# Personality, intelligence and health

**Personality, Intelligence and Health: The Role of Genetics**

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*Abstract*

Personality and intelligence—both partly heritable traits—are related to indices of health and disease. In this chapter we present literature showing that genes explain part of their associations. This finding is supported by both quantitative genetic (primarily twin studies) and molecular genetic (using information from genome-wide tests of common genetic polymorphisms) studies. This genetic relationship may arise from two potential mechanisms: mediated pleiotropy, whereby genes influence a trait that in turn influence another trait; or biological pleiotropy, whereby genes directly influence both traits. We discuss these potential mechanisms and describe methods which can help to test the competing explanations.

The role of heredity in influencing human behaviour was recognised by Galton (1869) decades before the terms ‘gene’ and ‘genetics’ were coined. Galton was interested in human mental abilities, and inferred the inheritance of genius from the fact that eminent individuals of his day had large numbers of eminent individuals in their family history. In the early 20th century, quantitative genetics provided statistical methods for partitioning genetic and environmental causes of variation in traits (Falconer & Mackay, 1996). Today, molecular genetics methods focussed on gene-trait associations enable us to estimate the amount of genetic variance influencing a trait, and to identify specific genes with notable effects on the trait. Since Galton, quantitative and molecular genetics studies of personality and intelligence, which support genetic contributions, have amassed. This literature is essential to understanding personality and intelligence. Less obvious are its implications for understanding health and disease.

Personality and intelligence are associated with health and disease (Deary et al., 2010; Kubzansky et al., 2009; Wraw et al., 2015). Genetic mechanisms might partially underlie these associations. In this chapter, we discuss potential mechanisms underlying genetic associations between personality/intelligence and health.

## 1 Personality and IQ traits as predictors of disease

### 1.1 Personality and disease

Personality describes differences in how people react in situations, how they interact with others, how they view the world, and their reactivity and stress-proneness. There are various models of personality (see Matthews et al., 2009). One of the more popular models is the Five-Factor Model, which posits that human personality can be represented by five traits or domains (Costa & McCrae, 1992). These traits include: Extraversion, a tendency to being outgoing, to seek excitement, and to experience positive emotions; Neuroticism, a tendency to being anxious, emotionally unstable, and experiencing low affect; Openness, a tendency to

having an active imagination, enjoying intellectual challenges, and having liberal views; Agreeableness the tendency to be altruistic, compliant, and cooperative; and Conscientiousness, a tendency to be goal-directed, self-disciplined, and exhibit self-control.

Research on personality and mental health outcomes has a long history. A meta-analysis of 33 studies found that higher Neuroticism was related to risk for all of the disorders except for child externalizing/conduct disorders; higher Conscientiousness and Agreeableness were both related to a reduced risk of all of the disorders except for anxiety disorders, somatoform disorders, and "other" disorders (Malouff et al., 2005). Of the other dimensions, Extraversion was associated with reduced risk of mood disorders, anxiety disorders, schizophrenia, and eating disorders, and there was some suggestion that higher Openness was associated with greater risk of mood and dissociative identity disorders. Personality disorders are also associated with the Five-Factor model as Neuroticism, Extraversion, Agreeableness, and Conscientiousness relate to and distinguish between personality disorders (Saulsman & Page, 2004).

Personality also plays a role in mental health comorbidity and severity. For example, Neuroticism was largely responsible for having multiple internalizing disorders, such as major depression or generalized anxiety disorder (Kahn et al., 2005) and better treatment outcome for depression over a short time span has been related to lower Neuroticism, higher Extraversion, and higher Conscientiousness (Hayward et al., 2013). Personality is also related to good mental health; people lower in Neuroticism and higher in Extraversion, Agreeableness, and Conscientiousness are happier (Steel et al., 2008).

It is perhaps unsurprising that personality traits relate to mental health, but personality is also robustly associated with physical health. In a nationally representative sample, participants who reported having one of several health conditions or diseases were higher in Neuroticism and lower in Conscientiousness, Extraversion, and Openness with the results for

Agreeableness being mixed (Goodwin & Friedman, 2006). However, some of the best evidence for the link between personality and health comes from studies of mortality risk. In general, higher Conscientiousness, Extraversion, Agreeableness, and Openness, and lower or higher Neuroticism, depending on the study, are associated with a reduced risk of dying early from all causes (Deary et al., 2010). At the level of death from specific diseases, risk of cardiac death, for example, has been associated with low Agreeableness (Almada et al., 1991; but see Tindle et al., 2009), as has been risk of cancer death (Tindle et al., 2009). In a second-order meta-analysis of 36 meta-analysis studies on the Five-Factor Model traits and health variables, Agreeableness, Conscientiousness and Neuroticism showed larger associations with overall health and wellbeing than did Extraversion or Openness to Experience; and the associations with mental health (e.g., depressive symptoms, schizophrenia, personality disorder) were larger than with physical health (e.g., cancer, diabetes, all-cause mortality) or health behaviours (e.g., physical activity, smoking, risky sexual behaviour) (Strickhouser et al., 2017).

### 1.2 IQ and disease

Intelligence refers to people's abilities to understand and manage cognitive complexity (Neisser et al., 1996). Standardised intelligence tests typically measure performance on verbal comprehension and knowledge, numerical skill, visuospatial manipulation, psychomotor speed, and memory. Scores on these tests are inter-correlated giving rise to a general factor, which can be represented by an aggregate score (e.g., IQ) (Deary, 2013). Research linking intelligence to disease tends to focus on IQ scores.

More intelligent children, adolescents, and young adults tend to live longer. A systematic review and meta-analysis of 16 studies showed that a standard deviation advantage in IQ was associated with a 24% lower risk of death over 17 to 69 year follow-up periods (Calvin et al., 2011). The fact that intelligence was assessed early in life, when

chronic disease is rare, all but rules out the possibility that these findings reflect the influence of poorer health on IQ scores and mortality risk. Importantly, adjusting for parental social class does not weaken these associations and so it is equally unlikely that the link is confounded by childhood socioeconomic background.

More intelligent people also appear to be less susceptible to physical disease. People who are more intelligent when young are less likely to develop coronary heart disease or have a stroke (Lawlor et al., 2008), and have healthier profiles as regards cardiovascular disease risk factors, including blood pressure, smoking, body mass index and levels of inflammatory factors(Luciano et al., 2010; Luciano et al., 2009) . In middle-age, higher IQ in youth is associated with lower levels of subclinical atherosclerosis (Roberts et al., 2013), though this association may not persist into old age (Gale et al., 2015). Some studies found that people who have a higher IQ when they are young eat a healthier diet and exercise more as adults (Batty et al., 2007). On the other hand, people who are more intelligent when they are young do not seem to be less likely to develop cancer (Batty et al., 2009), but they have better self-rated health as adults (Wraw et al., 2015) and are less likely to be absent from work due to sickness (Henderson et al., 2012).

There is also evidence to suggest that higher IQ in youth is linked with a lower likelihood of being admitted to a psychiatric hospital, and of being diagnosed with several specific mental disorders including schizophrenia, anxiety, substance-use disorders, and personality disorders (Gale et al., 2010).

## 2 Genetic influences on personality and IQ

Quantitative genetic research uses family designs—adoption studies, twin studies, and parent-offspring, extended pedigrees—to estimate the relative influence of genes and the environment on traits. Expectations of trait similarity between pairs of family members can be formulated based on their known genetic similarity (e.g., full siblings/non-identical twins

share 50% of their genes in common; identical twins share 100% of their traits in common) and compared with observed similarity in the trait. In adoption designs, for example, genetic influences would be apparent if adopted offspring resembled their biological parents more than their adoptive parents. The proportion of genetic to total variation in a trait is framed as the heritability and describes the extent to which genes cause the variation observed in a trait among individuals in a specific population. Heritability has most commonly been estimated using the classical twin design, which compares the similarity of identical and non-identical twins raised in the same household. This design thus allows one to test for the effects of sharing an environment in common. In this design, a greater similarity of identical than non-identical twins is suggestive of genetic effects. Analytic approaches, including structural equation models, to estimate genetic and environmental variance components in twin studies are described in Rijsdijk and Sham (2002).

Molecular genetic research, on the other hand, primarily concerns identifying the specific genes affecting a trait. Linkage studies have historically been useful in identifying regions of chromosomes that contain loci influencing a trait. However, in the last decade, the affordability of genome-wide association (GWA) methods has resulted in their being the preferred gene finding technique. In its simplest form, genetic association studies test for the linear relationship between the genotype of a specific gene (or genetic marker) defined by a pair of alleles (a variant form of a gene, with one inherited from each parent). Typically such studies are carried out in samples of unrelated individuals. This insures that the assumption of statistical independence is not violated and that very large samples can be recruited. Given that approximately 20,000 genes comprise the human genome, an *a priori* approach of focussing on candidate genes has mostly not proven to be an effective strategy. Consequently, researchers have turned to testing whether hundreds of thousands to millions of polymorphisms across the genome are related to traits, making sure to adjust for the large

number of statistical tests by correcting for the false-discovery rate (Johnson et al., 2010). To obtain sufficient power, meta-analysis of GWA results from independent cohort studies is performed. Typically, for psychological variables, the GWA analyses are run on standardised measures/latent traits to account for the variation in tests/scales often used across the studies.

A recent development in molecular genetic research is to estimate the heritability of traits due to common genetic variants (Yang et al., 2011). In unrelated individuals, the genetic relationship matrix between individuals (calculated from genome-wide single nucleotide polymorphism data; SNPs) is related to similarity on phenotypic measures of a trait to obtain an estimate of heritability for that trait from all SNPs. This is analogous to regression analysis of pairwise phenotypic similarity on pairwise genetic similarity (estimated across the entire genome) for all pairs of unrelated individuals in the sample (Visscher et al., 2014) and can be extended to examine whether two or more traits are genetically correlated.

## 2.1 Personality

Bouchard and Loehlin's (2001) review of the literature and meta-analysis focussing on the Five-Factor Model traits showed that approximately 50% of the variation was heritable and that the remaining variation was largely attributable to nonshared environmental effects. These findings indicate that people from the same family resemble one another in personality not because they share a family environment but because they share genes in common. The environmental influences onpersonality, and also the effect of measurement error, lead people within a family to differ.

Later studies have expanded on these results. A meta-analysis of 62 independent effect sizes incorporating over 100,000 participants estimated average personality trait heritability at 0.39 with the remaining 61% of variance due to environmental influences (Vukasovic & Bratko, 2015). There was no evidence of differential heritability for the broad traits. Heritability estimated from family and adoption studies (0.22) was lower than that

from twin studies (0.47) indicating the importance of non-additive genetic effects. Non-additive genetic effects include gene by gene interaction and dominance effects, so they contribute to sibling/twin covariance but not to other family relationships. Twin studies (and those incorporating additional data from non-twin family members) find that non-additive genetic effects account for up to half of the genetic variance on Extraversion, Neuroticism, and Conscientiousness broad domains (Hahn et al., 2013; Keller et al., 2005) and on narrow traits akin to facets (e.g., alienation, control) (Finkel & McGue, 1997). An extended pedigree design in an Italian population isolate sample also found non-additive genetic effects on all Five-Factor Model traits except Agreeableness (Pilia et al., 2006).

Estimates of the heritability of the Five-factor model personality traits based on common SNPs has also been examined. In a study comprising 5011 adults, Neuroticism and Openness showed significant heritabilities of 0.15 (s.e. = 0.08) and 0.21 (s.e. = 0.08), respectively (Power & Pluess, 2015). The estimate of 0.15 for Neuroticism has been confirmed in a sample of over 91,000 adults (Smith et al., 2016). SNP-heritability of Neuroticism and Extraversion based on 12,000 adults yielded heritability estimates of 0.06 for Neuroticism and 0.12 for Extraversion (Vinkhuyzen et al., 2012). This same study found family-based heritability estimates of around 0.45, leading the authors to argue the importance of rare genetic variants and the inflation of family-based estimates due to unmodelled non-additive genes. Another SNP-heritability study, this one of around 8,000 adults, found SNP-based heritabilities for harm avoidance (Neuroticism) and novelty seeking (Extraversion) and persistence (Conscientiousness) ranging from 7% and 10%, i.e., only one fourth the size of the twin-based heritabilities (Verweij et al., 2012).

In terms of specific genes affecting personality traits, early research focussed on monoaminergic (e.g., dopamine and serotonin) and neuropeptide (e.g., oxytocin and vasopressin) genes (for a review see Montag & Reuter, 2014). Inconsistent replication and

the lack of support for these genes from GWA studies indicate that any true effects of these genes are very specific to test sampling characteristics suggesting that interaction effects with other variables are important. A GWA meta-analysis of the NEO-FFI personality traits (N = 17,375) showed a significant association between Openness and a SNP near the *RASA1* gene, and between Conscientiousness and a SNP in the *KATNAL2* gene, although these were not replicated (de Moor et al., 2012). A GWA meta-analysis of over 63,000 individuals that included multiple Neuroticism and Extraversion scales (harmonising these through item response analysis) found no significant associations for Extraversion and one association of a SNP in *MAGI1* for Neuroticism that was not replicated in two independent studies (Genetics of Personality et al., 2015; Okbay et al., 2016). These cohorts were recently meta-analysed with 59,225 individuals from the consumer genomics company '23andMe', to reveal eight significant independent SNPs, six of which remained significant on inclusion of UK Biobank and DeCODE genetics replication cohorts (Lo et al., 2017). Neuroticism was associated with an inversion polymorphism in 8p23.1 and a SNP in *MTMR9*, and Extraversion was associated with a SNP in *WSCD2* and one near *PCDH15*. Individual SNP effects were reportedly small; a previous GWA of Neuroticism (N=106,716) showed the mode of their significant SNP effect size to be 0.03 of a SD per allele (Smith et al., 2016).

Individual genetic variants therefore have very small effects on personality, but when the cumulative effect of each gene is considered up to one fifth of the genetic variance can be explained (Lo et al., 2017), supporting a polygenetic model of personality. The heritability that is unexplained by common genetic variants suggests a need to explore other types of variants. There has been one such study, which found no association found between the Five-Factor Model traits and large uncommon copy number variants (Luciano, MacLeod, et al., 2012). As yet, there have been no studies of rare single nucleotide variants, partly because of the high cost of sequencing individuals and the challenge of obtaining large homogenous

samples needed to analyse variants with a frequency of less than 1%. Twin and family studies show that non-additive genetic effects contribute to personality, but there have been no systematic attempts to study non-additive genetic factors at the genome-wide level due to the weakened statistical power to detect these in the absence of hypothesised effects.

## 2.2 IQ

Hundreds of twin and family studies converge on the finding that around 50% of the variance in IQ is due to genes when all ages are included together (Devlin et al., 1997; Tucker-Drob & Briley, 2014). A meta-analysis of around 600 twin studies published between 1958 and 2012, which sampled higher-level cognitive functions reported an identical twin correlation of 0.71 (estimated from 152,197 twin pairs) versus a non-identical twin correlation of 0.44 (from 158,626 pairs) (Polderman et al., 2015). Respective additive genetic and shared environmental contributions to variance were estimated at 0.54 and 0.18 and were equal across sex. In contrast to personality, shared environmental influences are important for higher cognitive abilities, and non-additive genetic influences less so. A meta-analysis of the heritability of general cognitive ability from cross-sectional twin studies (total N of 11,000) showed a linear increase: from 41% in childhood to 55% in adolescence and to 66% in young adulthood (Haworth et al., 2010). A longitudinal twin study of adult men estimated a heritability of 0.49 for general cognitive ability in young adulthood (mean age of 19.8 years), which increased to 0.58 in late middle age (mean age of 55.4 years) (Lyons et al., 2009). Importantly, the genetic correlation of general cognitive ability across test occasion was 1, indicating that the genetic factors responsible for variation in general cognitive ability in young adulthood are exactly the same as those influencing this trait 35 years later. In a much older sample (≥80 years), a heritability of 0.62 was reported for general cognitive ability in a small Swedish sample of healthy twins (110 identical twins and 130 non-identical) (McClearn et al., 1997).

The heritability of general cognitive ability estimated by SNP-based molecular genetic methods has been derived in a number of independent cohort studies. Unlike personality, these estimates more closely resemble those obtained from family-based studies, suggesting that common additive genetic variants provide a good account of genetic variation in cognitive ability. In children, a SNP-based heritability of 0.35 (95% confidence intervals: 0.12, 0.58) was reported for general cognitive ability in a cohort of 3154 12-year olds which compared with a twin-based heritability of 0.46 (95% confidence intervals: 0.42, 0.52) (Plomin et al., 2013). In 5517 children, a heritability of 0.46 was observed for full scale IQ (Benyamin et al., 2014). In two samples of middle-aged and older adults (N ~ 6000), heritabilities of ~0.28 (s.e. ~ .06) were reported for fluid-type cognitive ability components (Davies et al., 2015). The stability of genetic effects on IQ across time has also been investigated via SNP-based methods. In a longitudinal cohort of 1940 individuals whose IQ was measured at age 11 and roughly 60 years later, a genetic correlation of 0.62 (s.e. = 0.22) was found (Deary et al., 2012).

Candidate genes likely to be involved in cognitive abilities were identified from a review of 200 genetic studies published between 1995 and 2009 on cognitive healthy samples (Payton, 2009). The genes had been related to neurotransmitter functioning genes, implicated in disease/disorder, or were related to developmental and metabolic processes. Many of these candidate genes have not stood up to replication attempts in sufficiently powered samples (e.g., Chabris et al., 2012; Houlihan et al., 2009; Mandelman & Grigorenko, 2012). Only one gene, *APOE*, the e4 variant of which increases risk of Alzheimer's disease, shows evidence of an effect on cognitive ability (Wisdom et al., 2011). The effect size for global cognitive ability was 0.09% although this was moderated by age (larger at older ages). It may be that *APOE* variation is more related to cognitive change, with a meta-analysis GWA study of

cognitive ageing in 3511 individuals showing a significant association with the *APOE* locus (Davies et al., 2014).

In the largest meta-analysis GWA study of adult general cognitive ability to date (N = 53,949), the *APOE* locus was again shown to be significant along with SNPs in two other regions containing *MIR2113* and *AKAP6/NPAS3* genes (Davies et al., 2015). A GWA of specific cognitive functions in 112,151 UK Biobank participants has recently replicated 12 of the 13 genome-wide SNPs from the meta-analysis GWA of general cognitive ability: 11 SNPs on chromosome 6 were associated with verbal-numerical reasoning and one SNP in the *AKAP6* gene was associated with verbal-numerical reasoning, reaction time and memory (Davies et al., 2016). Additionally, this study reported significance for SNPs in 20 genomic regions, with findings for the *ATXN2*, *CYP2DG*, *APBA1*, and *CADM2* genes replicating in existing GWA studies of childhood and adult cognitive ability, and educational attainment (which is strongly genetically correlated with intelligence). The small effect sizes (< 0.1%) for individual genes combined with the substantial SNP-based heritability highlights the polygenic nature of this trait.

## 3 Genetic covariance between personality and disease

### 3.1 Quantitative Genetics Findings

Twin studies have been used to estimate the genetic associations between personality and health variables, typically with the aim of establishing the proportion of the phenotypic correlation that is due to genes versus the environment and the similarity of the genes influencing personality and the health variable. For example, a study of 542 same-sex twins showed that Agreeableness ($r_g$ = -0.18), Openness ($r_g$ = 0.17), and Extraversion ($r_g$ = -0.06), Neuroticism ($r_g$ = 0.43), and Conscientiousness ($r_g$ = -0.36) were all genetically correlated with major depression (Kendler & Myers, 2010). Interestingly, the genetic overlap between Conscientiousness and depression decreased when Neuroticism was included in the same

model. The results of a much larger (7831 twin pairs) study yielded similar results for Neuroticism ($r_g$ = 0.46) and Extraversion ($r_g$ ~ 0.12) (Kendler et al., 2006). A study of over 8000 twins found evidence for genetic ($r_g$ = 0.80) and environmental ($r_g$ = 0.20) overlap between generalized anxiety disorder and Neuroticism (Hettema et al., 2004).

In terms of mental disorder comorbidity, Neuroticism (measured 25 years prior) accounted for a small proportion (~24%) of the covariance between major depression and generalized anxiety disorder in over 14,000 Swedish twin pairs (Kendler et al., 2007). For comorbidity among seven internalizing disorders, the genetic variance in Neuroticism explained one-third to two-thirds of the genetic liability for each disorder (Hettema et al., 2006). Personality genes also overlap with externalising disorders. For example, absolute genetic correlations between Five-Factor Model traits and alcohol and nicotine dependence ranged from 0.11 (Extraversion and cannabis dependence) to 0.46 (Agreeableness and nicotine dependence) (Few et al., 2014). What research there is on the topic suggests that the genetic overlap between personality traits and personality disorders is considerable (reviewed in South & DeYoung, 2013). With regard to positive mental health, all the genetic variance in subjective well-being has been found to overlap with genes influencing the Five Factor Model personality traits (especially Neuroticism, Extraversion and Agreeableness) (Weiss et al., 2008).

Very few studies have explored the genetic contribution to associations between personality and physical health. A pedigree study of 34,469 relative pairs drawn from the population of the island of Sardinia did not find genetic overlap between personality and cardiovascular traits (Pilia et al., 2006). In a study of longevity, higher scores on Psychoticism, which is associated with low Agreeableness and low Conscientiousness, and lower scores on a measure of Optimism showed a small genetic overlap with increased mortality risk (Mosing et al., 2012).

## 3.2 Molecular Genetics Findings

The first molecular genetic findings to relate genes for personality to mental health used polygenic profile scoring. This method uses results from GWA studies of the predictor to form a composite score by summing the effect of each genetic variant on that trait (see International Schizophrenia et al., 2009). These scores are then calculated in an independent sample who have been genotyped and who have been measured on the outcome variable of interest. The GWA-derived polygenic score is used to predict phenotypic variation in the outcome variable. The first studies found that polygenic scores for Extraversion and Neuroticism predicted measures of anxiety and depression (Luciano, Huffman, et al., 2012; Middeldorp et al., 2011). Luciano and colleagues (2012) showed that polygenic Extraversion scores based on a GWA of ~6260 individuals predicted symptoms of anxiety ($r = -0.09$) and depression ($r = -0.10$). Polygenic Neuroticism predicted normal variation in general psychological distress ($r = 0.04$). Middeldorp and colleagues (2011) used a larger GWA (N=13,835) to generate polygenic personality scores predicted into case-control samples and found that polygenic Neuroticism scores predicted depression and polygenic Extraversion scores predicted bipolar disorder. In both analyses, the amount of variance explained was around 0.1%. In an even larger GWA study of Neuroticism (N~55,000), polygenic scores explained 1% of variance in major depressive disorder (Genetics of Personality et al., 2015). Using polygenic risk scores for major depressive disorder (based on a GWA of 18,759 case-controls) to predict Neuroticism in UK Biobank explained only 0.001% of variance (Gale et al., 2016). In this same study, polygenic risk scores for bipolar disorder and schizophrenia explained 0.0003% and 0.001% of variance in Neuroticism, respectively; no variance was explained by polygenic scores for ADHD, Alzheimer's disease, or anorexia nervosa. UK Biobank participant response rates were low (around 5.5%) and a simulation study has shown that selection bias can generate biased gene association estimates, particularly for polygenic

scores, due to collider bias (Munafo et al., 2016). That is, traits in the general population emerge as correlated in samples where both traits influence study participation due to implicit conditioning on their shared effect. Unless the gene association analysis controls for each trait, bias in the genetic associations underlying the traits may occur. It is conceivable that both Neuroticism and health traits (and for that matter, IQ and health) might both influence study participation, so some caution is warranted in interpreting results from such studies. In adolescents, polygenic smoking risk has been negatively associated with Conscientiousness (r = -0.06) (Krapohl et al., 2015).

Cross-trait linkage disequilibrium (LD) regression enables genetic correlations to be estimated from separate GWA studies of diverse traits using only information about the signed effect of each variant (see Bulik-Sullivan et al., 2015). The technique capitalises on relationships between variants across the genome in known populations with test statistics from the association analysis being proportional to this linkage disequilibrium pattern if the variant is causal. The amount of (co)variance tagged by causal variants can then be estimated. Using this method, Gale et al. (2016) estimated genetic correlations between Neuroticism and mental health traits. The GWA results for Neuroticism came from a sample of 108,038 UK Biobank participants aged 40 to 73 years and for the mental health variables, samples ranging from ~4,000 (ADHD) to ~150,000 (schizophrenia) cases-controls. Significant correlations (see Figure 1) were found for anorexia nervosa (r = 0.17), major depressive disorder (r = 0.66), and schizophrenia (r = 0.21).

Turning to good mental health and using this same method, the genetic correlation between Neuroticism and subjective well-being has been reported at -0.75, and polygenic subjective well-being scores explained 0.7% of variance in neuroticism (Okbay et al., 2016). Using GWA results for Extraversion and Neuroticism in ~70,000 individuals from the Genetics of Personality Consortium, polygenic scores for Neuroticism and Extraversion

predicted up to 0.04% of the variance in positive affect and life satisfaction in UK Biobank (Weiss et al., 2016). In this same study, genetic correlations were around 0.50 for Neuroticism and well-being.

One study to date investigated genetic correlations between personality (Neuroticism only) and physical health (Gale et al., 2016). Using LD score regression, no significant correlations were found with systolic and diastolic blood pressure, BMI, coronary artery disease, longevity, or type 2 diabetes (see Figure 1). The strongest correlation was for type 2 diabetes ($r = -0.14$). Using GWA results from studies of physical health, a polygenic risk score for each health variable was used to predict Neuroticism. Lower polygenic risk for BMI and higher polygenic risk for coronary artery disease were associated with higher Neuroticism, with respective coefficients of -0.009 and 0.011. The very small effect sizes generally found for cross-trait polygenic prediction methods are typical of this kind of analysis. It is important to note that polygenic scores used to predict the same trait on which polygenic scores are based only explain a few percent of the total variance, so some of the small effect sizes (e.g., neuroticism polygenic scores predicting depression) are close to the theoretical maximum that could be obtained.

INSERT FIGURE 1 HERE

## 4 Genetic covariance between IQ and disease

### 4.1 Quantitative Genetic Findings

Investigations of the genetic and environmental contributions to the relationship between IQ and psychiatric disorders has been reported for ADHD, schizophrenia, and bipolar disorder. In 1116 families of 5 year-old twins, the relationship between IQ and ADHD symptoms was mediated mostly by genes (86%) and entirely by genes when

considering diagnosis (Kuntsi et al., 2004). Genetic correlations with IQ were -0.45 for symptoms and -0.59 for diagnosis. For schizophrenia, 92% of its covariance with IQ was due to genes, and the genetic correlation was -0.61 (Toulopoulou et al., 2007). Using data from over 1 million male Swedish Military conscripts, Kendler et al. (2015) showed that high IQ reduces the influence of genetic liability on schizophrenia risk. For bipolar disorder, the phenotypic correlation with IQ was primarily mediated by genes, and the genetic correlation was -0.51 (Georgiades et al., 2016). These associations were unchanged when controlling for current mood. The covariance of all of these disorders with IQ was due primarily to genes, but the exact genes influencing the variance in the traits, as judged by the genetic correlations, were different.

Few studies have explored the genetic relationship between intelligence and physical health. In the Longitudinal Study of Aging Danish Twins (1053 pairs), Johnson and colleagues (2009) derived latent cognitive ability and physical fitness factors from measures collected contemporaneously when participants were, on average, 76 years old. The phenotypic correlation was 0.46; the genetic correlation was 0.56. Luciano et al. (2010) investigated the aetiology of the associations between intelligence and risk factors of cardiovascular disease using an extended pedigree of 6118 individuals from 1983 families. Genetic correlations were found between general cognitive ability and height, lung function, neuroticism, psychological distress, physical activity, diet, smoking status and exposure, education and income. The correlations ranged 0.07 for lung function to 0.63 for education. For all associations the genetic contribution explained more than 50% of the variance, with the exception of lung function, which was lower. A recent study of American, Swedish, and Danish same-sex twins dissected the underlying association between intelligence and longevity (Arden et al., 2016). This study meta-analysed the results from the cohorts where

one or both members of a twin pair died. The genetic contribution to positive covariance between intelligence and lifespan was 95%.

### 4.2 Molecular Genetic Findings

Recently, there has been a flurry of research using polygenic score prediction and LD score regression to estimate the genetic overlap between intelligence and both physical and mental health (Clarke et al., 2016; Harris et al., 2016; Marioni et al., 2016). Hagenaars and colleagues (2016), for example, quantified the genetic overlap using GWA results of cognitive function in UK Biobank and meta-analysis GWA results for vascular-metabolic, neuropsychiatric, and physiological-anthropometric traits. Focussing on verbal-numerical reasoning (N = 36,035), significant genetic correlations were found for schizophrenia (-0.29), autism (0.19), Alzheimer's disease (-0.32), BMI (-0.12), and ischaemic stroke (-0.23). In terms of polygenic scores for the health-related variables predicting phenotypic variance in verbal-numerical reasoning, significant correlations were found for Alzheimer's disease (-0.02), autism (0.02), major depressive disorder (-0.02), schizophrenia (-0.06), coronary artery disease (-0.02), ischaemic stroke (-0.01), large vessel disease (-0.10), systolic blood pressure (0.01), BMI (-0.03), and height (0.02).

In 3152 adolescents, polygenic scores for 13 psychiatric and cognitive traits were related to 50 traits covering psychopathology, personality, cognitive and academic abilities, and physical traits (Krapohl et al., 2015). Polygenic scores for college attendance predicted continuous measures related to conduct disorder, ADHD, and autism (maximum r of -0.08), but psychiatric polygenic scores did not predict variance in cognitive traits. The discrepancies between this study and the UK Biobank study is probably because the latter was based on a larger sample size and had enough power to detect effect sizes as small as .0001% of variance. Indeed, in adolescents, correlations between polygenic ADHD, autism and major depressive disorder with cognitive ability were |0.05| but were not judged significant. An LD

score regression approach based on childhood IQ GWA results (N = 12,441) and six psychiatric GWA results found significant genetic correlations of IQ and autism spectrum disorder (0.36) and Alzheimer's disease (-0.34) (Hill et al., 2015). Using adult IQ GWA results, genetic correlations were found for schizophrenia (-0.23) and Alzheimer's disease (-0.32), but not autism. Whereas polygenic IQ predicts only miniscule variance in health (and vice-versa), the genetic correlations estimated from genome-wide common variants show a dependence on some of the same genes between intelligence and various mental and physical health conditions.

## 5 Potential mechanisms for the genetic covariation

Having found that common genes underlie the phenotypic relationships between IQ and personality on the one hand and physical and mental health on the other, leads one to ask what this all means? Prior to addressing this question it is important to note that in most cases, genetic effects explain more covariance than environmental effects. For now, however, let us consider what a complete genetic mediation of a phenotypic association means. In this case genes explain the observed correlation; however, if each trait is also influenced by independent genes, then the genetic correlation can take any value other than 0 or 1. Specifically, the genetic correlation will be closer to 1, the smaller the effects of unique genes on each trait being measured. What would this tell us? It may indicate that the genes affects both traits, but it does not tell us whether this pleiotropy is mediated or biological (Solovieff et al., 2013). The former occurs when a gene affects a trait only because it is caused by another trait which is directly influenced by that gene. The latter occurs when a gene directly influences multiple traits through its effects on a single biological pathway or multiple independent pathways.

Mediated pleiotropy supposes that one variable is more proximal to the gene function. Given that intelligence differences and, to a lesser extent, personality variation form earlier

than health outcomes, and longitudinal studies support a causal direction from trait to health outcome, the common genetic variance may reflect gene effects on intelligence or personality that are captured in any measures with which they relate. If the mechanism by which personality and intelligence influence health is via health behaviour, we would expect health behaviours to be influenced by the same genes. Clearly, though, genetic influences on health behaviours and disease traits are due to other genes unrelated to intelligence or personality and therefore genetic correlations are always less than 1.

Biological pleiotropy is more compatible with a system integrity type approach to explain shared genetic variance between intelligence with disease. Here, mental, physiological, and physical traits are considered to partly derive from the same biological factors that lead to a better overall functioning (Deary, 2012). This general system integrity might arise then from genes that have their effects in multiple biological pathways. Such pleiotropy might contribute to a so-called latent 'fitness factor' (Arden et al., 2009) of system integrity, especially given that a comparison of genomic patterns of pleiotropy in baker's yeast, the nematode worm, and the house mouse suggest that pleiotropy may have supported the evolution of complexity (Wang et al., 2010). Knowing the function of the genes implicated in intelligence, personality, and disease is needed to establish whether these genetic correlations reflect biological pleiotropy. As reviewed, however, there are no single genes with so large an effect that they have been pursued functionally.

Given that a variant is associated with two traits, mediated pleiotropy can be investigated by testing whether the genetic association is still significant after controlling for or stratifying on the causal trait (i.e., a proposed mediator such as IQ). If it still is significant it would mean that the genetic effect is not completely mediated and would support biological pleiotropy assuming that there is no third variable influenced by the gene and related to both traits (see Figure 2). Mendelian randomization incorporates this procedure to disentangle

causal relationships between modifiable exposures, such as smoking, and disease (Smith & Ebrahim, 2003). An extension to Mendelian randomization is to use polygenic risk scores for the exposure and outcome to test whether there is support for a particular causal direction (Gage et al., 2016). For personality traits and intelligence there are no reliable individual genetic associations that could be selected as instruments in this type of analysis, although polygenic scores might be used with some success.

INSERT FIGURE 2 HERE

Twin methods are also able to distinguish direction of causality between two traits when certain conditions are met concerning their variance structure. For example, Toulopoulou and colleagues (2015) tested causation between latent cognitive and brain volumetric factors and liability to schizophrenia. They found evidence for a causal link from cognitive function (influenced by genes and the environment) to schizophrenia liability, which explained 26% of variance. In a cross-lagged design of ADHD symptoms and intelligence at three time-points, the genetic association between the two were influenced by time-specific factors plus covariance transmitted from previous time points (Rommel et al., 2015). ADHD symptoms at age 12 were a better predictor of IQ at age 14 than the reverse. This exemplifies the potential for disorders to influence intelligence, and even personality, where a direct causal effect of depression on neuroticism has been shown in addition to shared genetic aetiology (Kendler et al., 1993).

Of course, the possible explanations given above are not mutually exclusive, and different explanations might be preferred for different associations. For example, the genetic correlation between IQ and schizophrenia might not operate solely through an IQ to schizophrenia causal chain, whereas a genetic correlation between IQ and lung cancer might.

In a GWA study of parental longevity, variants near the *nicotinic acetylcholine receptor subunit alpha 5* and *APOE* genes were significant (Joshi et al., 2016). In the case of the nicotinic receptor, which is associated with smoking quantity and nicotine dependence, one might expect that controlling for intelligence would weaken this effect (at least in samples collected today). Genetic effects on health outcomes might also be moderated by IQ; this has been shown for diabetes polygenic risk which is more strongly associated with glycated haemoglobin levels in less intelligent individuals (Mottus et al., 2015). In the case of personality and mental health, where there is item overlap, for example, between Neuroticism measures and depression inventories, genetic correlations could further arise from shared item variance and leakage of state affect into personality measurement. Genetic analysis of individual personality inventory items in relation to mental health variables might be a means to better appreciate these measurement dependencies.

Reports of genetic correlations between personality traits and intelligence, on the one hand, and disease, on the other, are accumulating rapidly, but these discoveries represent the first step in what we believe will be a long hike to understand the mechanisms that underlie these relationships. Any full understanding will necessarily involve untangling any phenotypic causal pathways between personality/IQ and health (longitudinal family designs might be most helpful to this) and identifying the biological pathways affected by genes that are associated with both personality/intelligence and health (functional and gene expression studies will be useful) to confirm biological pleiotropy. Furthermore, the potential for moderation of genetic effects on health via intelligence and personality need to be examined. Progress in these areas will not only help us better understand the causes of disease but will translate into strategies that we can use to minimise it in the population.

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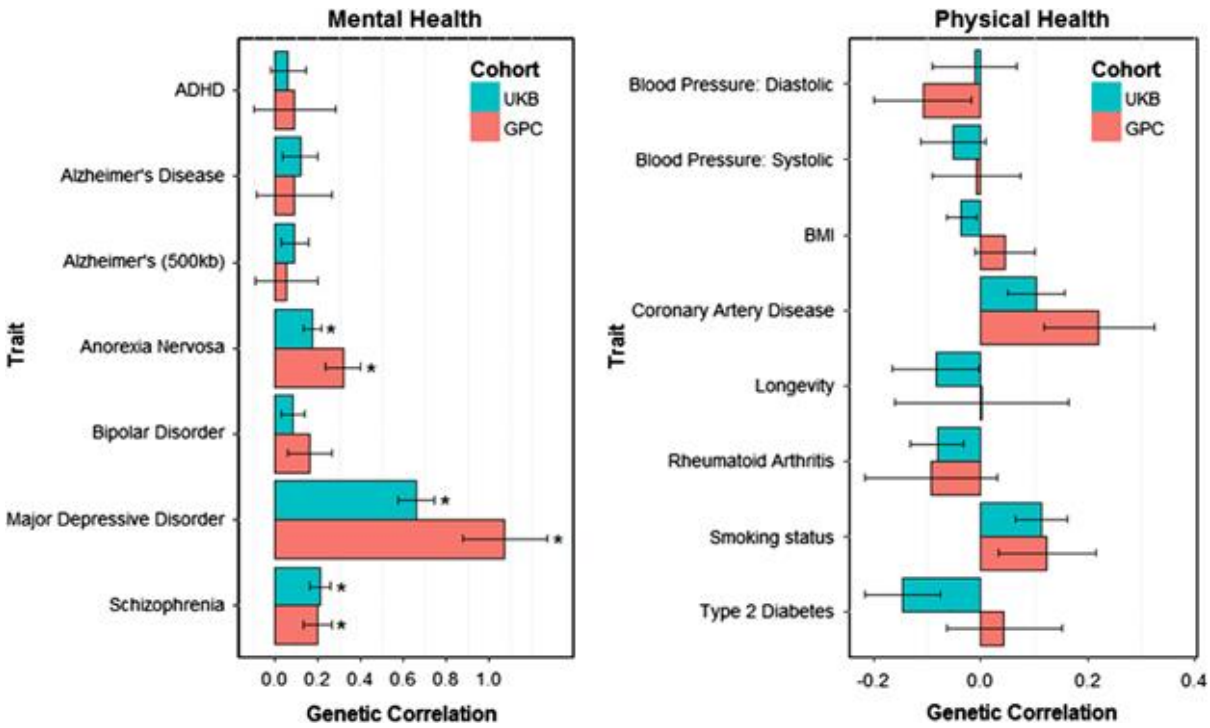


Figure 1. Barplot of genetic correlations (s.e.) calculated using linkage disequilibrium score regression between neuroticism in UK Biobank (UKB) and the Genetics of Personality Consortium (GPC), and mental and physical health measures from genome-wide association study consortia. *$P$<0.0033. ADHD, attention-deficit hyperactivity disorder; BMI, body mass index. [Figure and caption originally published in Translational Psychiatry, 2016 (Gale et al., 2016)]

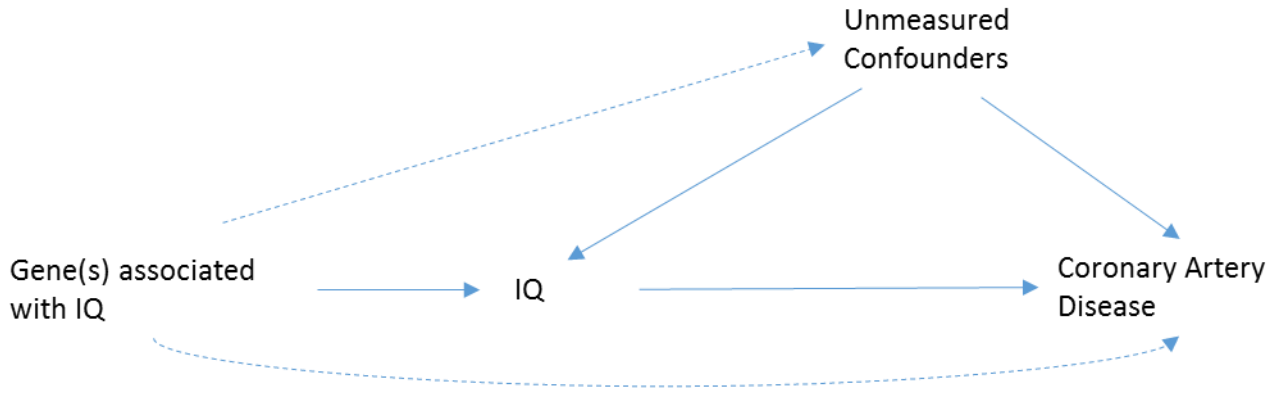


Figure 2. Example of a model in which mediated pleiotropy (genes influence IQ, which in turn, influences coronary artery disease) would be supported. The dashed lines are non-significant for this causal model to be true.