)	382,868	0.6 (.16)	1.25	1.19 (.01)	.79 (.04)	0.5 (.13)	1.04
2015 - Physical activity	382,868	2.1 (.24)	1.43	1.28 (.01)	.62 (.02)	1.7 (.18)	1.12
2015 - Vegetable consumption	382,868	1.2 (.17)	1.31	1.21 (.01)	.69 (.03)	1.0 (.13)	1.06
2015 - Fruit consumption	382,868	1.0 (.17)	1.20	1.14 (.01)	.64 (.04)	0.9 (.14)	1.06
2017 - Regional density of fast food outlets	382,868	1.3 (.19)	1.31	1.21 (.01)	.67 (.03)	1.1 (.14)	1.08
2011 - Proportion of non-religious individuals	416,061	1.2 (.17)	1.31	1.19 (.01)	.67 (.03)	1.0 (.13)	1.08
2016 - Brexit	446,910	3.0 (.22)	1.56	1.31 (.01)	.52 (.02)	2.3 (.16)	1.19
2016 - Non-voters	446,910	1.3 (.17)	1.20	1.12 (.01)	.50 (.04)	1.2 (.14)	1.09
1970 - Labour Party (centre-left)	422,189	2.3 (.22)	1.49	1.30 (.01)	.60 (.02)	1.8 (.15)	1.14
1970 - Liberal Democrats (centre)	207,045	0.9 (.30)	1.15	1.12 (.01)	.75 (.05)	0.8 (.25)	1.04
1970 - Conservative and Unionist Party (centre-right)	421,940	1.6 (.18)	1.37	1.27 (.01)	.66 (.02)	1.3 (.13)	1.10
1970 - Non-voters	422,415	0.6 (.17)	1.31	1.28 (.01)	.83 (.02)	0.5 (.12)	1.04
2015 - Green Party of England and Wales (left-wing)	449,553	2.2 (.16)	1.25	1.08 (.01)	.27 (.03)	2.0 (.14)	1.18
2015 - Labour Party (centre-left)	449,553	1.8 (.19)	1.37	1.22 (.01)	.57 (.02)	1.4 (.14)	1.13
2015 - Liberal Democrats (centre)	449,553	1.2 (.15)	1.20	1.08 (.01)	.42 (.05)	1.1 (.14)	1.09
2015 - Conservative and Unionist Party (centre-right)	449,553	1.5 (.17)	1.31	1.17 (.01)	.56 (.03)	1.2 (.14)	1.11
2015 - UKIP (right-wing)	449,553	3.1 (.21)	1.56	1.29 (.01)	.50 (.02)	2.4 (.15)	1.20
2015 - Non-voters	449,553	2.6 (.19)	1.43	1.19 (.01)	.43 (.02)	2.2 (.15)	1.19
2015 - Green/(Green+Liberals+Conservative)	449,553	1.2 (.14)	1.15	1.06 (.01)	.31 (.04)	1.2 (.13)	1.11
2015 - Liberals/(Green+Liberals+Conservative)	449,553	0.3 (.12)	1.10	1.08 (.01)	.72 (.07)	0.3 (.11)	1.03
2015 - Conservative /(Green+Liberals+Conservative)	449,553	0.9 (.13)	1.15	1.08 (.01)	.51 (.05)	0.8 (.11)	1.07
2015 - Labour/(UKIP+Labour)	449,553	0.7 (.14)	1.20	1.15 (.01)	.70 (.04)	0.6 (.11)	1.05
2015 - UKIP/(UKIP+Labour)	449,553	0.7 (.14)	1.20	1.15 (.01)	.70 (.04)	0.6 (.11)	1.05

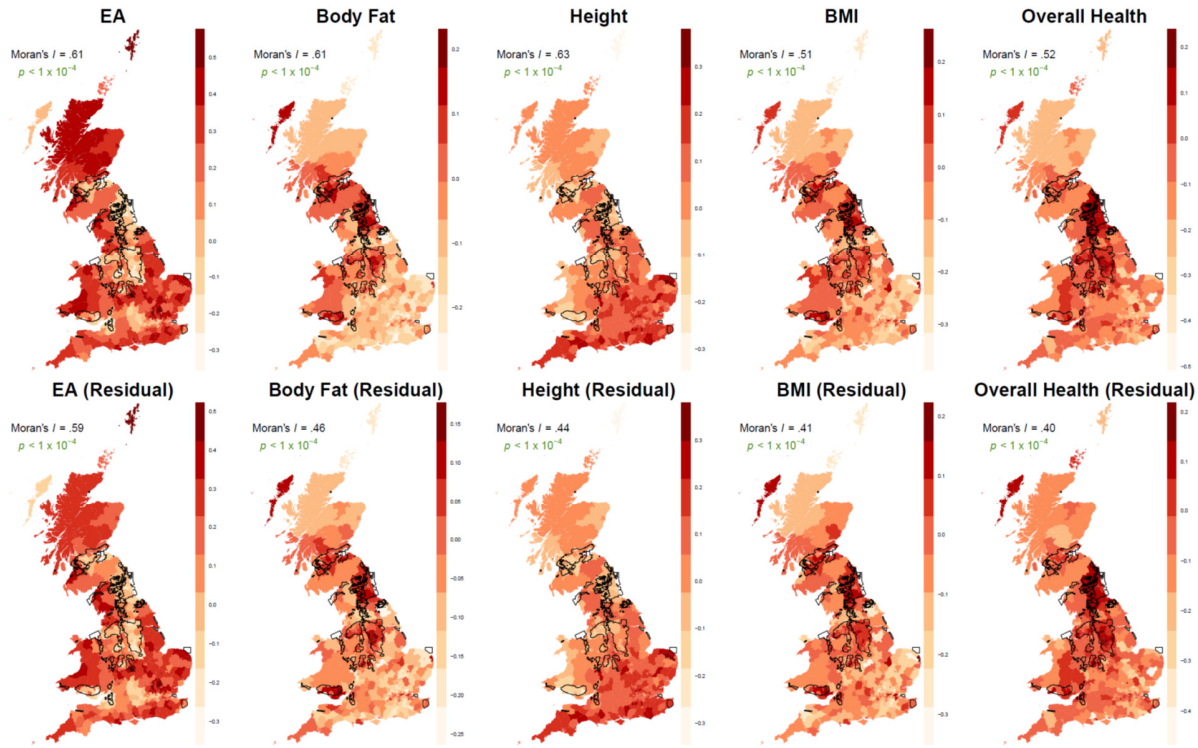
Supplementary Table 3: Overview of GWASs that provided the effect size estimates that were used to compute genetic correlations with RGWASs using LD score regression.

Trait Name	N_{GWAS}	N_{cases}	$N_{controls}$	$N_{effective}$	h^2_{SNP}	LDSC Intercept
Cognition and SES:						
Childhood IQ[35]	12,441	-	-	12,441	.28	1.00
Adult IQ[36]	78,308	-	-	78,308	.19	1.02
Educational Attainment[1]	245,621	-	-	245,621	.10	1.00
Income[37]	112,151	-	-	112,151	.06	1.03
Townsend[37]	112,151	-	-	112,151	.04	1.01
Personality:						
Openness[14,15]	76,551	-	-	76,551	.10	.95
Conscientiousness[14,15]	76,551	-	-	76,551	.08	.96
Extraversion[14,15]	76,600	-	-	76,600	.14	.92
Agreeableness[14,15]	76,548	-	-	76,548	.07	.96
Neuroticism[14,15]	76,581	-	-	76,581	.09	.94
Other Psychology:						
Subjective Well-being[38]	298,420	-	-	298,420	.03	1.00
Tiredness[39]	108,976	-	-	108,976	.07	.99
Loneliness[40]	332,991	-	-	332,991	.08	1.01
Risk Taking[40]	332,991	-	-	332,991	.06	1.01
Psychiatric Traits:						
Schizophrenia[16]	150,064	36,989	113,075	111,486.6	.18	1.05
Bipolar[17]	63,766	11,974	51,792	38,902.1	.14	1.02
Anorexia[18]	14,477	3,495	10,982	10,605	.22	1.01
Autism[19]	46,350	18,381	27,969	44,366.62	.11	1.01
Alzheimer[20]	54,162	17,008	37,154	46,668.5	.08	1.04
ADHD[21]	55,374	20,183	35,191	51,306.4	.21	1.03
MDD[22]	431,394	116,404	314,990	161,089.68	.08	1.01
Substance Use:						
Alcohol Consumption[41]	112,117	-	-	112,117	.08	1.01
Alcohol Dependence[42]	46,568	11,569	34,999	34,779.54	.18	1.02
Drinks per week[24]	537,349	-	-	226,223	.05	.93
Age at smoking Initiation[24]	632,802	-	-	138,400	.07	.90
Cigarettes per day[24]	263,954	-	-	143,210	.07	.96
Smoking Cessation[24]	312,821	-	-	143,851	.03	.98
Smoking Initiation[24]	262,990	-	-	249,171	.05	.98
Cannabis (ever vs never)[43]	162,081	43,444	118,637	127,197.3	.10	.90
Caffeine[26]	91,462	-	-	91,462	.04	1.01
Health & Longevity:						
Self-rated health[44]	111,749	-	-	111,749	.10	1.01
Coronary Artery Disease[27]	86,995	22,233	64,762	66,204	.28	.87
Type-2 Diabetes[28]	69,033	12,171	56,862	40,100.7	.18	1.01
Age of Parents Death[45]	45,627	-	-	45,627	.05	1.02
Age of Fathers Death[45]	63,775	-	-	63,775	.05	1.02
Age of Mothers Death[45]	52,776	-	-	52,776	.05	1.01
Reproduction:						
Age at First Birth[46]	251,151	-	-	251,151	.05	.96
Nr of Children Ever Born[46]	343,072	-	-	343,072	.02	.97
Age at Menarche[29]	87,802	-	-	87,802	.24	.98
Age at Menopauze[30]	69,360	-	-	69,360	.13	.99
Antropomorphic:						
BMI[32]	322,154	-	-	322,154	.13	.67
Height[31]	253,280	-	-	253,280	.31	1.33
Body Fat[33]	100,716	-	-	100,716	.10	.91
Waist Circumference[34]	232,101	-	-	232,101	.13	.76
Hip Circumference[34]	213,038	-	-	213,038	.14	.78
Waist-to-hip-ratio[34]	212,248	-	-	212,248	.10	.84

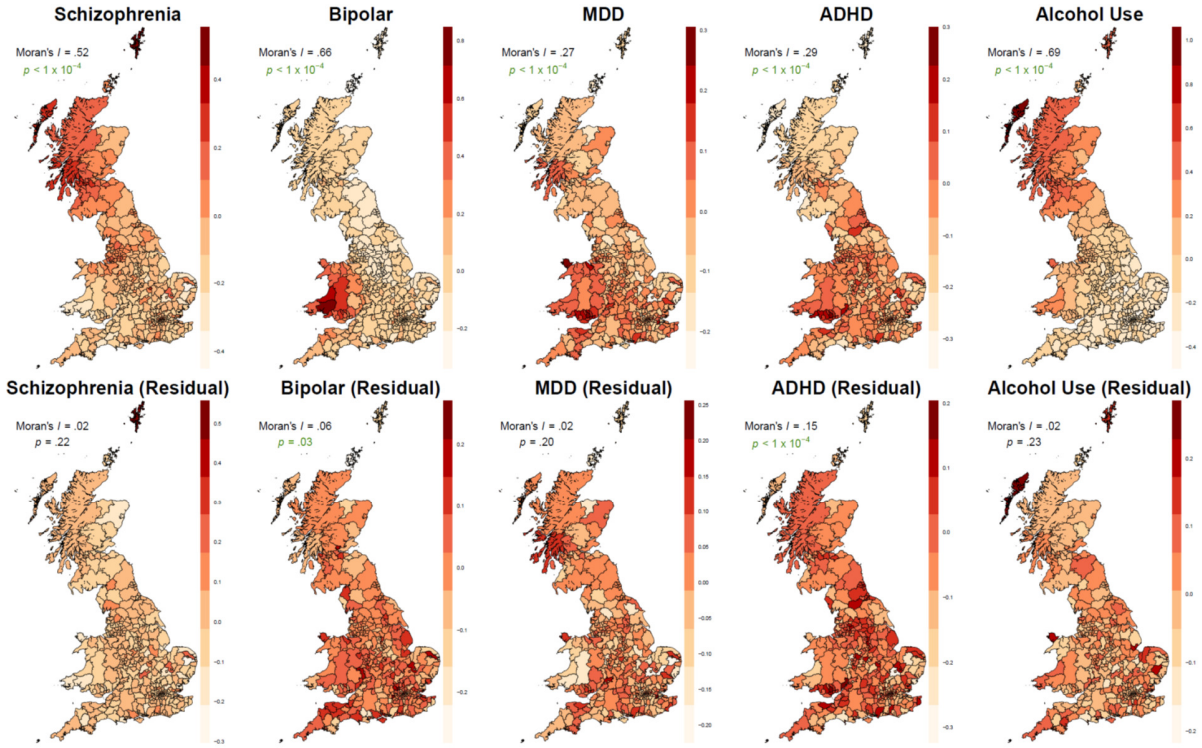
SUPPLEMENTARY FIGURES



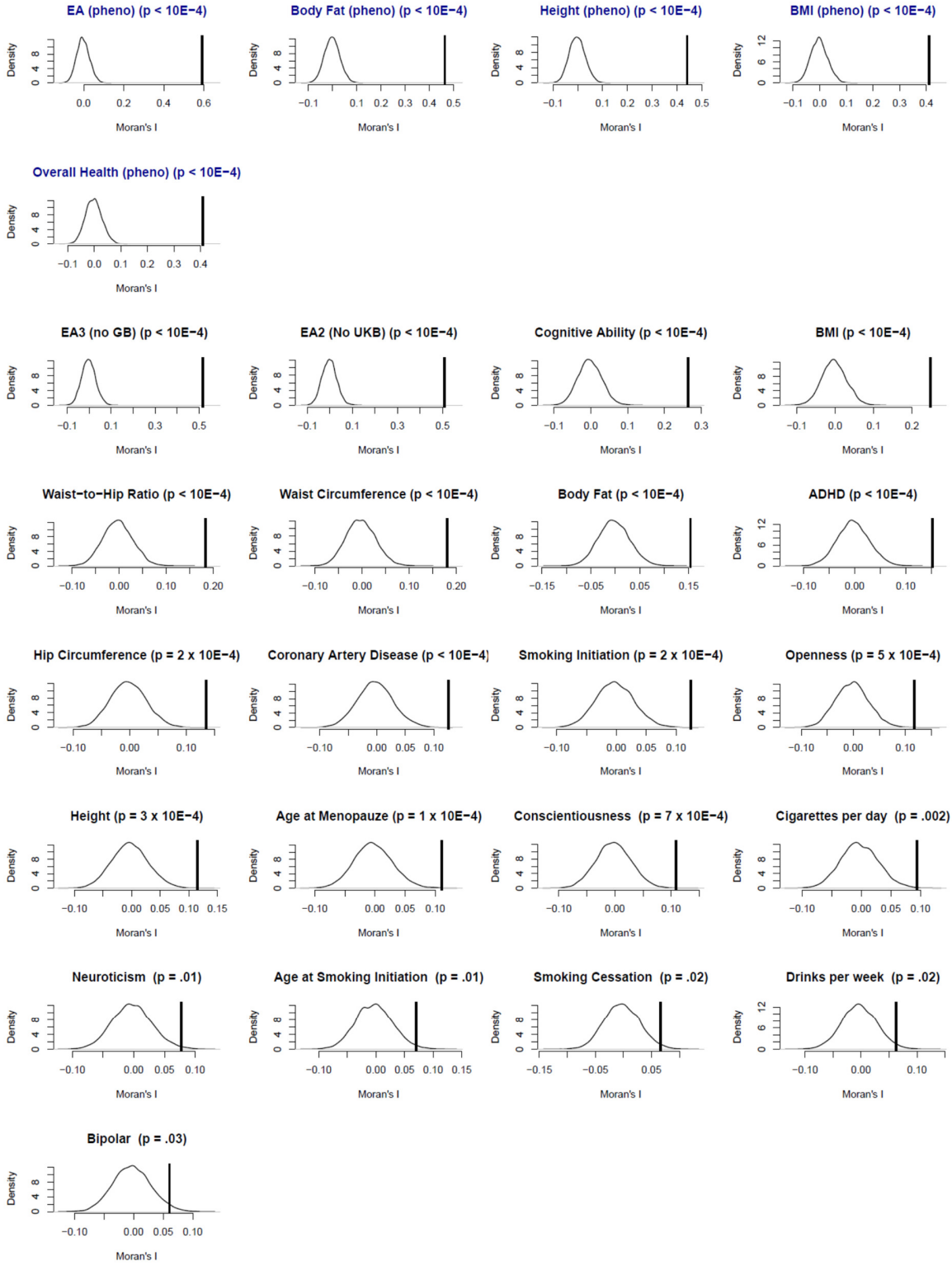
Supplementary Figure 1: The geographic locations of the UK Biobank participants (each dot represents a participant). The left map shows the current living address (N=497,673). The right plot shows the birth places (N=444,992).



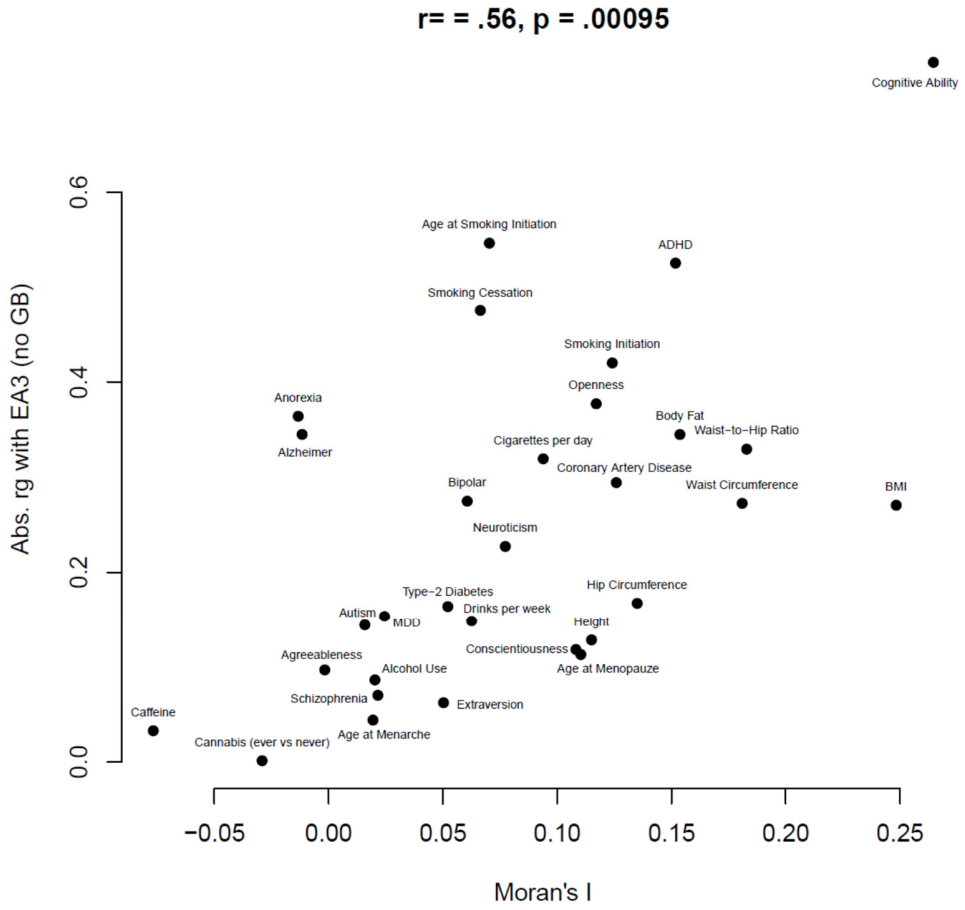
Supplementary Figure 2: Geographic distribution (birthplace) and Moran's I values for five phenotypic measurements (N ~320k unrelated individuals) before (top row) and after (bottom row) regressing out 100 ancestry-informative PCs. Green p-values are significant after FDR correction. The black lines indicate coal mining areas.



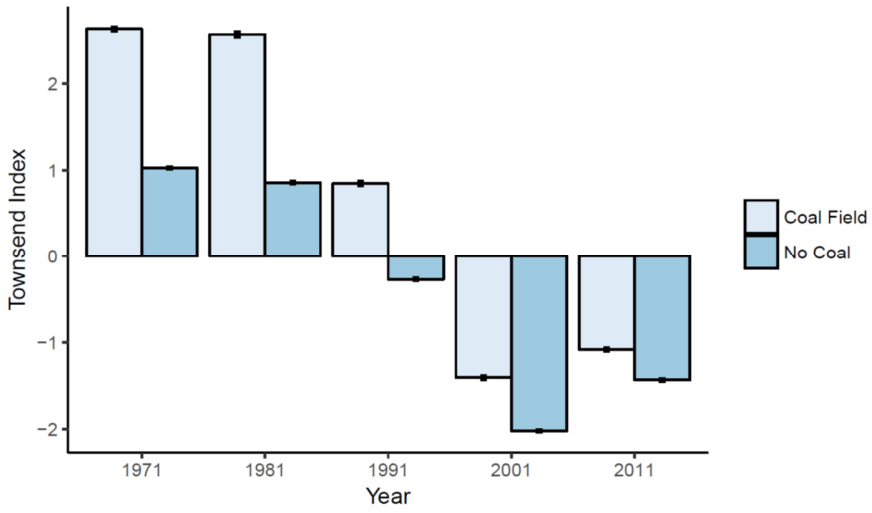
Supplementary Figure 3: Geographic distribution (birthplace) and Moran's I values for polygenic scores of four major psychiatric disorders (based on GWASs from the Psychiatric Genomics Consortium (PGC): schizophrenia[16], bipolar[17], MDD[22], and ADHD[21]) and alcohol use[23] before (top row) and after (bottom row) regressing out 100 ancestry-informative PCs (N = 320,940 unrelated individuals). Green p-values are significant after FDR correction.



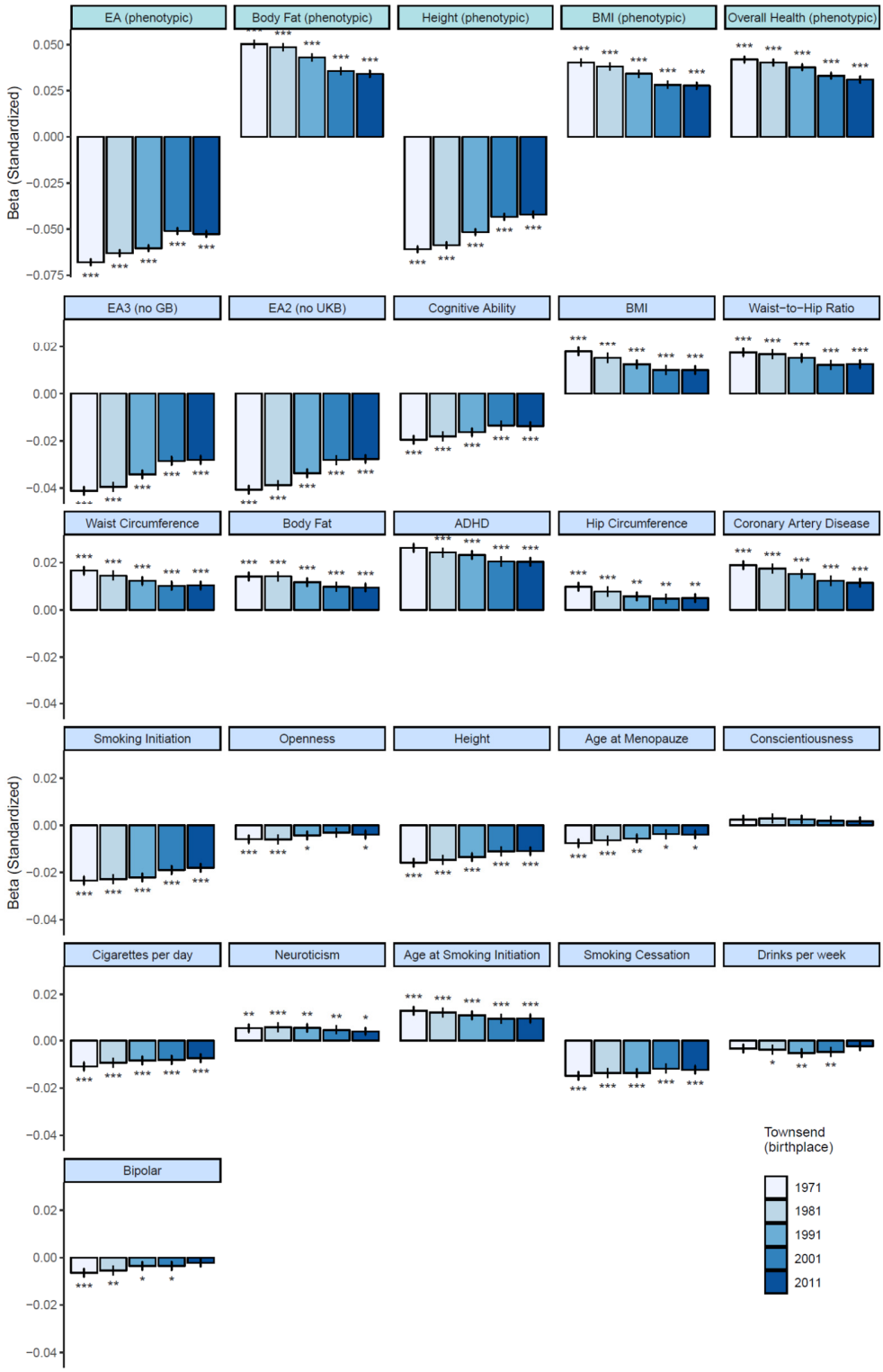
Supplementary Figure 4: The distributions of significant Moran's I statistics from 10,000 permutations that were conducted to obtain an empirical p-value for Moran's I for the five phenotypic measurements and the SBLUP polygenic scores (see Figure 2). The vertical line to the right of the permutation distribution shows the observed Moran's I of the actual data.



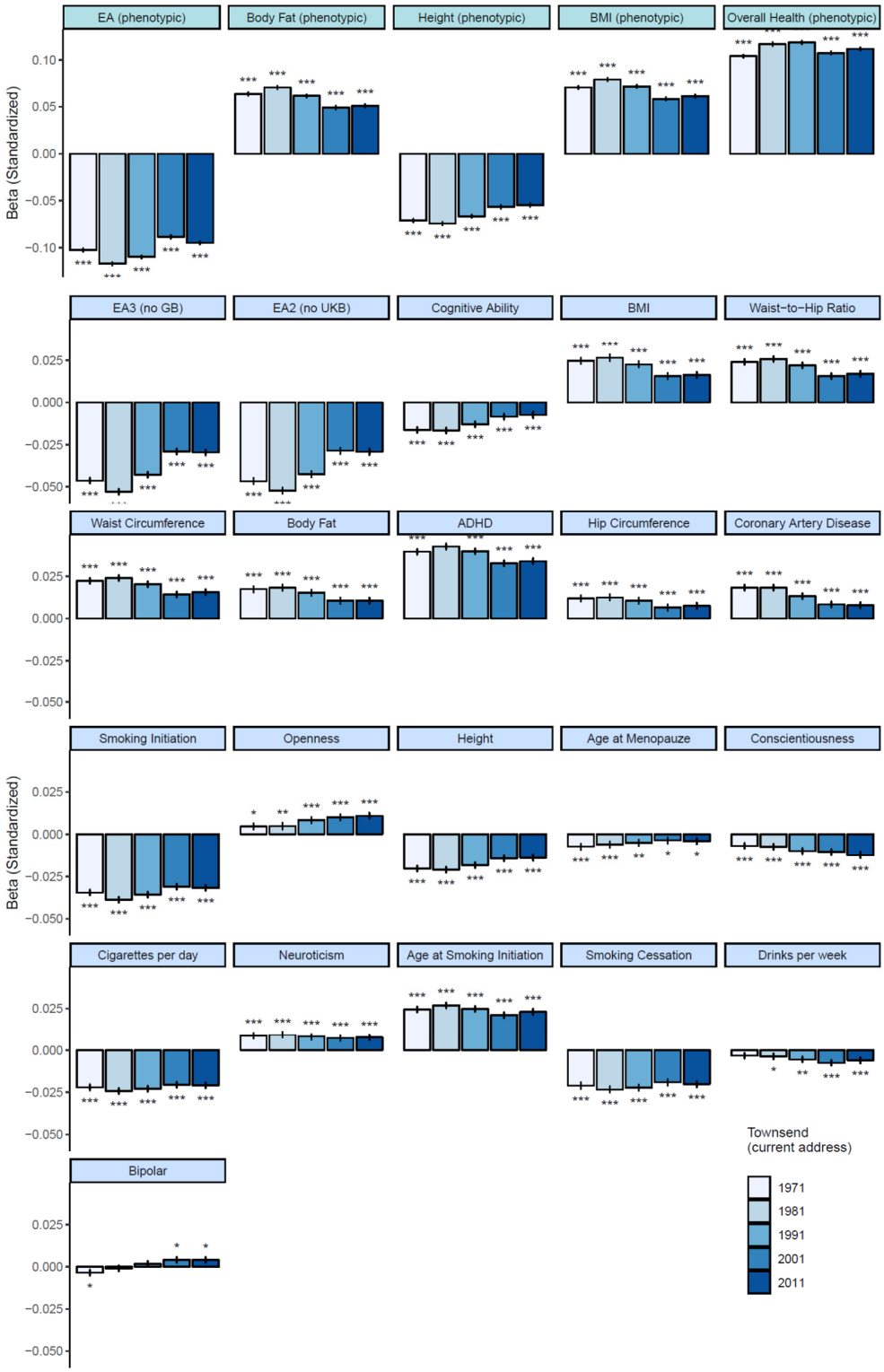
Supplementary Figure 5: Scatterplot and correlation between Moran's I on the x-axis and the absolute genetic correlation with EA3 (no GB) computed with LD Score regression on the y-axis (N = 31 traits). We looked at the absolute effect size estimate on the x-axis because we were interested in the strength of the effect (the direction differs per trait).



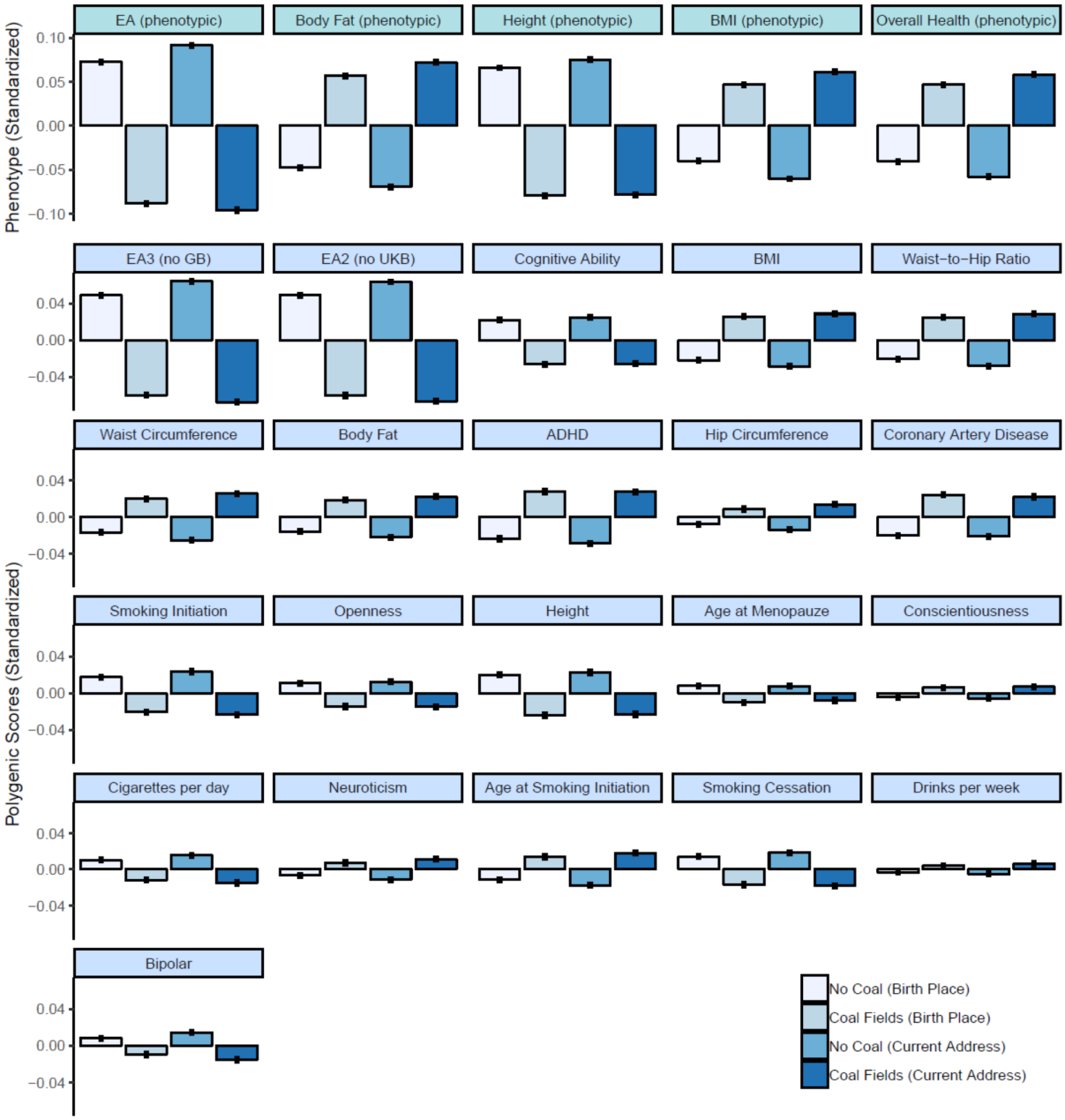
Supplementary Figure 6: The average Townsend indices from 1971 to 2011 for coal fields and regions without coal.



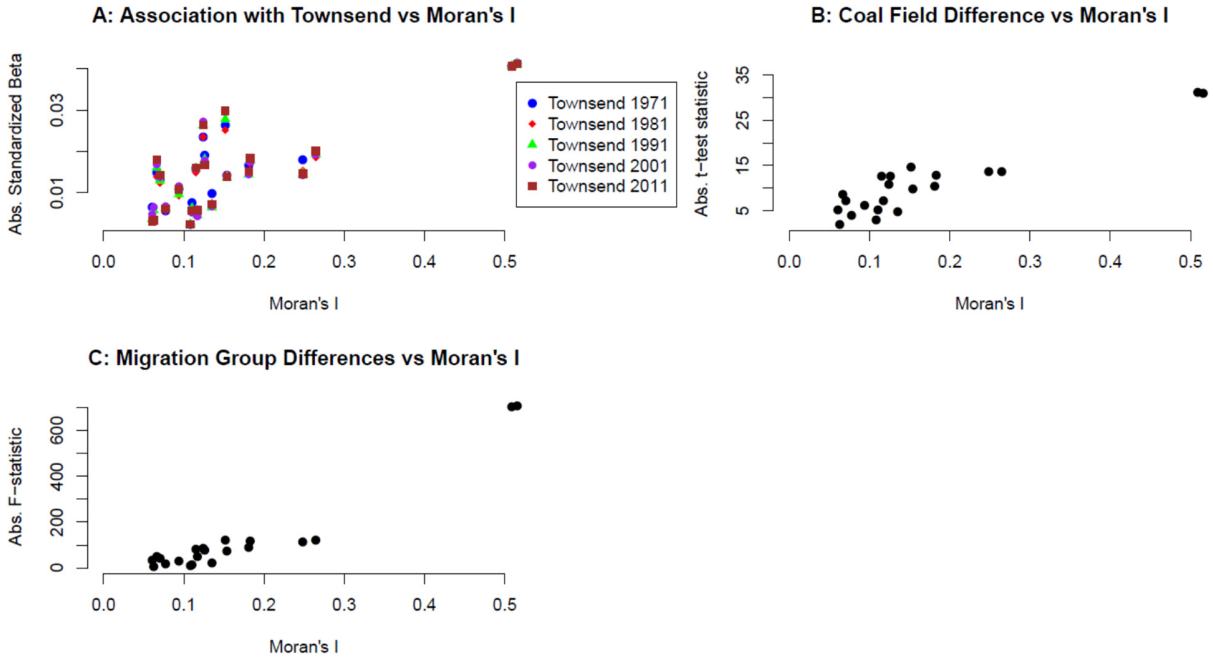
*Supplementary Figure 7: The standardized regression coefficients and standard errors for the 5 phenotypes and 21 geographically clustered polygenic scores (ordered by Moran's I) of the associations with the Townsend indices of 1971 to 2011 of the birth places of the subjects (N = 320,940 unrelated individuals). All polygenic scores shown are standardized residuals after regressing out 100 PCs. * = p < .05, ** = p < .01, *** = p < .001.*



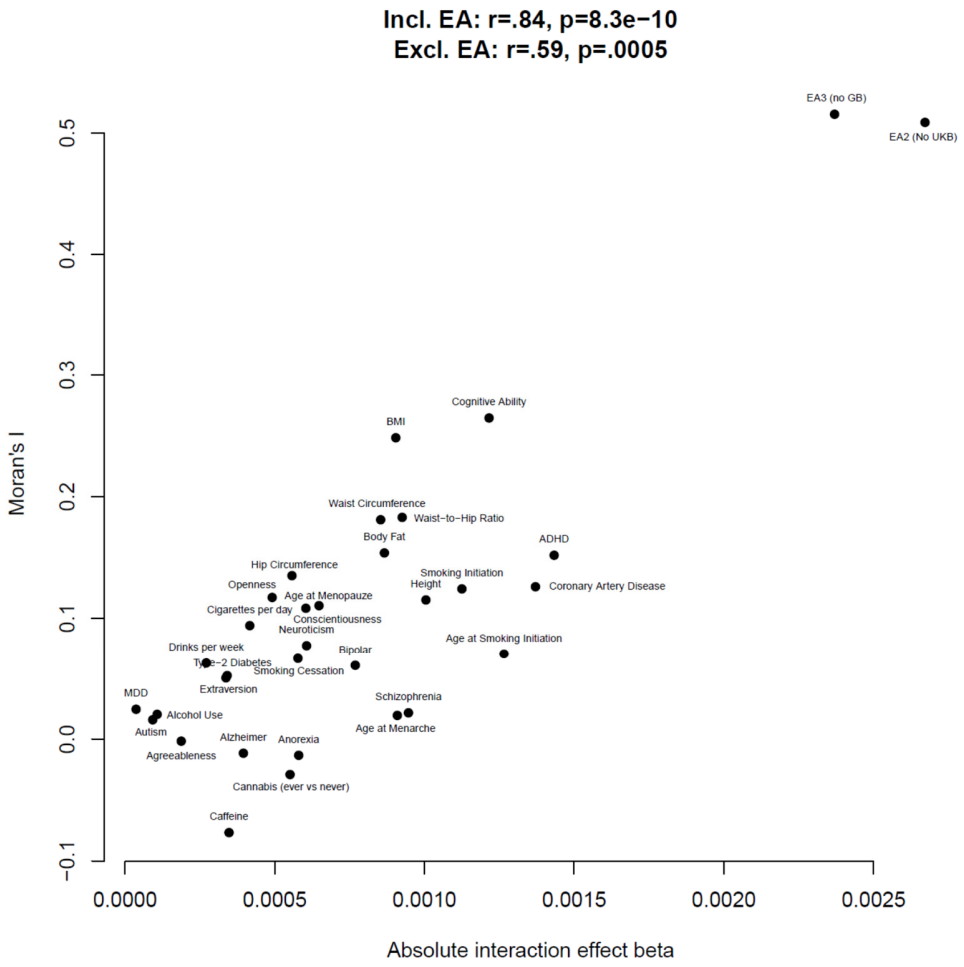
*Supplementary Figure 8: The standardized regression coefficients and standard errors for the 16 geographically clustered polygenic scores (ordered by Moran's I) of the associations with the Townsend indices of 1971 to 2011 of the current address of the subjects (N = 320,940 unrelated individuals). All polygenic scores shown are standardized residuals after regressing out 100 PCs. * = p < .05, ** = p < .01, *** = p < .001.*



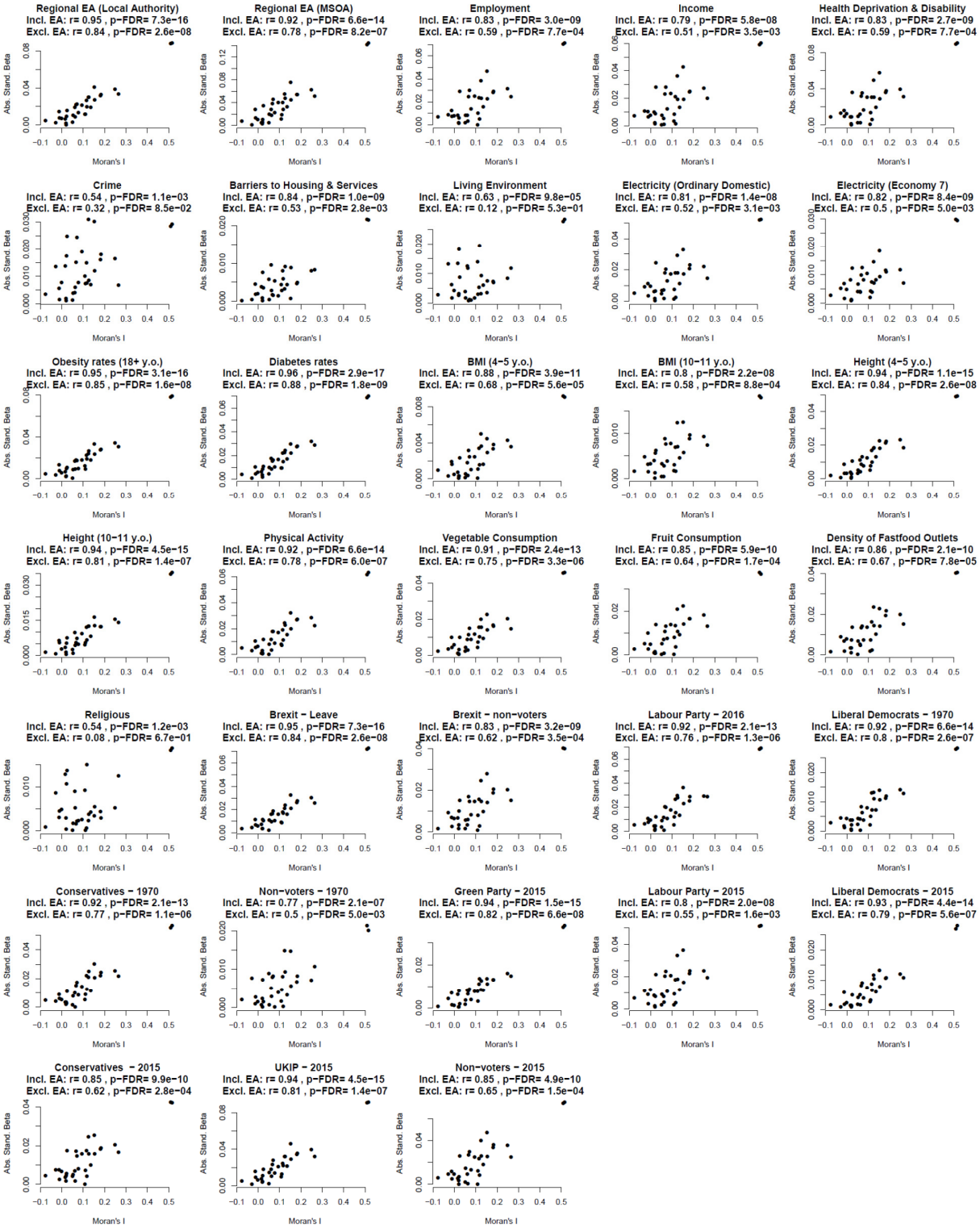
Supplementary Figure 9: The average and standard errors for the 5 phenotypes and 21 geographically clustered polygenic scores (ordered by Moran's I) within coal mining regions vs the rest of Great Britain based on the birth place of the participants and on the current addresses separately (N = 320,940 unrelated individuals). All polygenic scores shown are standardized residuals after regressing out 100 ancestry-informative PCs. The differences between Coal Fields and No Coal are all significant with an FDR corrected p-value < .05.



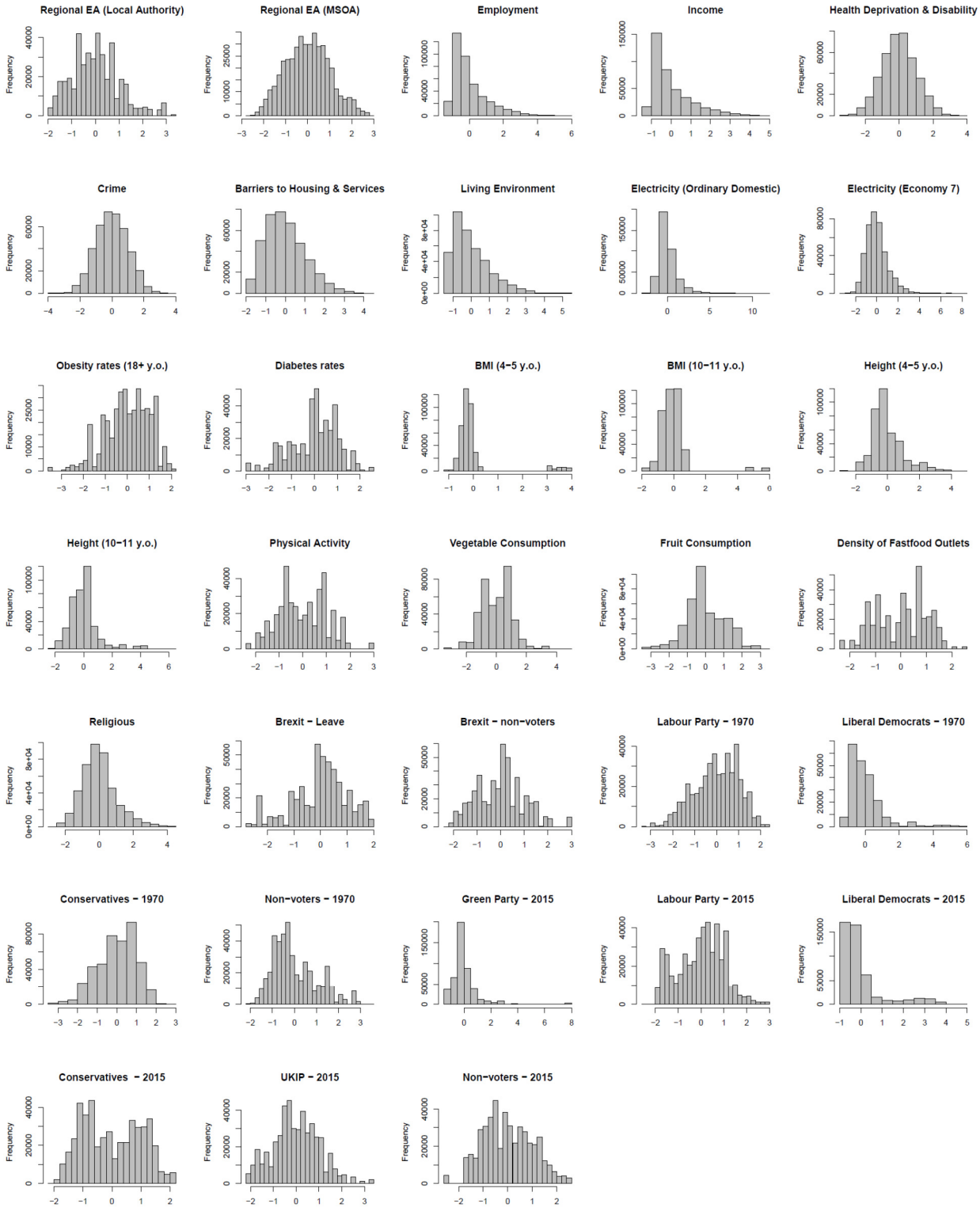
Supplementary Figure 10: Scatterplots showing the relationships between Moran's I of the significantly clustering polygenic scores and their association with indicators of economic deprivation (Townsend and the presence of coal fields) and migration. ***A*** *shows on the y-axis the absolute regression coefficients of the regressions with birthplace Townsend shown in Supplementary Figure 7. The correlations between the absolute regression coefficients and Moran's I are .86 for 1971 ($p = 6 \times 10^{-7}$), .86 for 1981 ($p = 5 \times 10^{-7}$), .82 for 1991 ($p = 6 \times 10^{-6}$), .80 for 2001 ($p = 2 \times 10^{-5}$), .80 for 2011 ($p = 1 \times 10^{-5}$). Excluding the two outlier educational attainment scores (EA2 [no UKB] & EA3 [no GB]), the correlations between the absolute regression coefficients and Moran's I are .55 for 1971 (p = .01), .52 for 1981 (p = .02), .44 for 1991 (p = .06), .39 for 2001 (p = .10), .44 for 2011 (p = .06).* ***B*** *shows on the y-axis the absolute test statistic of the t-test for group differences between coal fields and the rest of Great Britain (based on birth place) from Supplementary Figure 9. The correlation between the absolute test statistic and Moran's I is .93 ($p = 6 \times 10^{-10}$). Excluding the two outlier educational attainment scores, the correlations between the absolute test statistic and Moran's I is .70 ($p = 9 \times 10^{-4}$).* ***C*** *shows on the y-axis the absolute test statistic of the ANOVA for group differences between the four migration groups from Figure 4. The correlation between the absolute test statistic and Moran's I is .95 ($p = 4 \times 10^{-11}$). Excluding the outlier educational attainment, the correlations between the absolute test statistic and Moran's I is .78 ($p = 9 \times 10^{-5}$).*



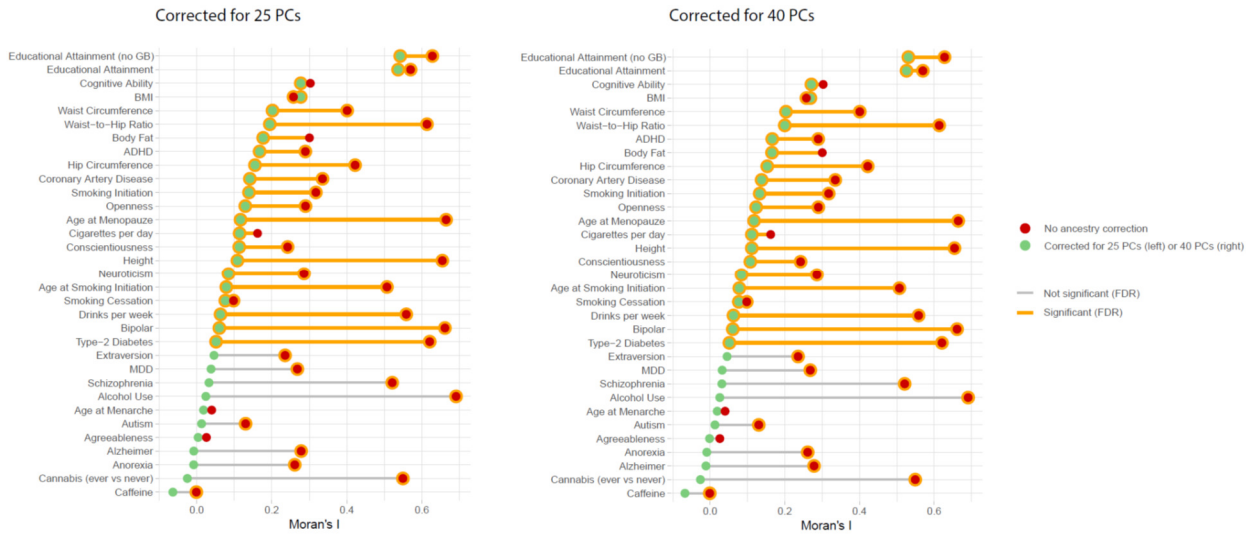
Supplementary Figure 11: Scatterplot and correlation between Moran's I on the y-axis and the interaction effect between YOB and coal region (i.e., the test for whether the increase/decline in PRS is stronger in coal regions than outside of coal regions) the x-axis for all 33 polygenic scores. We looked at the absolute effect size estimate on the x-axis because we were interested in the strength of the effect (the direction differs per trait).



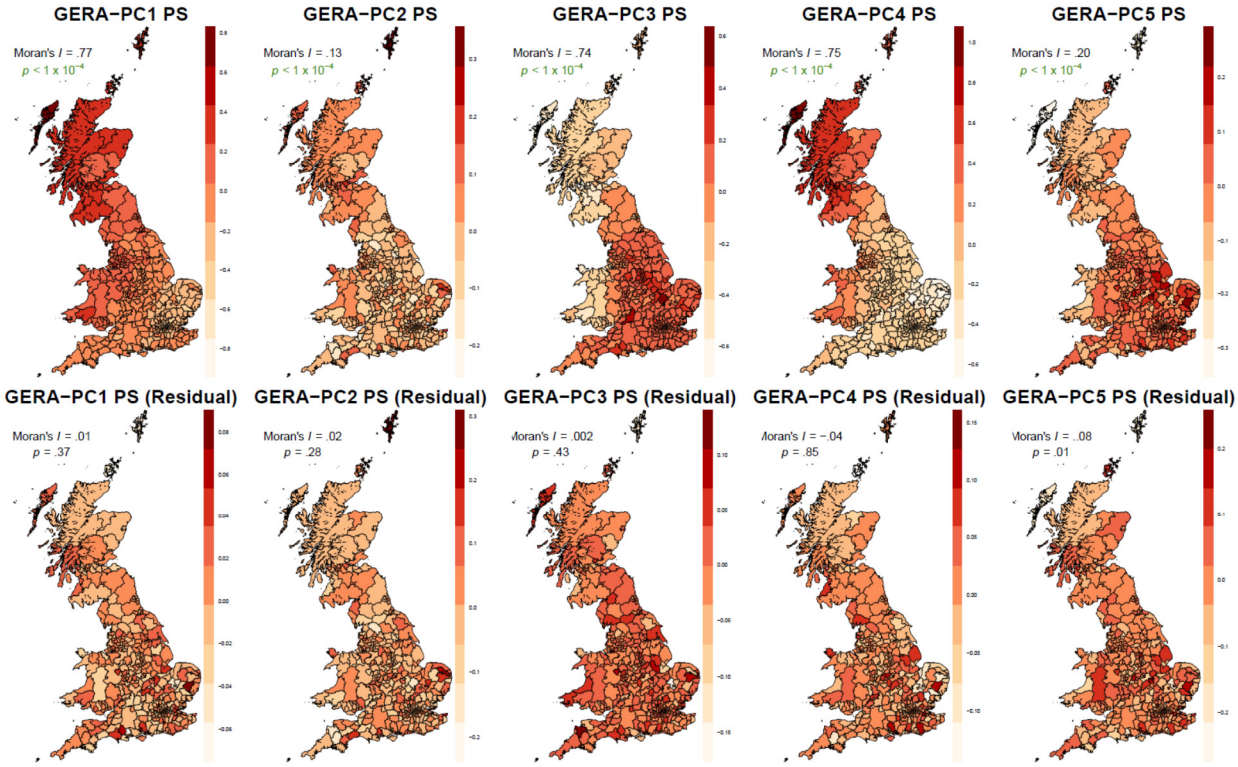
Supplementary Figure 12: The scatterplots and correlations between Moran's I of the ancestry-corrected polygenic scores and their absolute standardized effect sizes from the associations between regional measures and polygenic scores depicted in Extended Data Figures 4-7. The correlations are reported with and without the two EA polygenic scores, which show much higher Moran's I's than the rest of the polygenic scores.



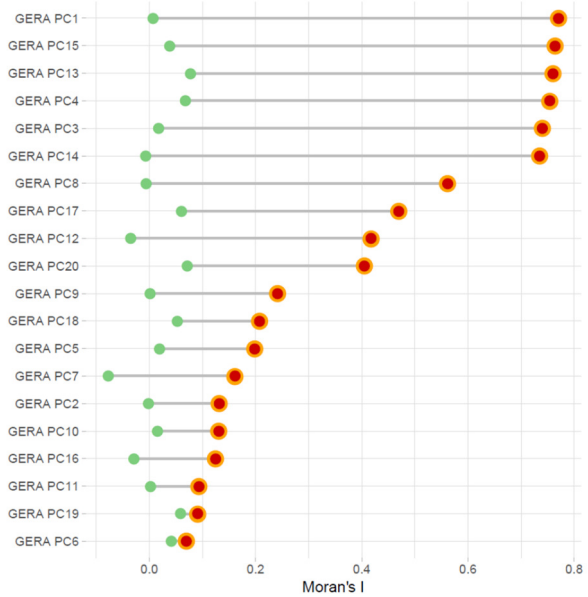
Supplementary Figure 13: Distributions of regional-level phenotypes. The distributions show all subjects included in the RGWASs, where all subjects from the same region were assigned the same phenotypic value (see Supplementary Table 2 for sample sizes).



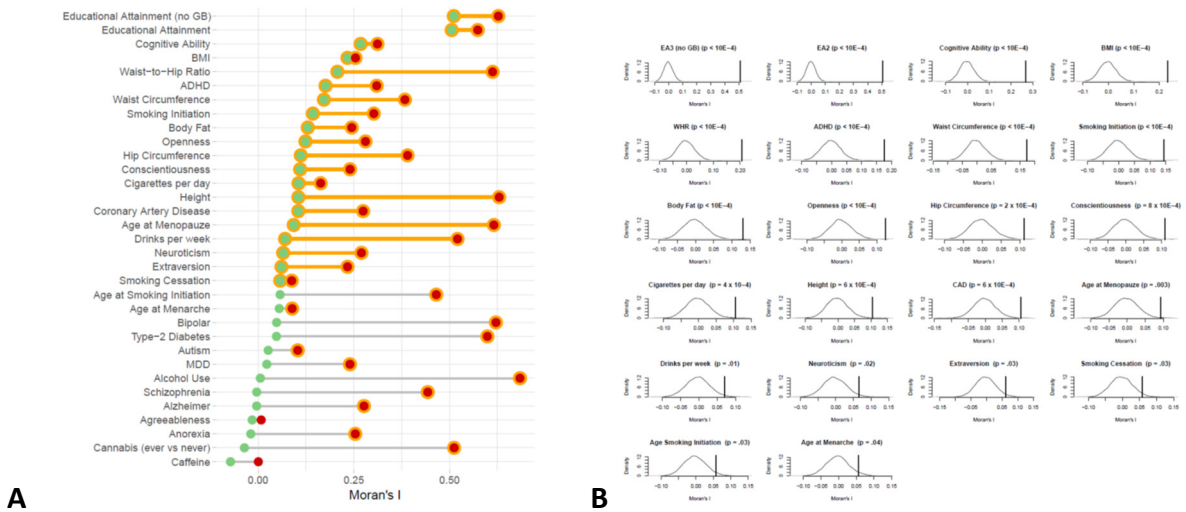
Supplementary Figure 14: Moran's I of 33 SBLUP polygenic scores computed using the average polygenic score per region in 378 local authority regions (N = 320,940 unrelated individuals). The Figure shows the Moran's I of the polygenic scores unadjusted for PCs (red) and adjusted for 25 PCs (green, left) or 40 PCs (green, right), where orange means a significant FDR corrected p-value < .05 (corrected for 33 tests). If the line in between is orange, it means that Moran's I was significantly larger than 0 both before and after correcting for 100 PCs.



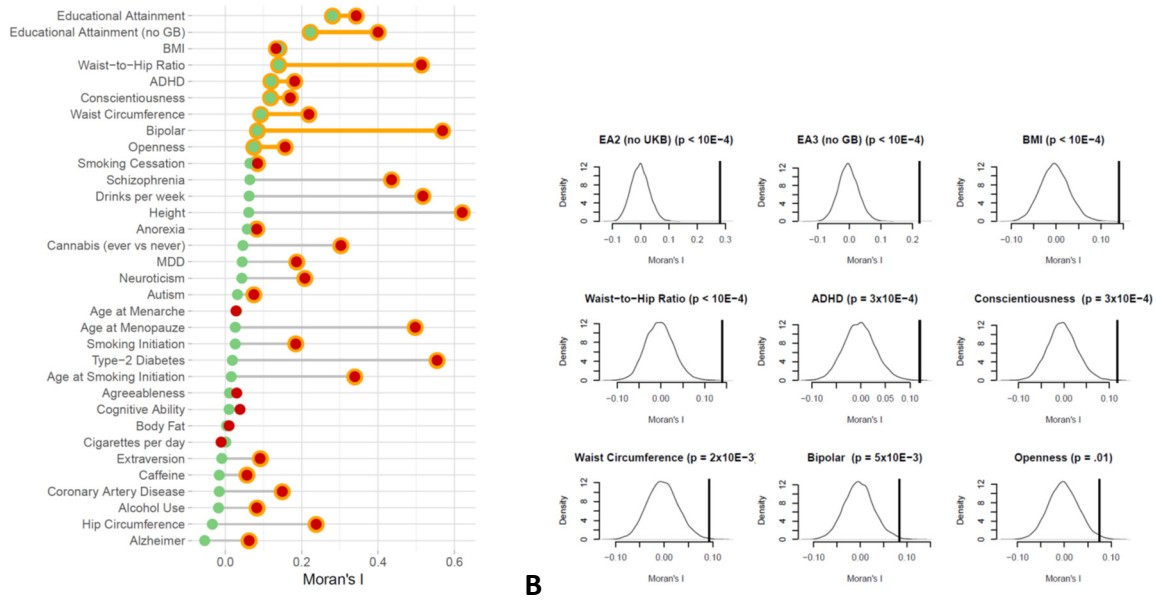
Supplementary Figure 15: Geographic distribution and Moran's I values for polygenic scores (PS) based on GWASs on the first 5 ancestry-informative PCs from the GERA dataset (N = 320,940 unrelated individuals). The upper five maps display uncorrected polygenic score, while the five maps below display the residuals of the polygenic scores after regressing out 100 PCs. Green p-values are significant after FDR correction.



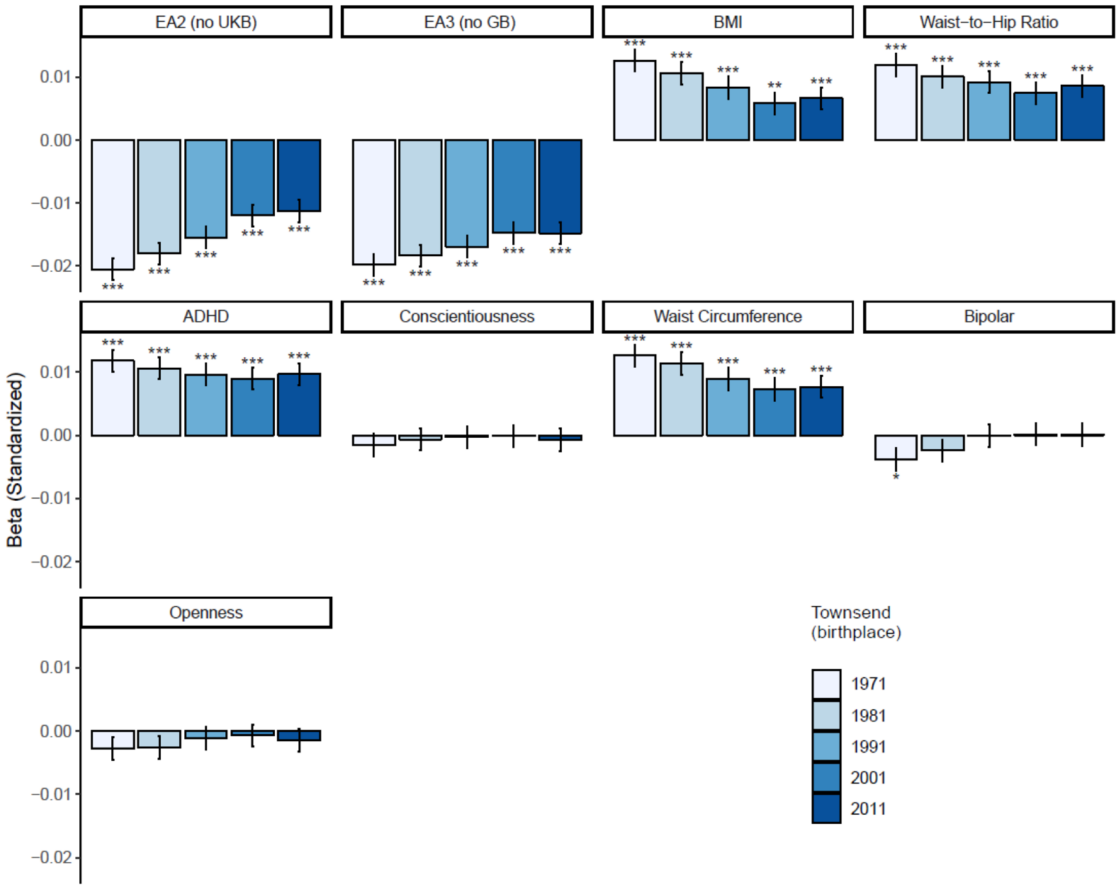
Supplementary Figure 16: Moran's I of polygenic scores based on GWASs on the first 20 ancestry-informative PCs from the GERA dataset computed using the average polygenic score per region in 378 local authority regions (N = 320,940 unrelated individuals). The Figure shows the Moran's I of the polygenic scores uncorrected for PCs (red) and corrected for 100 PCs (green), where orange means a significant FDR corrected p-value < .05 (corrected for 20 tests).



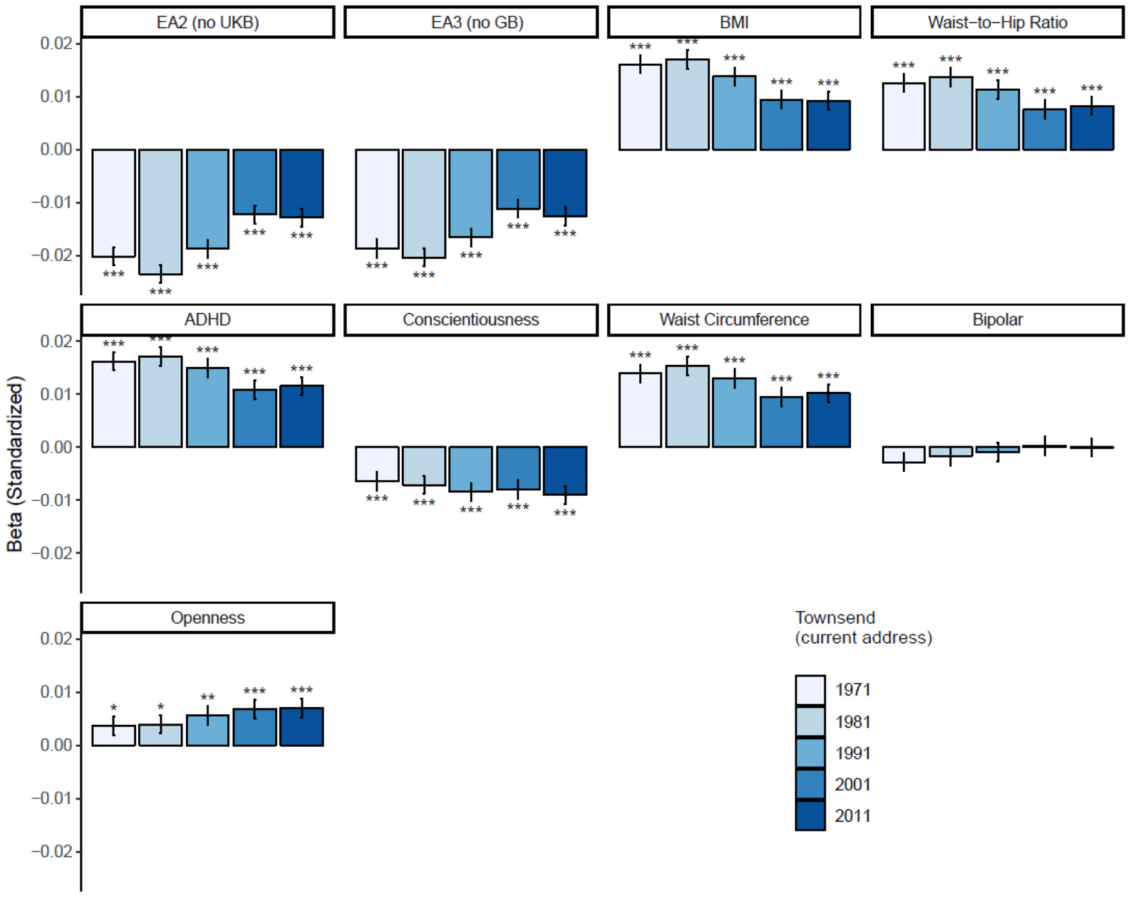
Supplementary Figure 17: Moran's I of 33 SBLUP polygenic scores based on SNPs with MAF < .1. Moran's I were computed using the average polygenic score per region in 378 local authority regions (N = 320,940 unrelated individuals). ***A*** *shows the Moran's I of the polygenic scores uncorrected for PCs (red) and corrected for 100 PCs (green), where orange means a significant FDR corrected p-value < .05 (corrected for 33 tests).* ***B*** *shows the permutation distributions for the SBLUP polygenic scores that have an FDR corrected p-value < .05 compared to the observed Moran´s I (vertical line to the right of the permutation distribution).*



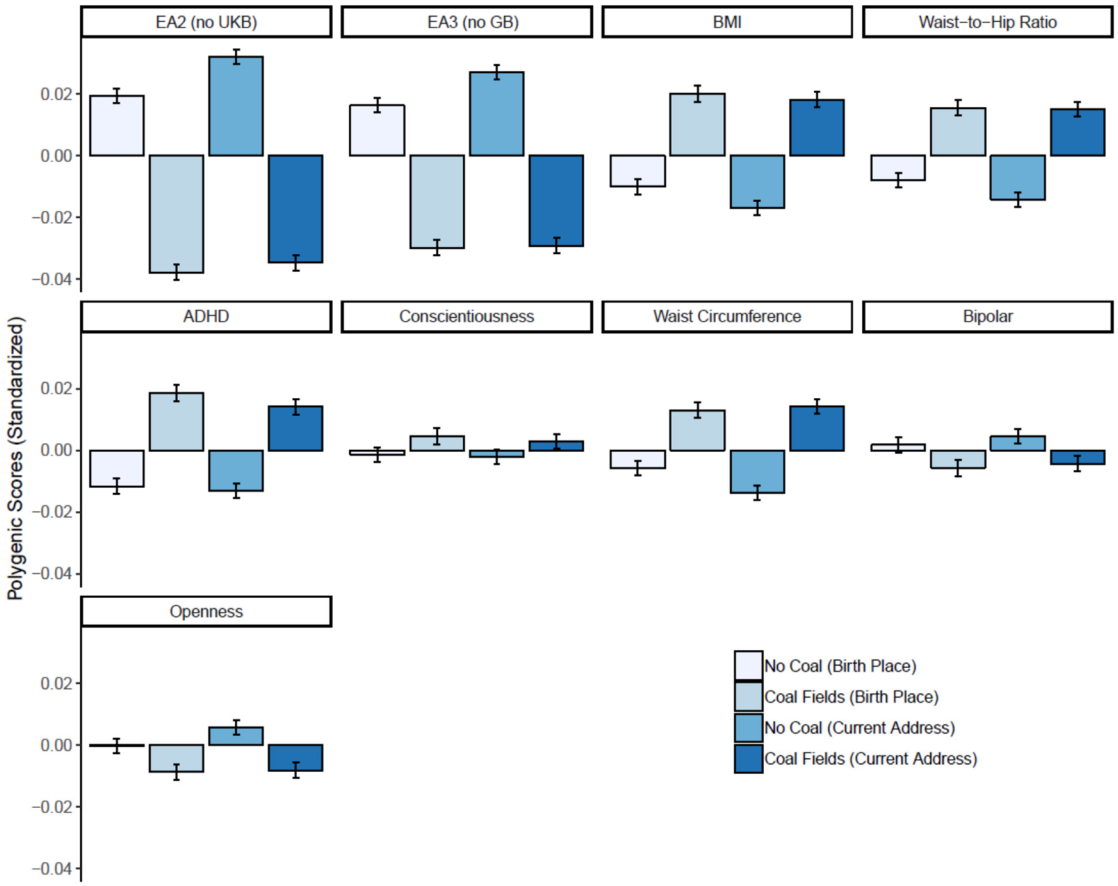
Supplementary Figure 18: Moran's I of 33 polygenic scores based on independent SNPs with p < .05. Moran's I were computed using the average polygenic score per region in 378 local authority regions (N = 320,940 unrelated individuals). ***A*** *shows the Moran's I of the polygenic scores uncorrected for PCs (red) and corrected for 100 PCs (green), where orange means a significant FDR corrected p-value < .05 (corrected for 33 tests).* ***B*** *shows the permutation distributions for the polygenic scores that have an FDR corrected p-value < .05 compared to the observed Moran´s I (vertical line to the right of the permutation distribution).*



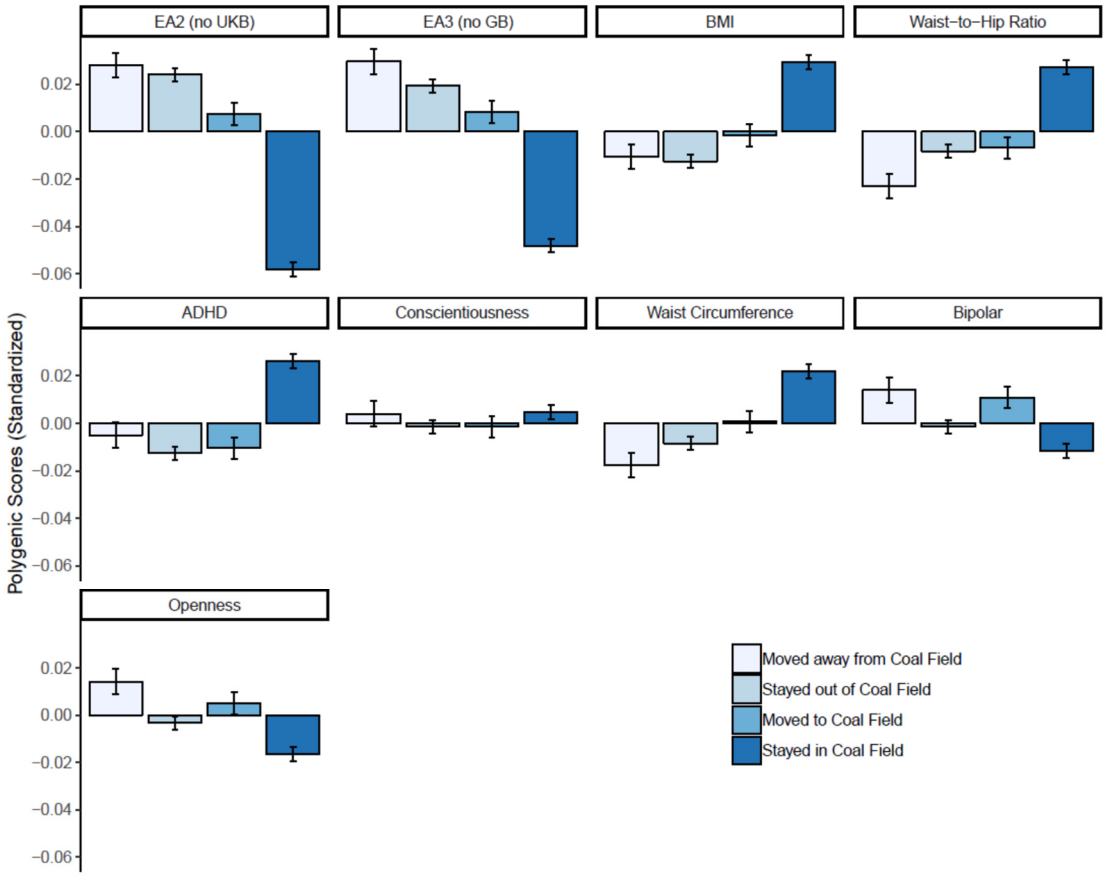
Supplementary Figure 19: The standardized regression coefficients and standard errors for the 8 significantly clustering polygenic scores (clumped, i.e., based on independent SNPs with p-values <.05; ordered by Moran's I) of the associations with the Townsend indices of 1971 to 2011 of the birth places of the subjects (N = 320,940 unrelated individuals). All polygenic scores shown are standardized residuals after regressing out 100 PCs.



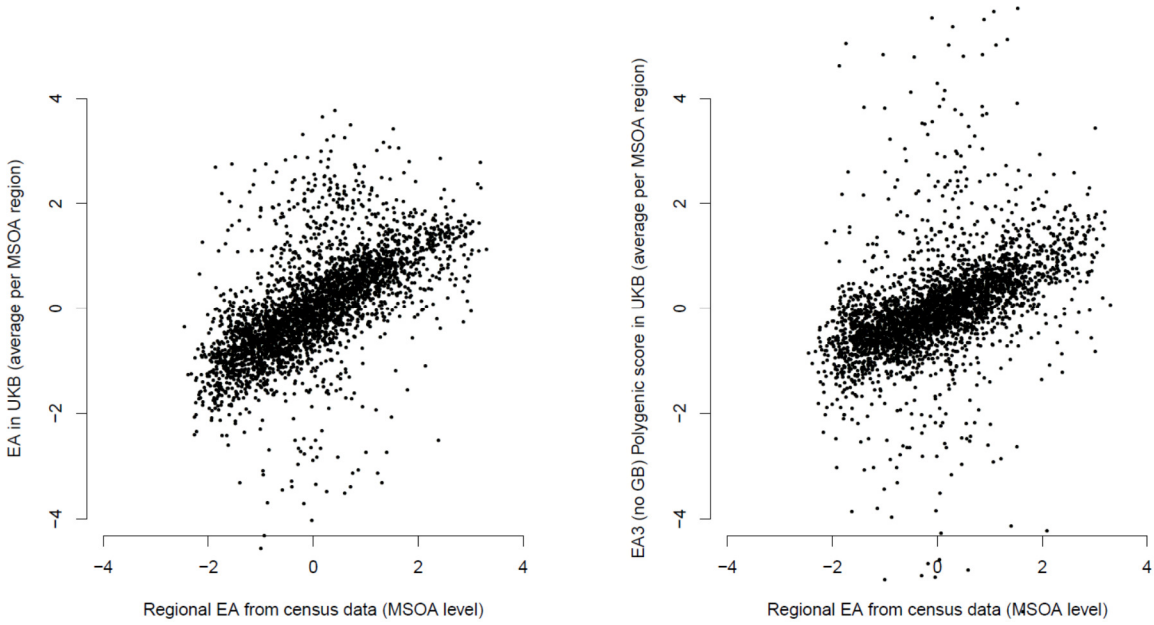
Supplementary Figure 20: The standardized regression coefficients and standard errors for the 8 significantly clustering polygenic scores (clumped, i.e., based on independent SNPs with p-values <.05; ordered by Moran's I) of the associations with the Townsend indices of 1971 to 2011 of the current address of the subjects (N = 320,940 unrelated individuals). All polygenic scores shown are standardized residuals after regressing out 100 PCs.



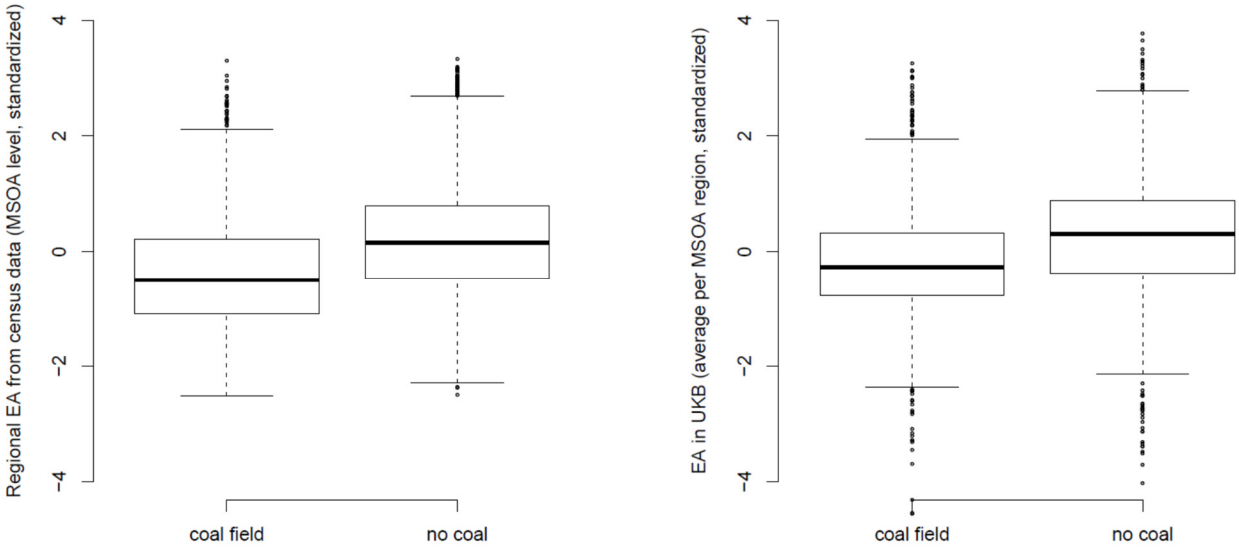
Supplementary Figure 21: The average and standard errors for 8 significantly clustering polygenic scores (clumped, i.e., based on independent SNPs with p-values <.05; ordered by Moran's I) within coal mining regions vs the rest of Great Britain for the birth place and the current address (N = 320,940 unrelated individuals). All polygenic scores shown are standardized residuals after regressing out 100 ancestry-informative PCs. The differences between Coal Fields and No Coal are significant for all scores except conscientiousness for both current address and birth place with an FDR corrected p-value < .05.



Supplementary Figure 22: The average and standard errors for 8 significantly clustering polygenic scores (clumped, i.e., based on independent SNPs with p-values <.05; ordered by Moran's I) for four migration groups: born in coal field area and moved out (N=35,024), born outside of coal mining area and stayed out (N=129,298), born outside of coal mining area and moved to coal mining area (N=47,505), born in coal mining area and stayed (N=111,838). All polygenic scores shown are standardized residuals after regressing out 100 ancestry-informative PCs. All polygenic scores show significant group differences after (FDR corrected p < .05), except conscientiousness.



Supplementary Figure 23: Regional educational attainment (EA) on MSOA level obtained from census data (Office of National Statistics) plotted against the average EA in UK Biobank corrected for age, year of birth, and sex (left plot; R^2 = 40%) and the EA3[1] (without Brits) polygenic scores corrected for 100 PCs (right plot; R^2 = 20%). All measures have been standardized to have mean 0 and SD 1.



Supplementary Figure 24: The difference between coal mining regions and the rest of the country in regional educational attainment (EA) on MSOA level obtained from census data (Office of National Statistics) in the left plot and the average EA in UK Biobank corrected for age, year of birth, and sex in the right plot. All measures have been standardized to have mean 0 and SD 1. Both differences are significant ($p < 10^{-16}$), but the EA from census data shows larger differences (mean in coal fields = -.39, mean outside coal field = .19; t(4764.9) = -24.7) than EA as measured in UK Biobank, which are somewhat higher overall (mean in coal fields = -.20, mean outside coal field = .25; t(3331.6) = -13.9).