Polygenic prediction of the phenome, across ancestry, in emerging adulthood

Anna R. Docherty, Ph.D.*[1,2], Arden Moscati, Ph.D.*[3,4], Danielle Dick, Ph.D.[5-7], Jeanne E. Savage, Ph.D.[3,8], Jessica E. Salvatore, Ph.D.[3,5], Megan Cooke, Ph.D.[3], Fazil Aliev, Ph.D.[5,9], Ashlee A. Moore, M.A.[3], Alexis C. Edwards, Ph.D.[3], Brien P. Riley, Ph.D.[3], Daniel E. Adkins, Ph.D.[1,2], Roseann Peterson, Ph.D.[3], Bradley T. Webb, Ph.D.[3], Silviu A. Bacanu, Ph.D.[3], Kenneth S. Kendler, M.D.[3]

RUNNING HEAD: Genome-Phenome Prediction in Emerging Adulthood

1. Departments of Psychiatry & Human Genetics, University of Utah School of Medicine, Salt Lake City, UT, USA
2. Consortium for Families and Health Research, University of Utah, Salt Lake City, UT, USA
3. Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University School of Medicine, Richmond, VA, USA
4. Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA.
5. Department of Psychology, Virginia Commonwealth University, Richmond, VA, USA
6. Department of Human & Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA
7. College Behavioral and Emotional Health Institute, Virginia Commonwealth University, Richmond, VA, USA
8. Department of Health Sciences, Vrije Universiteit Amsterdam, Amsterdam, Netherlands
9. Department of Business, Karabuk University, Turkey

*Both authors contributed equally to the manuscript.

[+]Corresponding author: Departments of Psychiatry and Human Genetics, University of Utah School of Medicine, 501 Chipeta Way, Salt Lake City, Utah, USA. Tel. +1 763 516 7367, fax. +1 804 828 1471, email: anna.docherty@utah.edu

Article word count: 3,540 (excluding title page, abstract, references, figure captions, tables, author contributions, and financial disclosures)

Abstract

Background: Identifying genetic relationships between complex traits in emerging adulthood can provide useful etiological insights into risk for psychopathology. College-age individuals are under-represented in genomic analyses thus far, and the majority of work has focused on clinical disorder or cognitive abilities rather than normal-range behavioral outcomes.

Methods: This study examined a sample of emerging adults 18-22 years of age (N = 5,947) to construct an atlas of polygenic risk for 33 traits predicting relevant phenotypic outcomes. Twenty-eight hypotheses were tested based on the previous literature on samples of European ancestry, and the availability of rich assessment data allowed for polygenic predictions across 55 psychological and medical phenotypes.

Results: Polygenic risk for schizophrenia in emerging adults predicted anxiety, depression, nicotine use, trauma, and family history of psychological disorders. Polygenic risk for neuroticism predicted anxiety, depression, phobia, panic, neuroticism, and was correlated with polygenic risk for cardiovascular disease.

Conclusions: These results demonstrate the extensive impact of genetic risk for schizophrenia, neuroticism, and major depression on a range of health outcomes in early adulthood. Minimal cross-ancestry replication of these phenomic patterns of polygenic influence underscores the need for more genome-wide association studies of non-European populations.

Keywords: phenome; genetic; polygenic; schizophrenia; neuroticism; cardiovascular

Introduction

Broad phenotyping can greatly enhance our understanding of the underlying structure of genetic vulnerability to psychiatric disorders. Thus, genome-wide polygenic risk research is increasingly considering batteries of clinical phenotypes in "phenome-wide" studies (Bulik-Sullivan *et al.* 2015; Krapohl *et al.* 2015; Hagenaars *et al.* 2016). One promising approach emerging from the phenome-wide genomic literature uses published summary statistics from large genome-wide association studies to calculate genome-wide polygenic scores (GPS) for an array of major disorders and clinically relevant traits. These scores are then used to predict a number of potentially informative psychiatric, psychological and physical health phenotypes. Along with cross-disorder genomic research examining the co-heritability of major psychiatric disorders (e.g., LD regression) (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), polygenic phenomic approaches are among the most promising methods for elucidating the complex overlapping genetic architecture of psychiatric disorders and discovering unexpected genotype-phenotype associations (Docherty et al. 2016). However, previous research has suffered from a restricted range of phenotypes, and has not included, for instance, GPS of anxiety, eating, and inflammatory disorders, personality, lipid levels and puberty traits in the prediction of outcome phenotypes (which have generally focused on cognitive abilities) and has not examined samples between the ages of 17 and 35, the developmentally critical stage encompassing emerging and young adulthood.

This study applied such an approach to GPS (33 total) in a phenotypically extensive genetic study of emerging adulthood outcomes. Emerging adulthood, a period starting at the age of 18 when adolescents begin to develop the roles and independence of adulthood, reflects a high-risk age range for the onset of many psychiatric and substance use disorders, including schizophrenia, affective disorders, anxiety disorders and alcohol and drug use disorders. Data from the National Comorbidity Survey Replication sample indicate that three quarters of all lifetime cases of DSM-IV diagnoses start by age 24 (Kessler *et al.* 2005), and WHO's World Mental Health data indicates that approximately three quarters of lifetime psychiatric disorders begin by the mid-20′s (Kessler *et al.* 2007).

The University Student Survey (called "Spit for Science", or S4S) was developed to identify risk factors for onset of mental health disorders with large-scale assessment of genetic, environmental, and developmental influences. Discovery summary statistics from 33 genome-wide association studies (GWAS) were used to derive GPSs in this large sample of young adults (N = 5,947) across a range of psychiatric, psychological, and physical health traits (Table S1 in online supplementary materials). Expanding on previous research, twenty-eight hypotheses

of genetic prediction were tested based on selected studies in past literature. Further, the availability of rich clinical assessment data allowed for the calculation of polygenic predictions across a greater number of outcomes than has ever been studied previously, many of which were completely novel in phenomic studies. These included 55 psychiatric, psychological and medical phenotypes (listed in Table S2 in the online supplementary material).

Moreover, the GPS metrics were powerful enough to examine relationships across subsamples of different ancestries. While GWAS approaches require tens of thousands of individuals to locate "hits," continuous polygenic scores require far smaller samples for adequate power. This sample was suitably diverse in ancestry to map the GPS-phenotype in young adults of European ancestry (EUR, N=3,016) and then to replicate these findings across non-European ancestry groups including of African origin (AFR, N=1,339), native American origin (AMR, N=581), and East Asian (EAS, N=557), and South Asian origin (SAS, N=454). Separate association matrices were created for the empirically categorized AFR, AMR, EAS, and SAS samples and are provided here and in the supplemental figures available online.

We can learn much from the study of emerging adults over and above adolescent samples, as early behavioral patterns that may precede adult psychopathology can be studied, and new hypotheses about critical exposures and environmental risk factors can emerge. The results presented here reflect a polygenic modeling framework in a large young adult sample, and provides evidence that the integration of phenotypic and genotypic data will be useful in the prediction of negative health outcomes in emerging adults.

Methods

Sample Ascertainment and Phenotyping

Phenome-wide behavioral data (N=7,592) were drawn from young adults from the first three cohorts in S4S, samples drawn from a large urban university in the Mid-Atlantic United States, which included 5,947 unrelated individuals with genome-wide genotypes (Dick *et al.* 2014). The S4S sample does not overlap with any of the discovery GWAS samples used in these analyses. Details of participant ascertainment have been published elsewhere (Dick *et al.* 2014) but briefly, emerging adults ages 18-22 were recruited across multiple cohorts, for a campus-wide study of genetic and environmental factors contributing to alcohol and substance use. The protocol was approved by the university Institutional Review Board, and carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki. Participants were 61.1% female with a mean age of 18.59 at

first assessment. Representativeness of this sample is strong and has been reported elsewhere (Dick *et al.* 2014). Assignment to ancestry group was empirically based on greatest similarity to 1000 Genomes Phase 3 super-populations. The present analyses included 55 traits from the domains of psychopathology, personality, health factors, and educational achievement (Table S2 in the online supplementary materials). All analyses included age, sex, and 10 ancestry principal components as covariates. Variables assessed at multiple occasions or in multiple cohorts were adjusted for number of assessments and cohort group. Sample sizes for each of the phenotypic measures are also provided in Table S2.

Genetic Risk Scoring

DNA collection, calling, and imputation is detailed elsewhere (Dick *et al.* 2014). We processed genotypes using standard quality control procedures followed by imputation of SNPs using the 1000 Genomes Project reference panel. After imputation and quality control, we included approximately 2.3 million variants into the polygenic scoring analyses. A GPS for each discovery phenotype was calculated using the summary statistics we obtained from 33 GWAS (Table S1 in the online supplementary materials). Python-based LDpred (Vilhjálmsson *et al.* 2015) was used for these analyses because of its ability to account for linkage disequilibrium (LD) structure (Krapohl *et al.* 2015) using our own large EUR test sample, and its use of all genetic variants (instead of specified p-value threshold for inclusion of the genetic variants in the GPS). LDpred allows for the modeling of LD based on LD in the discovery sample to weight the relative contributions of syntenic variants to the outcome phenotype. LDpred uses postulated proportions of causal variants in the genome as Bayesian prior probabilities for GPS calculations, and we tested a range of different priors (proportions of 0.3, 0.1, 0.03, 0.01, 0.003, and 0.001), as well as the model of infinite variants of infinitesimally small effect (Fisher, 1919) to construct scores.

Phenotype Prediction

A flowchart depicting the GPS-phenome cross-ancestry prediction and GPS-GPS correlation procedure is presented in Figure 1. Regressions were run using R to compare full (GPS, ten ancestry principal components, age, sex, cohort, and number of measurements when applicable) and restricted models where GPS was removed. Prior to the global analyses, a set of *a priori* hypotheses, gathered from previous research, were tested (Table 1). We elected to generate several hypotheses prior to analysis, because some literature was available to support previous evidence of relationships between GPS and outcome. We elected to forgo experimental binning (into quantiles, for example) in order to minimize the number of exploratory analyses beyond regressions of GPS on the phenotypes. Multiple

testing was corrected for using a False Discovery Rate (FDR) of 5% (Benjamini & Hochberg, 1995) within each ancestry group using the p.adjust function in R; the FDR is appropriate for an analysis designed to evaluate the pattern of relationships between many constructs because it treats each combination of discovery phenotype, outcome, and LDpred prior level as an independent test, despite the presence of positive dependency between many of these tests. It should be noted that this multiple testing correction did not account for previously established associations or for the correlations observed in our sample, between multiple prior levels tested in the same discovery phenotypes. This was an added attempt to filter out potentially spurious results.

Cross-Disorder GPS Partial Correlations and GPS-GPS Replication Hypotheses Across Ancestry

In addition to testing the GPSs prediction of the phenotypes, GPSs were also examined for correlations with each other in all ethnicities. These provide different results than genetic correlation estimates, but are intended to demonstrate that GPS scores are not independent, and that variance attributable to a particular discovery phenotype may be partially shared with another. This sharing may be due to common genetic factors between phenotypes, possible sample overlap, and error variance. GPS correlations have been previously reported in EUR, but this analysis added phenotypes such as cardiovascular and triglyceride factors. Correlation coefficients, *p*-values, and *q*-values (after correcting the p-values for the FDR of 5%) were derived for GPS partial correlations using R and adjusting for the ancestry principal components. We chose to use partial correlations in order to standardize the weights across phenotype and provide more direct comparisons of statistics for plotting purposes. Based on the cross-disorder psychiatric genomics findings to date (Bulik-Sullivan *et al.* 2015), we expected significant GPS associations between schizophrenia (SZ) and bipolar disorder (BP), SZ and autism (AUT), SZ and major depressive disorder (MDD), BP and MDD, and AUT and attention deficit hyperactivity disorder (ADHD) across each of the ancestry groups (see Table 2).

Results

Genetic Profile Score-Phenotype Prediction

A Priori Replication Analyses

We evaluated previous cross-phenotype predictions based on recent work—for example, that age at menarche had an inverse association with obesity/body mass index (Bulik-Sullivan *et al.* 2015). We tested several hypotheses in the European group, in order to maximize sample size without introducing potential population

stratification. The multiple testing correction procedure we chose (FDR) was suitable for these analyses, given the positive dependency between many of the tests, allowing us to correct uniformly for the total number of tests while still keeping type I error rate relatively controlled. Of the 28 predictions tested, 22 showed effects in the expected direction (p=0.002, one-tailed sign test), and 7 were significant after stringent multiple-testing correction. Two previous notable null associations, MDD GPS predicting Grade Point Average (GPA), and Type 2 Diabetes GPS predicting GPA, were also null in our sample. Full results are presented in Table 1, including additional associations with the listed GPS phenotypes.

Phenome-Wide Prediction

We also performed hypothesis-free analyses across all 33 GPS and 55 S4S phenotypes to explore potentially novel associations. Multiple prior proportions of causal variants in the genome were tested, as detailed in Methods. Figure 2 presents notable results for GPS prediction of phenotypes in the European group for the prior proportion of 0.3 (that is, an initial assumption that 30% of the genome is associated with the GPS phenotype). The 0.3 prior level showed stronger prediction in past work (Krapohl *et al.* 2015), and corresponds to a plausible assumption about the genetic architecture of many complex traits, due to instances of increasing sample size of GWAS proportionally increasing numbers of associated loci. In this group and prior proportion level, out of 1,815 associations 35 were between $q < 0.16$ and $q > 0.05$ (0.16 being the P-value threshold corresponding to Akaike Information Criterion (Akaike, 1974)), 11 between $q < 0.05$ and $q > 0.01$, and 26 $q < 0.01$. An additional 53 associations showed at least suggestive significance at other prior levels. A heatmap of analyses at can be found in Figure 2 (EUR; and for replications in all ancestries, Figures S1-S4 available in the online supplementary materials). Each plot presents significant associations as well as the direction of effect. Because of the uniform correction for multiple testing, we included of interest q<0.16 associations, which would be significant with more traditional correction methods accounting for previously established associations.

Notable results included SZ GPS significantly predicting nicotine use, depression and anxiety symptoms, and family history of depression, anxiety, alcohol use disorder, and drug use. In addition, GPS for neuroticism (N) predicted a number of relevant psychiatric phenotypes, including neuroticism, depression and anxiety symptoms.

Genetic Profile Score Prediction of the Phenome Across Non-European Ancestries

As noted earlier, most discovery GWAS have used European samples, and while there is good evidence for cross-ancestral replication for some traits, the generalizability of many of these relationships across ancestry is not

known. The diverse ancestry groups within S4S allowed cross-ancestral replication, and the use of continuous GPS metrics made the sample sizes available powerful enough to examine these hypotheses. A small proportion of the strongest predictors observed in the EUR were replicated across the other ancestries, with a broadly similar pattern of results across all ancestry groups only for "basic" traits such as height and BMI. While some outcome phenotypes were strongly predicted by GPS, a few outcome phenotypes, including physical activity, lifetime history of panic attack, age at first sexual intercourse, and bulimia nervosa were not predicted by any GPS in any ancestry group. In addition, some expected associations (e.g., PRS for nicotine use predicting smoking behaviors) while in the expected direction, were not significant in this sample.

Most associations of SZ GPS with outcome traits observed in EUR did not reach significance in other ancestry samples. In addition, some novel associations were observed in other ancestries. For example, lifetime smoking GPS was positively associated with number of alcoholic drinks per day in AMR. Neuroticism GPS was positively associated with stressful life events, trauma (interpersonal and general), and PTSD in SAS. These patterns of effects are based on EUR GWAS summary statistics, and must be replicated using AMR and SAS GWAS summary statistics in the future. However, they suggest potential pleiotropic effects relevant to outcomes in these populations.

GPS-GPS Correlations

A Priori Hypothesis Testing and Global Cross-Disorder Genetic Profile Analyses

A priori hypotheses (described in the Methods and listed in Table 2) of relationships between GPS scores were tested at a prior proportion level of 0.3. Figure 3 presents the results for GPS-GPS partial correlations at a GPS $p = 0.3$, and these results are presented because some phenotypes studied here (e.g., Neuroticism) were not included in previous analyses. Notable unexpected correlations were observed, including significant positive correlations of neuroticism GPS with GPSs for triglycerides and coronary artery disease. These associations also serve as evidence of non-independence across traits in this sample. Finally, Figures S5-S8 (available in the online supplementary materials) present these same correlations across the four non-EUR ancestry groups. There is some overlap between the discovery samples for neuroticism and triglycerides, but no overlapping studies were included in the neuroticism and the coronary artery disease discovery samples. Therefore, the correlation of neuroticism and coronary artery disease is especially likely to reflect underlying genetic correlation between neuroticism and artery disease. Despite

overlap in the discovery samples for the neuroticism and triglycerides polygenic scores, validation using LD score regression supported the existence of a genetic relationship between them (r_G = 0.53; *SE* = 0.04; $p = 1.5 \times 10^{-36}$).

Discussion

The findings here present a wide-ranging and nuanced picture of major dimensions of vulnerability to psychopathology at a genetic level. This study includes substantial sample sizes of emerging adults, uses outcome measures (with novel phenotypes in phenomic analyses; see Table S2 in the online supplement for details of assessment scales), includes a wide range of discovery GWAS, and is powerful enough to draw preliminary conclusions about several ancestries. Because this study does not look for "hits" in the traditional GWAS sense and instead uses continuous GPS metrics, sample sizes provide adequate power across all separate ancestries in this study.

Importantly, results reflect EUR relationships between anxiety, depressive, and schizophrenia-spectrum disorders that are largely consistent with current conceptualizations of diagnostic classification, and confirm the important involvement of a network of medical and risk phenotypes in genetic predisposition to these disorders. Informative genetic associations between medical and clinical phenotypes exist despite the relative dearth of individual loci of genome-wide significance.

We can learn a lot from the study of emerging adults relative to younger, adolescent samples, as more targeted theories about critical exposures and environmental risk factors can emerge. For example, GPS for SZ predicted anxiety, depression, nicotine use, experiences of interpersonal trauma, and family history of mental health problems. Importantly, these results expand on recent evidence that genetic risk for SZ can successfully predict diverse risk phenotypes such as anxiety and negative symptoms (Kendler *et al.* 1996; Fanous *et al.* 2001; Docherty & Sponheim, 2008; Docherty & Sponheim, 2014; Docherty *et al.* 2015; Jones *et al.* 2016; Kendler, 2016), and demonstrate important links between SZ genetic risk and health factors in early adulthood. Significant association of GPS with easily measured, specific risk factors (e.g., nicotine use, family history, trauma) indicates that GPS could be useful in predicting psychopathology, particularly in conjunction with environmental moderators.

The incorporation of personality traits such as neuroticism was also quite informative. For example, neuroticism GPS significantly predicted a broad network of general anxiety, phobia, panic, neuroticism, and depression phenotypes in EUR, as well as multiple health-related GPSs. This is consistent with previous biometrical

and genomic research reporting significant relationships of neuroticism with MDD (Kendler & Myers, 2010; Genetics of Personality Consortium *et al.* 2015; Docherty *et al.* 2016), and preliminary findings from the UKBiobank suggesting a genetic overlap of neuroticism with cardiovascular health (Gale *et al.* 2016). Conversely, GPS for extraversion predicted fewer depressive symptoms, fewer anxiety symptoms, and less family history of mental health problems, though these associations did not remain significant after multiple testing correction. Associations pertaining to GPS for well-being in this sample are forthcoming from our research group.

Notable unexpected GPS-GPS results included positive correlations of neuroticism GPS with GPSs for coronary artery disease, which is likely to reflect underlying genetic correlation, as well as with triglycerides. This is the first study we know of to document significant positive genetic associations between neuroticism and cardiac health, despite the high public health cost of neuroticism being well-documented (Cuijpers *et al.* 2010; cardiovascular risk and association with psychiatric phenotypes like neuroticism may be of special interest to public health efforts). Most of the GPS-GPS *a priori* relationships chosen for replication testing were represented in the same direction across all ancestry groups, corroborating previous efforts to map relationships between genetic risk profiles.

The abundance of significant relationships between intuitive combinations of GPSs and related outcomes is reassuring considering the many factors that could attenuate the statistical link between them. Association between a GPS and an outcome not only reflects correlation between the phenotype in the original ('discovery') GWAS that produced the statistics used to compute the GPS and the outcome phenotype, but is also related to a number of other factors. The link is limited by how accurately the GWAS measured the initial phenotype, how similar the discovery and test samples are (in age, ancestry composition, proportions of each sex, etc.), how well the test phenotype is measured by the data collection instrument, and how well it can incorporate indirect pathways from the genetic architectures to either phenotype.

For example, physical activity increases HDL levels (Kokkinos & Fernhall, 1999), so those who had higher HDL levels in the discovery GWAS (Teslovich *et al.* 2010) were likely a mix of those with innately high levels, those who engaged in higher levels of physical activity, and those with both traits. Therefore, HDL GPS perhaps indexes some propensity to engage in HDL-promoting behaviors, in addition to HDL metabolic variation such as a slower rate of HDL catabolism, which is thought to be the most common genetically determined mechanism of increased HDL levels in humans (Rader, 2006). The portion of the HDL GPS due to fitness behaviors may

explain some of the polygenic association with the test phenotypes of BMI and weight. Of note, while the HDL GPS did not significantly predict the physical activity phenotype in S4S, the direction of effect was positive, and that particular phenotype had one of the smallest sample sizes, at 433 EUR individuals, and therefore lower power than others.

Using EUR GWAS summary statistics produced differential relationships of GPS with outcomes across ancestry, with few effects replicating across ancestry groups. This could be due to decreased power to detect effects given the smaller sample sizes of the other ancestry groups. However, within each ancestry group, new significant effects across GPS and outcome measures were observed as well. These effects suggest ancestry-specific summary statistics, or those with larger samples, may reveal differences in the pattern of relationships between phenotypes in different groups. Results underscore a need for more GWAS of non-EUR ancestry samples.

There are a number of limitations to be aware of when interpreting these results. The synthesis of information from so many sources compounds any methodological and psychometric issues present in the original studies, so there is probable bias in multiple levels of the analysis that is difficult to measure. It is unclear how generalizable our results are to the general population. However, we might assume that bias in the college sample would cause less robust associations with psychopathology, and that effects might be more pronounced in the general population. In order to maintain proximity with real outcomes, we did not transform our phenotypic variables to increase normality, but standardized the continuous variables computed from the participant responses to maintain comparable ranges of measurement. However, none of the phenotypes in which we found significant results evidenced high skew or kurtosis, so it is unlikely that significant effects were due to non-normal phenotype distributions. While LDpred performs adequately across ancestry groups, the accuracy in non-European ancestry groups is attenuated to the degree that multiple causal variants fall in regions where LD patterns differ across ancestry. In addition, a recent pre-print (Martin *et al.* 2016) shows biased predictions in several different populations using GPS for phenotypes that are also used in this paper (for example, Type 2 diabetes and SZ). Finally, we observed some differential effects across priors in our analyses. Until these effects are replicated at a given prior, or there is justified precedent in the literature, we are unable to choose one ideal prior.

Overall, this broader picture of genetic vulnerability has important implications for how we study risk and resilience in emerging adulthood. While the variance explained by any of these GPSs is small, (for instance, the largest R^2 for predicting the height phenotype was 0.055, from the height GPS at a prior level of 1) they provide

easily accessible information to guide future prediction, prevention, and intervention efforts to improve health and quality of life outcomes. Future longitudinal and intervention research could elaborate on this atlas to examine the predictive validity and prevention utility of many of the phenotypes here, such as neuroticism, family history, trauma, and nicotine use. This research also suggests that future polygenic work would benefit from GPSs based on non-European ancestry groups when such summary statistics are available. Phenome-wide research utilizing deeper phenotyping methods will likely further enhance results, and thus future prediction of positive and negative health outcomes.

Finally, the relationships outlined here provide implicit suggestions for studies of the causal structure of the GPS phenotypes themselves. The genetic architecture of most of the traits and disorders in the atlas display substantial overlap; a significant portion of genetic variation involved in the etiology of these constructs does not selectively contribute to risk for one phenotype as we know it, but rather has effects that act on some axis of liability that increases the likelihood of many phenotypes. Analyzing multiple related phenotypes in a holistic fashion allows elucidation of the individual patterns of genetic and environmental factors that may explain causal mechanisms—which risk factors they share, and which are unique to one phenotype, thus serving to refine our nosological theories. Any epidemiological analysis is limited if the construct under study is not a uniform disease entity, but as characterization of constructs improves, the power to find their correlates does as well. The better we ask the questions, the more useful the answers become, for both clinical and scientific purposes.

Author Contributions

A. R. Docherty, A. Moscati, and K. S. Kendler developed the study concept. A. Moscati, J. E. Savage, J. E. Salvatore, and M. Cooke contributed to psychometric analyses and data collection. D. Dick and K. S. Kendler oversaw data collection. A. Moscati and A. R. Docherty performed the data analysis and interpretation under the supervision of B. T. Webb, S. A. Bacanu, D. E. Adkins, F. Aliev, A. C. Edwards, and B. P. Riley. A. R. Docherty and A. Moscati drafted the manuscript, and K. Kendler, A. C. Edwards, J. E. Savage, J. E., Salvatore, M. Cooke, B. T. Webb, S. A. Bacanu, D. E. Adkins, A. Moore, R. Peterson, and D. Dick provided edits. All authors approved the final version of the manuscript for submission.

Acknowledgements

We would like to thank the participants and the many VCU faculty, students, and staff who contributed to the design and implementation of this project.

Financial Disclosures

All authors declare no conflict of interest with respect to the authorship or publication of this article. Data collection for the study was funded by R37AA011408, P20AA107828, K02AA018755, and P50AA022537 from the National Institute on Alcohol Abuse and Alcoholism, by Virginia Commonwealth University, and by UL1RR031990 from the National Center for Research Resources and National Institutes of Health Roadmap for Medical Research. A. Docherty was funded by K01MH109765 from the National Institute of Mental Health, and by a Brain & Behavior Research Foundation (formerly NARSAD) Young Investigator Award. A. Moscati, A. Moore were supported by institutional training grant T32MH20030. J. Salvatore was supported by F32AA22269 and K01AA024152. M. Cooke received support from UL1TR000058 from the National Institutes of Health National Center for Advancing Translational Science. A. Edwards was supported by K01AA021399.

Declaration of Interest

Authors report no conflicts of interest.

References

Akaike H (1974). A new look at the statistical model identification. *IEEE Transactions on Automatic Control* **19**, 716-723.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorder (*4th ed.). Washington, DC: American Psychiatric Association

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Association.

Benyamin B, Pourcain B, Davis OS, Davies G, Hansell NK, Brion MJ, Kirkpatrick RM, Cents RA, Franic S, Miller MB, Haworth CM, Meaburn E, Price TS, Evans DM, Timpson N, Kemp J, Ring S, McArdle W, Medland SE, Yang J, Harris SE, Liewald DC, Scheet P, Xiao X, Hudziak JJ, de Geus EJ, Jaddoe VW, Starr JM, Verhulst FC, Pennell C, Tiemeier H, Iacono WG, Palmer LJ, Montgomery GW, Martin NG, Boomsma DI, Posthuma D, McGue M, Wright MJ, Davey Smith G, Deary IJ, Plomin R, Visscher PM (2014). Childhood intelligence is heritable, highly polygenic and associated with FNBP1L. *Molecular Psychiatry* **19**, 253-258.

Benjamini Y, Hochberg Y (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B (Methodological)* **57**, 289-300.

Brener ND, Kann L, Kinchen SA, Grunbaum JA, Whalen L, Eaton D, Hawkins J, Ross JG (2004). Methodology of the youth risk behavior surveillance system. *MMWR Recommendations and Reports* **53**, 1-13.

Brown KW, Ryan RM (2003). The benefits of being present: Mindfulness and its role in psychological well-being. *Journal of Personality and Social Psychology* **84**, 822-848.

Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI, Schuckit MA (1994). A new, semi-structured psychiatric interview for use in genetic linkage studies: A report on the reliability of the SSAGA. *Journal of Studies on Alcohol* **55**, 149-158.

Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, Duncan L, Perry JR, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM ((2015). An atlas of genetic correlations across human diseases and traits. *Nature Genetics* **47**, 1236-1241.

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research* **28**, 193-213.

Connor KM, Davidson JR (2003). Development of a new resilience scale: The Connor-Davidson Resilience Scale (CD-RISC). *Depression and Anxiety* **18**, 76-82.

Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine & Science in Sports & Exercise* **35**, 1381-1395.

Cross-Disorder Group of the Psychiatric Genomics Consortium (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *Lancet* **381**, 1371-1379.

Cuijpers P, Smit F, Penninx BW, de Graaf R, ten Have M, Beekman AT (2010). Economic costs of neuroticism: A population-based study. *Archives of General Psychiatry* **67,** 1086-1093.

Derogatis LR, Cleary PA (1977). Confirmation of the dimensional structure of the SCL-90: A study in construct validation. *Journal of Clinical Psychology* **33**, 981-989.

Dick DM, Nasim A, Edwards AC, Salvatore JE, Cho SB, Adkins A, Meyers J, Yan J, Cooke M, Clifford J, Goyal N, Halberstadt L, Ailstock K, Neale Z, Opalesky J, Hancock L, Donovan KK, Sun C, Riley B, Kendler KS (2014). Spit for Science: Launching a longitudinal study of genetic and environmental influences on substance use and emotional health at a large US university. *Fronteirs in Genetics* **5**, 47.

Docherty AR, Moscati AA, Fanous AH (2016). Cross-disorder psychiatric genomics: A review. *Current Behavioral Neuroscience Reports* **3**, 256-263.

Docherty AR, Moscati A, Peterson R, Edwards AC, Bigdeli TB, Adkins DE, Bacanu SA, Bigdeli TB, Webb BT, Flint J, Kendler KS (2016). SNP-based heritability estimates of the personality dimensions and polygenic prediction of both neuroticism and major depression: Findings from CONVERGE. *Translational Psychiatry* **6**, e926.

Docherty AR, Sponheim SR (2008). Anhedonia as a phenotype for the Val158Met COMT polymorphism in relatives of patients with schizophrenia. *Journal of Abnormal Psychology* **117**, 788-798.

Docherty AR, Sponheim SR (2014). Anhedonia as an indicator of genetic liability to schizophrenia. In M. Ritsner (Ed.), *Anhedonia: A Comprehensive Handbook*. Dordecht: Springer.

Docherty AR, Sponheim SR, Kerns JG (2015). Self-reported affective traits and current affective experiences of biological relatives of people with schizophrenia. *Schizophria Research* **161**, 340-344.

Fanous A, Gardner C, Walsh D, Kendler KS (2001). Relationship between positive and negative symptoms of schizophrenia and schizotypal symptoms in nonpsychotic relatives. *Archives of General Psychiatry* **58**, 669-673.

Fisher RA (1919). On the correlation between relatives on the supposition of mendelian inheritance. *Transactions of the Royal Society of Edinburgh: Earth and Environmental Science* **52**, 399-433.

Gale CR, Hagenaars SP, Davies G, Hill WD, Liewald DC, Cullen B, Penninx BW, Boomsma DI, Pell J, McIntosh AM, Smith DJ, Deary IJ, Harris SE (2016). Pleiotropy between neuroticism and physical and mental health: Findings from 108,038 men and women in UK Biobank. *Translational Psychiatry* **6**, e791.

Genetics of Personality Consortium, de Moor MH, van den Berg SM, Verweij KJ, Krueger RF, Luciano M, . . . Boomsma DI (2015). Meta-analysis of genome-wide association studies for neuroticism, and the polygenic association with major depressive disorder. *JAMA Psychiatry* **72**, 642-650.

Gray MJ, Litz BT, Hsu JL, Lombardo TW (2004). Psychometric properties of the life events checklist. *Assessment* **11**, 330-341.

Hagenaars SP, Harris SE, Davies G, Hill WD, Liewald DC, Ritchie SJ, Marioni RE, Fawns-Ritchie C, Cullen B, Malik R, Worrall BB, Sudlow CL, Wardlaw JM, Gallacher J, Pell J, McIntosh AM, Smith DJ, Gale CR, Deary IJ (2016). Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112 151) and 24 GWAS consortia. *Molecular Psychiatry* **21**, 1624-1632.

Hays RD, Sherbourne CD, Mazel RM (1995). *User's manual for the Medical Outcomes Study (MOS): Core measures of health-related quality of life*. Santa Monica, CA: RAND.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO (1991). The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction* **86**, 1119-1127.

Hendrick SS (1988). A generic measure of relationship satisfaction. *Journal of Marriage and Family* **50**, 93-98.

Hibar DP, Stein JL, Renteria ME, Arias-Vasquez A, Desrivieres S, Jahanshad N, Toro R, Wittfeld K, Abramovic L, Andersson M, Aribisala BS, Armstrong NJ, Bernard M, Bohlken MM, Boks MP, Bralten J, Brown AA, Chakravarty MM, Chen Q, Ching CR, Cuellar-Partida G, den Braber A,

Giddaluru S, Goldman AL, Grimm O, Guadalupe T, Hass J, Woldehawariat G, Holmes AJ, Hoogman M, Janowitz D, Jia T, Kim S, Klein M, Kraemer B, Lee PH, Olde Loohuis LM, Luciano M, Macare C, Mather KA, Mattheisen M, Milaneschi Y, Nho K, Papmeyer M, Ramasamy A, Risacher SL, Roiz-Santianez R, Rose EJ, Salami A, Samann PG, Schmaal L, Schork AJ, Shin J, Strike LT, Teumer A, van Donkelaar MM, van Eijk KR, Walters RK, Westlye LT, Whelan CD, Winkler AM, Zwiers MP, Alhusaini S, Athanasiu L, Ehrlich S, Hakobjan MM, Hartberg CB, Haukvik UK, Heister AJ, Hoehn D, Kasperaviciute D, Liewald DC, Lopez LM, Makkinje RR, Matarin M, Naber MA, McKay DR, Needham M, Nugent AC, Putz B, Royle NA, Shen L, Sprooten E, Trabzuni D, van der Marel SS, van Hulzen KJ, Walton E, Wolf C, Almasy L, Ames D, Arepalli S, Assareh AA, Bastin ME, Brodaty H, Bulayeva KB, Carless MA, Cichon S, Corvin A, Curran JE, Czisch M, de Zubicaray GI, Dillman A, Duggirala R, Dyer TD, Erk S, Fedko IO, Ferrucci L, Foroud TM, Fox PT, Fukunaga M, Gibbs JR, Goring HH, Green RC, Guelfi S, Hansell NK, Hartman CA, Hegenscheid K, Heinz A, Hernandez DG, Heslenfeld DJ, Hoekstra PJ, Holsboer F, Homuth G, Hottenga JJ, Ikeda M, Jack CR, Jr., Jenkinson M, Johnson R, Kanai R, Keil M, Kent JW, Jr., Kochunov P, Kwok JB, Lawrie SM, Liu X, Longo DL, McMahon KL, Meisenzahl E, Melle I, Mohnke S, Montgomery GW, Mostert JC, Muhleisen TW, Nalls MA, Nichols TE, Nilsson LG, Nothen MM, Ohi K, Olvera RL, Perez-Iglesias R, Pike GB, Potkin SG, Reinvang I, Reppermund S, Rietschel M, Romanczuk-Seiferth N, Rosen GD, Rujescu D, Schnell K, Schofield PR, Smith C, Steen VM, Sussmann JE, Thalamuthu A, Toga AW, Traynor BJ, Troncoso J, Turner JA, Valdes Hernandez MC, van 't Ent D, van der Brug M, van der Wee NJ, van Tol MJ, Veltman DJ, Wassink TH, Westman E, Zielke RH, Zonderman AB, Ashbrook DG, Hager R, Lu L, McMahon FJ, Morris DW, Williams RW, Brunner HG, Buckner RL, Buitelaar JK, Cahn W, Calhoun VD, Cavalleri GL, Crespo-Facorro B, Dale AM, Davies GE, Delanty N, Depondt C, Djurovic S, Drevets WC, Espeseth T, Gollub RL, Ho BC, Hoffmann W, Hosten N, Kahn RS, Le Hellard S, Meyer-Lindenberg A, Muller-Myhsok B, Nauck M, Nyberg L, Pandolfo M, Penninx BW, Roffman JL, Sisodiya SM, Smoller JW, van Bokhoven H, van Haren NE, Volzke H, Walter H, Weiner MW, Wen W, White T, Agartz I, Andreassen OA, Blangero J, Boomsma DI, Brouwer RM, Cannon DM, Cookson MR, de Geus EJ, Deary IJ, Donohoe G, Fernandez G, Fisher SE, Francks C, Glahn DC, Grabe HJ, Gruber O, Hardy J, Hashimoto R, Hulshoff Pol HE, Jonsson

EG, Kloszewska I, Lovestone S, Mattay VS, Mecocci P, McDonald C, McIntosh AM, Ophoff RA, Paus T, Pausova Z, Ryten M, Sachdev PS, Saykin AJ, Simmons A, Singleton A, Soininen H, Wardlaw JM, Weale ME, Weinberger DR, Adams HH, Launer LJ, Seiler S, Schmidt R, Chauhan G, Satizabal CL, Becker JT, Yanek L, van der Lee SJ, Ebling M, Fischl B, Longstreth WT, Jr., Greve D, Schmidt H, Nyquist P, Vinke LN, van Duijn CM, Xue L, Mazoyer B, Bis JC, Gudnason V, Seshadri S, Ikram MA, Martin NG, Wright MJ, Schumann G, Franke B, Thompson PM, Medland SE (2015). Common genetic variants influence human subcortical brain structures. *Nature* **520,** 224-229.

Horikoshi M, Yaghootkar H, Mook-Kanamori DO, Sovio U, Taal HR, Hennig BJ, Bradfield JP, St Pourcain B, Evans DM, Charoen P, Kaakinen M, Cousminer DL, Lehtimaki T, Kreiner-Moller E, Warrington NM, Bustamante M, Feenstra B, Berry DJ, Thiering E, Pfab T, Barton SJ, Shields BM, Kerkhof M, van Leeuwen EM, Fulford AJ, Kutalik Z, Zhao JH, den Hoed M, Mahajan A, Lindi V, Goh LK, Hottenga JJ, Wu Y, Raitakari OT, Harder MN, Meirhaeghe A, Ntalla I, Salem RM, Jameson KA, Zhou K, Monies DM, Lagou V, Kirin M, Heikkinen J, Adair LS, Alkuraya FS, Al-Odaib A, Amouyel P, Andersson EA, Bennett AJ, Blakemore AI, Buxton JL, Dallongeville J, Das S, de Geus EJ, Estivill X, Flexeder C, Froguel P, Geller F, Godfrey KM, Gottrand F, Groves CJ, Hansen T, Hirschhorn JN, Hofman A, Hollegaard MV, Hougaard DM, Hypponen E, Inskip HM, Isaacs A, Jorgensen T, Kanaka-Gantenbein C, Kemp JP, Kiess W, Kilpelainen TO, Klopp N, Knight BA, Kuzawa CW, McMahon G, Newnham JP, Niinikoski H, Oostra BA, Pedersen L, Postma DS, Ring SM, Rivadeneira F, Robertson NR, Sebert S, Simell O, Slowinski T, Tiesler CM, Tonjes A, Vaag A, Viikari JS, Vink JM, Vissing NH, Wareham NJ, Willemsen G, Witte DR, Zhang H, Zhao J, Wilson JF, Stumvoll M, Prentice AM, Meyer BF, Pearson ER, Boreham CA, Cooper C, Gillman MW, Dedoussis GV, Moreno LA, Pedersen O, Saarinen M, Mohlke KL, Boomsma DI, Saw SM, Lakka TA, Korner A, Loos RJ, Ong KK, Vollenweider P, van Duijn CM, Koppelman GH, Hattersley AT, Holloway JW, Hocher B, Heinrich J, Power C, Melbye M, Guxens M, Pennell CE, Bonnelykke K, Bisgaard H, Eriksson JG, Widen E, Hakonarson H, Uitterlinden AG, Pouta A, Lawlor DA, Smith GD, Frayling TM, McCarthy MI, Grant SF, Jaddoe VW, Jarvelin MR, Timpson NJ, Prokopenko I, Freathy RM (2013). New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism. *Nature Genetics* **45**, 76-82.

John OP, Srivastava S (1999). The Big-Five trait taxonomy: History, measurement, and theoretical perspectives. In L. A. Pervin (Ed.), *Handbook of Personality: Theory and Research* (pp. 102-183). New York: Guilford Press.

Jones HJ, Stergiakouli E, Tansey KE, Hubbard L, Heron J, Cannon M, Holmans P, Lewis G, Linden DE, Jones PB, Davey Smith G, O'Donovan MC, Owen MJ, Walters JT, Zammit S (2016). Phenotypic manifestation of genetic risk for schizophrenia during adolescence in the general population. *JAMA Psychiatry* **73,** 221-228.

Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleynen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar JP, Ahmad T, Amininejad L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balschun T, Bampton PA, Bitton A, Boucher G, Brand S, Buning C, Cohain A, Cichon S, D'Amato M, De Jong D, Devaney KL, Dubinsky M, Edwards C, Ellinghaus D, Ferguson LR, Franchimont D, Fransen K, Gearry R, Georges M, Gieger C, Glas J, Haritunians T, Hart A, Hawkey C, Hedl M, Hu X, Karlsen TH, Kupcinskas L, Kugathasan S, Latiano A, Laukens D, Lawrance IC, Lees CW, Louis E, Mahy G, Mansfield J, Morgan AR, Mowat C, Newman W, Palmieri O, Ponsioen CY, Potocnik U, Prescott NJ, Regueiro M, Rotter JI, Russell RK, Sanderson JD, Sans M, Satsangi J, Schreiber S, Simms LA, Sventoraityte J, Targan SR, Taylor KD, Tremelling M, Verspaget HW, De Vos M, Wijmenga C, Wilson DC, Winkelmann J, Xavier RJ, Zeissig S, Zhang B, Zhang CK, Zhao H, Silverberg MS, Annese V, Hakonarson H, Brant SR, Radford-Smith G, Mathew CG, Rioux JD, Schadt EE, Daly MJ, Franke A, Parkes M, Vermeire S, Barrett JC, Cho JH (2012). Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 491, 119-124.

Kendler KS (2016). The schizophrenia polygenic risk score: To what does it predispose in adolescence? *JAMA Psychiatry* **73**, 193-194.

Kendler KS, Gardner CO, Prescott CA (1997). Religion, psychopathology, and substance use and abuse; A multimeasure, genetic-epidemiologic study. *American Journal of Psychiatry* **154**, 322-329.

Kendler KS, Jacobson K, Myers JM, Eaves LJ (2008). A genetically informative developmental study of the relationship between conduct disorder and peer deviance in males. *Psychologial Medicine* **38**, 1001-1011.

Kendler KS, Karkowski LM, Prescott CA (1999) Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry* **156**, 837-841.

Kendler KS, Karkowski-Shuman L, Walsh D (1996). The risk for psychiatric illness in siblings of schizophrenics: The impact of psychotic and non-psychotic affective illness and alcoholism in parents. *Acta Psychiatrica Scandinavica* **94**, 49-55.

Kendler KS, Myers J (2010). The genetic and environmental relationship between major depression and the five-factor model of personality. *Psychological Medicine* **40**, 801-806.

Kendler KS, Prescott CA (1999). Caffeine intake, tolerance, and withdrawal in women: A population-based twin study. *American Journal of Psychiatry* **156**, 223-228.

Kessler RC, Angermeyer M, Anthony JC, R DEG, Demyttenaere K, Gasquet I, G DEG, Gluzman S, Gureje O, Haro JM, Kawakami N, Karam A, Levinson D, Medina Mora ME, Oakley Browne MA, Posada-Villa J, Stein DJ, Adley Tsang CH, Aguilar-Gaxiola S, Alonso J, Lee S, Heeringa S, Pennell BE, Berglund P, Gruber MJ, Petukhova M, Chatterji S, Ustun TB (2007): Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* **6**, 168-176.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry* **62**, 593-602.

Kokkinos PF, Fernhall B (1999). Physical activity and high density lipoprotein cholesterol levels: What is the relationship? *Sports Medicine* **28**, 307-314.

Krapohl E, Euesden J, Zabaneh D, Pingault JB, Rimfeld K, von Stumm S, Dale PS, Breen G, O'Reilly PF, Plomin R (2015). Phenome-wide analysis of genome-wide polygenic scores. *Molecular Psychiatry* **21**, 1188-1193.

Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thorton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S,

Letenneur L, Moron FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fievet N, Huentelman MW, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuiness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossu P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Deniz Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannefelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH, Jr., Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltuenen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nothen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics* **45**, 1452-1458.

Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, Croteau-Chonka DC, Esko T, Fall T, Ferreira T, Gustafsson S, Kutalik Z, Luan J, Magi R, Randall JC, Winkler TW, Wood AR, Workalemahu T, Faul JD, Smith JA, Zhao JH, Zhao W, Chen J, Fehrmann R, Hedman AK, Karjalainen J, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bolton JL, Bragg-Gresham JL, Buyske S, Demirkan A, Deng G, Ehret GB, Feenstra B, Feitosa MF, Fischer K, Goel A, Gong J, Jackson AU, Kanoni S, Kleber ME, Kristiansson K, Lim U, Lotay V, Mangino M, Leach IM, Medina-Gomez C, Medland SE, Nalls MA, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Shungin D, Stancakova A, Strawbridge RJ, Sung YJ, Tanaka T, Teumer A, Trompet S, van der Laan SW, van Setten J, Van Vliet-Ostaptchouk JV, Wang

564 **Z, Yengo L, Zhang W, Isaacs A, Albrecht E, Arnlov J, Arscott GM, Attwood AP, Bandinelli S,**
565 **Barrett A, Bas IN, Bellis C, Bennett AJ, Berne C, Blagieva R, Bluher M, Bohringer S, Bonnycastle**
566 **LL, Bottcher Y, Boyd HA, Bruinenberg M, Caspersen IH, Chen YI, Clarke R, Daw EW, de Craen**
567 **AJM, Delgado G, Dimitriou M, Doney ASF, Eklund N, Estrada K, Eury E, Folkersen L, Fraser RM,**
568 **Garcia ME, Geller F, Giedraitis V, Gigante B, Go AS, Golay A, Goodall AH, Gordon SD, Gorski M,**
569 **Grabe HJ, Grallert H, Grammer TB, Grassler J, Gronberg H, Groves CJ, Gusto G, Haessler J, Hall**
570 **P, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heard-Costa NL, Helmer Q,**
571 **Hengstenberg C, Holmen O, Hottenga JJ, James AL, Jeff JM, Johansson A, Jolley J, Juliusdottir T,**
572 **Kinnunen L, Koenig W, Koskenvuo M, Kratzer W, Laitinen J, Lamina C, Leander K, Lee NR,**
573 **Lichtner P, Lind L, Lindstrom J, Lo KS, Lobbens S, Lorbeer R, Lu Y, Mach F, Magnusson PKE,**
574 **Mahajan A, McArdle WL, McLachlan S, Menni C, Merger S, Mihailov E, Milani L, Moayyeri A,**
575 **Monda KL, Morken MA, Mulas A, Muller G, Muller-Nurasyid M, Musk AW, Nagaraja R, Nothen**
576 **MM, Nolte IM, Pilz S, Rayner NW, Renstrom F, Rettig R, Ried JS, Ripke S, Robertson NR, Rose**
577 **LM, Sanna S, Scharnagl H, Scholtens S, Schumacher FR, Scott WR, Seufferlein T, Shi J, Smith AV,**
578 **Smolonska J, Stanton AV, Steinthorsdottir V, Stirrups K, Stringham HM, Sundstrom J, Swertz MA,**
579 **Swift AJ, Syvanen AC, Tan ST, Tayo BO, Thorand B, Thorleifsson G, Tyrer JP, Uh HW, Vandenput**
580 **L, Verhulst FC, Vermeulen SH, Verweij N, Vonk JM, Waite LL, Warren HR, Waterworth D,**
581 **Weedon MN, Wilkens LR, Willenborg C, Wilsgaard T, Wojczynski MK, Wong A, Wright AF, Zhang**
582 **Q, Brennan EP, Choi M, Dastani Z, Drong AW, Eriksson P, Franco-Cereceda A, Gadin JR, Gharavi**
583 **AG, Goddard ME, Handsaker RE, Huang J, Karpe F, Kathiresan S, Keildson S, Kiryluk K, Kubo**
584 **M, Lee JY, Liang L, Lifton RP, Ma B, McCarroll SA, McKnight AJ, Min JL, Moffatt MF,**
585 **Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Okada Y, Perry JRB, Dorajoo R,**
586 **Reinmaa E, Salem RM, Sandholm N, Scott RA, Stolk L, Takahashi A, Tanaka T, van 't Hooft FM,**
587 **Vinkhuyzen AAE, Westra HJ, Zheng W, Zondervan KT, Heath AC, Arveiler D, Bakker SJL, Beilby**
588 **J, Bergman RN, Blangero J, Bovet P, Campbell H, Caulfield MJ, Cesana G, Chakravarti A,**
589 **Chasman DI, Chines PS, Collins FS, Crawford DC, Cupples LA, Cusi D, Danesh J, de Faire U, den**
590 **Ruijter HM, Dominiczak AF, Erbel R, Erdmann J, Eriksson JG, Farrall M, Felix SB, Ferrannini E,**
591 **Ferrieres J, Ford I, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gejman PV, Gieger C,**

Gottesman O, Gudnason V, Gyllensten U, Hall AS, Harris TB, Hattersley AT, Hicks AA, Hindorff LA, Hingorani AD, Hofman A, Homuth G, Hovingh GK, Humphries SE, Hunt SC, Hypponen E, Illig T, Jacobs KB, Jarvelin MR, Jockel KH, Johansen B, Jousilahti P, Jukema JW, Jula AM, Kaprio J, Kastelein JJP, Keinanen-Kiukaanniemi SM, Kiemeney LA, Knekt P, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuusisto J, Lakka TA, Langenberg C, Marchand LL, Lehtimaki T, Lyssenko V, Mannisto S, Marette A, Matise TC, McKenzie CA, McKnight B, Moll FL, Morris AD, Morris AP, Murray JC, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Madden PAF, Pasterkamp G, Peden JF, Peters A, Postma DS, Pramstaller PP, Price JF, Qi L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Rioux JD, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schunkert H, Schwarz PEH, Sever P, Shuldiner AR, Sinisalo J, Stolk RP, Strauch K, Tonjes A, Tregouet DA, Tremblay A, Tremoli E, Virtamo J, Vohl MC, Volker U, Waeber G, Willemsen G, Witteman JC, Zillikens MC, Adair LS, Amouyel P, Asselbergs FW, Assimes TL, Bochud M, Boehm BO, Boerwinkle E, Bornstein SR, Bottinger EP, Bouchard C, Cauchi S, Chambers JC, Chanock SJ, Cooper RS, de Bakker PIW, Dedoussis G, Ferrucci L, Franks PW, Froguel P, Groop LC, Haiman CA, Hamsten A, Hui J, Hunter DJ, Hveem K, Kaplan RC, Kivimaki M, Kuh D, Laakso M, Liu Y, Martin NG, Marz W, Melbye M, Metspalu A, Moebus S, Munroe PB, Njolstad I, Oostra BA, Palmer CNA, Pedersen NL, Perola M, Perusse L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sattar N, Schadt EE, Schlessinger D, Slagboom PE, Snieder H, Spector TD, Thorsteinsdottir U, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Walker M, Wallaschofski H, Wareham NJ, Watkins H, Weir DR, Wichmann HE, Wilson JF, Zanen P, Borecki IB, Deloukas P, Fox CS, Heid IM, O'Connell JR, Strachan DP, Stefansson K, van Duijn CM, Abecasis GR, Franke L, Frayling TM, McCarthy MI, Visscher PM, Scherag A, Willer CJ, Boehnke M, Mohlke KL, Lindgren CM, Beckmann JS, Barroso I, North KE, Ingelsson E, Hirschhorn JN, Loos RJF, Speliotes EK (2015). Genetic studies of body mass index yield new insights for obesity biology. *Nature* **518**, 197-206.

Lynam DR, Smith GT, Whiteside SP, Cyders MA (2006). *The UPPS-P: Assessing five personality pathways to impulsive behavior. Technical report.* West Lafayette, IN: Purdue University.

Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (2013). A mega-analysis of genome-wide association studies for major depressive disorder. *Molecular Psychiatry* **18**, 497-511.

Marigorta UM, Navarro A (2013): High trans-ethnic replicability of GWAS results implies common causal variants. *PLoS Genetics* **9**, e1003566.

Martin AR, Gignoux CR, Walters RK, Wojcik GL, Neale BM, Gravel S, Daly MJ, Bustamante CD, Kenny EE (2016). Population genetic history and polygenic risk biases in 1000 genomes. Unpublished manuscript. Available at: http://biorxiv.org/content/early/2016/08/23/070797

Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, Strawbridge RJ, Khan H, Grallert H, Mahajan A, Prokopenko I, Kang HM, Dina C, Esko T, Fraser RM, Kanoni S, Kumar A, Lagou V, Langenberg C, Luan J, Lindgren CM, Muller-Nurasyid M, Pechlivanis S, Rayner NW, Scott LJ, Wiltshire S, Yengo L, Kinnunen L, Rossin EJ, Raychaudhuri S, Johnson AD, Dimas AS, Loos RJ, Vedantam S, Chen H, Florez JC, Fox C, Liu CT, Rybin D, Couper DJ, Kao WH, Li M, Cornelis MC, Kraft P, Sun Q, van Dam RM, Stringham HM, Chines PS, Fischer K, Fontanillas P, Holmen OL, Hunt SE, Jackson AU, Kong A, Lawrence R, Meyer J, Perry JR, Platou CG, Potter S, Rehnberg E, Robertson N, Sivapalaratnam S, Stancakova A, Stirrups K, Thorleifsson G, Tikkanen E, Wood AR, Almgren P, Atalay M, Benediktsson R, Bonnycastle LL, Burtt N, Carey J, Charpentier G, Crenshaw AT, Doney AS, Dorkhan M, Edkins S, Emilsson V, Eury E, Forsen T, Gertow K, Gigante B, Grant GB, Groves CJ, Guiducci C, Herder C, Hreidarsson AB, Hui J, James A, Jonsson A, Rathmann W, Klopp N, Kravic J, Krjutskov K, Langford C, Leander K, Lindholm E, Lobbens S, Mannisto S, Mirza G, Muhleisen TW, Musk B, Parkin M, Rallidis L, Saramies J, Sennblad B, Shah S, Sigurethsson G, Silveira A, Steinbach G, Thorand B, Trakalo J, Veglia F, Wennauer R, Winckler W, Zabaneh D, Campbell H, van Duijn C, Uitterlinden AG, Hofman A, Sijbrands E, Abecasis GR, Owen KR, Zeggini E, Trip MD, Forouhi NG, Syvanen AC, Eriksson JG, Peltonen L, Nothen MM, Balkau B, Palmer CN, Lyssenko V, Tuomi T, Isomaa B, Hunter DJ, Qi L, Shuldiner AR, Roden M, Barroso I, Wilsgaard T, Beilby J, Hovingh K, Price JF, Wilson JF, Rauramaa R, Lakka TA, Lind L, Dedoussis G, Njolstad I, Pedersen NL, Khaw KT, Wareham NJ, Keinanen-Kiukaanniemi SM, Saaristo TE, Korpi-Hyovalti E, Saltevo J, Laakso M, Kuusisto J, Metspalu A, Collins FS, Mohlke KL, Bergman RN, Tuomilehto J, Boehm BO, Gieger C, Hveem K, Cauchi S, Froguel P, Baldassarre

D, Tremoli E, Humphries SE, Saleheen D, Danesh J, Ingelsson E, Ripatti S, Salomaa V, Erbel R, Jockel KH, Moebus S, Peters A, Illig T, de Faire U, Hamsten A, Morris AD, Donnelly PJ, Frayling TM, Hattersley AT, Boerwinkle E, Melander O, Kathiresan S, Nilsson PM, Deloukas P, Thorsteinsdottir U, Groop LC, Stefansson K, Hu F, Pankow JS, Dupuis J, Meigs JB, Altshuler D, Boehnke M, McCarthy MI (2012). Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nature Genetics* **44**, 981-990.

Neale BM, Medland SE, Ripke S, Asherson P, Franke B, Lesch KP, Faraone SV, Nguyen TT, Schafer H, Holmans P, Daly M, Steinhausen HC, Freitag C, Reif A, Renner TJ, Romanos M, Romanos J, Walitza S, Warnke A, Meyer J, Palmason H, Buitelaar J, Vasquez AA, Lambregts-Rommelse N, Gill M, Anney RJ, Langely K, O'Donovan M, Williams N, Owen M, Thapar A, Kent L, Sergeant J, Roeyers H, Mick E, Biederman J, Doyle A, Smalley S, Loo S, Hakonarson H, Elia J, Todorov A, Miranda A, Mulas F, Ebstein RP, Rothenberger A, Banaschewski T, Oades RD, Sonuga-Barke E, McGough J, Nisenbaum L, Middleton F, Hu X, Nelson S (2010). Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* **49**, 884-897.

Okbay A, Baselmans BM, De Neve JE, Turley P, Nivard MG, Fontana MA, Meddens SF, Linner RK, Rietveld CA, Derringer J, Gratten J, Lee JJ, Liu JZ, de Vlaming R, Ahluwalia TS, Buchwald J, Cavadino A, Frazier-Wood AC, Furlotte NA, Garfield V, Geisel MH, Gonzalez JR, Haitjema S, Karlsson R, van der Laan SW, Ladwig KH, Lahti J, van der Lee SJ, Lind PA, Liu T, Matteson L, Mihailov E, Miller MB, Minica CC, Nolte IM, Mook-Kanamori D, van der Most PJ, Oldmeadow C, Qian Y, Raitakari O, Rawal R, Realo A, Rueedi R, Schmidt B, Smith AV, Stergiakouli E, Tanaka T, Taylor K, Wedenoja J, Wellmann J, Westra HJ, Willems SM, Zhao W, Amin N, Bakshi A, Boyle PA, Cherney S, Cox SR, Davies G, Davis OS, Ding J, Direk N, Eibich P, Emeny RT, Fatemifar G, Faul JD, Ferrucci L, Forstner A, Gieger C, Gupta R, Harris TB, Harris JM, Holliday EG, Hottenga JJ, De Jager PL, Kaakinen MA, Kajantie E, Karhunen V, Kolcic I, Kumari M, Launer LJ, Franke L, Li-Gao R, Koini M, Loukola A, Marques-Vidal P, Montgomery GW, Mosing MA, Paternoster L, Pattie A, Petrovic KE, Pulkki-Raback L, Quaye L, Raikkonen K, Rudan I, Scott RJ, Smith JA, Sutin AR, Trzaskowski M, Vinkhuyzen AE, Yu L, Zabaneh D, Attia JR, Bennett DA, Berger K, Bertram

L, Boomsma DI, Snieder H, Chang SC, Cucca F, Deary IJ, van Duijn CM, Eriksson JG, Bultmann U, de Geus EJ, Groenen PJ, Gudnason V, Hansen T, Hartman CA, Haworth CM, Hayward C, Heath AC, Hinds DA, Hypponen E, Iacono WG, Jarvelin MR, Jockel KH, Kaprio J, Kardia SL, Keltikangas-Jarvinen L, Kraft P, Kubzansky LD, Lehtimaki T, Magnusson PK, Martin NG, McGue M, Metspalu A, Mills M, de Mutsert R, Oldehinkel AJ, Pasterkamp G, Pedersen NL, Plomin R, Polasek O, Power C, Rich SS, Rosendaal FR, den Ruijter HM, Schlessinger D, Schmidt H, Svento R, Schmidt R, Alizadeh BZ, Sorensen TI, Spector TD, Steptoe A, Terracciano A, Thurik AR, Timpson NJ, Tiemeier H, Uitterlinden AG, Vollenweider P, Wagner GG, Weir DR, Yang J, Conley DC, Smith GD, Hofman A, Johannesson M, Laibson DI, Medland SE, Meyer MN, Pickrell JK, Esko T, Krueger RF, Beauchamp JP, Koellinger PD, Benjamin DJ, Bartels M, Cesarini D (2016). Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nature Genetics* **48**, 624-633.

Otowa T, Hek K, Lee M, Byrne EM, Mirza SS, Nivard MG, Bigdeli T, Aggen SH, Adkins D, Wolen A, Fanous A, Keller MC, Castelao E, Kutalik Z, der Auwera SV, Homuth G, Nauck M, Teumer A, Milaneschi Y, Hottenga JJ, Direk N, Hofman A, Uitterlinden A, Mulder CL, Henders AK, Medland SE, Gordon S, Heath AC, Madden PA, Pergadia ML, van der Most PJ, Nolte IM, van Oort FV, Hartman CA, Oldehinkel AJ, Preisig M, Grabe HJ, Middeldorp CM, Penninx BW, Boomsma D, Martin NG, Montgomery G, Maher BS, van den Oord EJ, Wray NR, Tiemeier H, Hettema JM (2016) Meta-analysis of genome-wide association studies of anxiety disorders. *Molecular Psychiatry* **21**, 1391-1399.

Perry JR, Day F, Elks CE, Sulem P, Thompson DJ, Ferreira T, He C, Chasman DI, Esko T, Thorleifsson G, Albrecht E, Ang WQ, Corre T, Cousminer DL, Feenstra B, Franceschini N, Ganna A, Johnson AD, Kjellqvist S, Lunetta KL, McMahon G, Nolte IM, Paternoster L, Porcu E, Smith AV, Stolk L, Teumer A, Tsernikova N, Tikkanen E, Ulivi S, Wagner EK, Amin N, Bierut LJ, Byrne EM, Hottenga JJ, Koller DL, Mangino M, Pers TH, Yerges-Armstrong LM, Zhao JH, Andrulis IL, Anton-Culver H, Atsma F, Bandinelli S, Beckmann MW, Benitez J, Blomqvist C, Bojesen SE, Bolla MK, Bonanni B, Brauch H, Brenner H, Buring JE, Chang-Claude J, Chanock S, Chen J, Chenevix-Trench G, Collee JM, Couch FJ, Couper D, Coveillo AD, Cox A, Czene K, D'Adamo A P, Smith GD, De Vivo I,

Demerath EW, Dennis J, Devilee P, Dieffenbach AK, Dunning AM, Eiriksdottir G, Eriksson JG, Fasching PA, Ferrucci L, Flesch-Janys D, Flyger H, Foroud T, Franke L, Garcia ME, Garcia-Closas M, Geller F, de Geus EE, Giles GG, Gudbjartsson DF, Gudnason V, Guenel P, Guo S, Hall P, Hamann U, Haring R, Hartman CA, Heath AC, Hofman A, Hooning MJ, Hopper JL, Hu FB, Hunter DJ, Karasik D, Kiel DP, Knight JA, Kosma VM, Kutalik Z, Lai S, Lambrechts D, Lindblom A, Magi R, Magnusson PK, Mannermaa A, Martin NG, Masson G, McArdle PF, McArdle WL, Melbye M, Michailidou K, Mihailov E, Milani L, Milne RL, Nevanlinna H, Neven P, Nohr EA, Oldehinkel AJ, Oostra BA, Palotie A, Peacock M, Pedersen NL, Peterlongo P, Peto J, Pharoah PD, Postma DS, Pouta A, Pylkas K, Radice P, Ring S, Rivadeneira F, Robino A, Rose LM, Rudolph A, Salomaa V, Sanna S, Schlessinger D, Schmidt MK, Southey MC, Sovio U, Stampfer MJ, Stockl D, Storniolo AM, Timpson NJ, Tyrer J, Visser JA, Vollenweider P, Volzke H, Waeber G, Waldenberger M, Wallaschofski H, Wang Q, Willemsen G, Winqvist R, Wolffenbuttel BH, Wright MJ, Boomsma DI, Econs MJ, Khaw KT, Loos RJ, McCarthy MI, Montgomery GW, Rice JP, Streeten EA, Thorsteinsdottir U, van Duijn CM, Alizadeh BZ, Bergmann S, Boerwinkle E, Boyd HA, Crisponi L, Gasparini P, Gieger C, Harris TB, Ingelsson E, Jarvelin MR, Kraft P, Lawlor D, Metspalu A, Pennell CE, Ridker PM, Snieder H, Sorensen TI, Spector TD, Strachan DP, Uitterlinden AG, Wareham NJ, Widen E, Zygmunt M, Murray A, Easton DF, Stefansson K, Murabito JM, Ong KK (2014). Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature* **514**, 92-97.

Psychiatric GWAS Consortium Bipolar Disorder Working Group (2011). Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nature Genetics* **43**, 977-983.

Rader DJ (2006). Molecular regulation of HDL metabolism and function: Implications for novel therapies. *The Journal of Clinical Investigation* **116**, 3090-3100.

Rietveld CA, Medland SE, Derringer J, Yang J, Esko T, Martin NW, Westra HJ, Shakhbazov K, Abdellaoui A, Agrawal A, Albrecht E, Alizadeh BZ, Amin N, Barnard J, Baumeister SE, Benke KS, Bielak LF, Boatman JA, Boyle PA, Davies G, de Leeuw C, Eklund N, Evans DS, Ferhmann R, Fischer K, Gieger C, Gjessing HK, Hagg S, Harris JR, Hayward C, Holzapfel C, Ibrahim-Verbaas CA, Ingelsson E, Jacobsson B, Joshi PK, Jugessur A, Kaakinen M, Kanoni S, Karjalainen J, Kolcic I, Kristiansson K,

Kutalik Z, Lahti J, Lee SH, Lin P, Lind PA, Liu Y, Lohman K, Loitfelder M, McMahon G, Vidal PM, Meirelles O, Milani L, Myhre R, Nuotio ML, Oldmeadow CJ, Petrovic KE, Peyrot WJ, Polasek O, Quaye L, Reinmaa E, Rice JP, Rizzi TS, Schmidt H, Schmidt R, Smith AV, Smith JA, Tanaka T, Terracciano A, van der Loos MJ, Vitart V, Volzke H, Wellmann J, Yu L, Zhao W, Allik J, Attia JR, Bandinelli S, Bastardot F, Beauchamp J, Bennett DA, Berger K, Bierut LJ, Boomsma DI, Bultmann U, Campbell H, Chabris CF, Cherkas L, Chung MK, Cucca F, de Andrade M, De Jager PL, De Neve JE, Deary IJ, Dedoussis GV, Deloukas P, Dimitriou M, Eiriksdottir G, Elderson MF, Eriksson JG, Evans DM, Faul JD, Ferrucci L, Garcia ME, Gronberg H, Guethnason V, Hall P, Harris JM, Harris TB, Hastie ND, Heath AC, Hernandez DG, Hoffmann W, Hofman A, Holle R, Holliday EG, Hottenga JJ, Iacono WG, Illig T, Jarvelin MR, Kahonen M, Kaprio J, Kirkpatrick RM, Kowgier M, Latvala A, Launer LJ, Lawlor DA, Lehtimaki T, Li J, Lichtenstein P, Lichtner P, Liewald DC, Madden PA, Magnusson PK, Makinen TE, Masala M, McGue M, Metspalu A, Mielck A, Miller MB, Montgomery GW, Mukherjee S, Nyholt DR, Oostra BA, Palmer LJ, Palotie A, Penninx BW, Perola M, Peyser PA, Preisig M, Raikkonen K, Raitakari OT, Realo A, Ring SM, Ripatti S, Rivadeneira F, Rudan I, Rustichini A, Salomaa V, Sarin AP, Schlessinger D, Scott RJ, Snieder H, St Pourcain B, Starr JM, Sul JH, Surakka I, Svento R, Teumer A, Tiemeier H, van Rooij FJ, Van Wagoner DR, Vartiainen E, Viikari J, Vollenweider P, Vonk JM, Waeber G, Weir DR, Wichmann HE, Widen E, Willemsen G, Wilson JF, Wright AF, Conley D, Davey-Smith G, Franke L, Groenen PJ, Hofman A, Johannesson M, Kardia SL, Krueger RF, Laibson D, Martin NG, Meyer MN, Posthuma D, Thurik AR, Timpson NJ, Uitterlinden AG, van Duijn CM, Visscher PM, Benjamin DJ, Cesarini D, Koellinger PD (2013). GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science* **340**, 1467-1471.

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421-427.

Schuckit MA, Smith TL, Tipp JE (1997). The Self-Rating of the Effects of alcohol (SRE) form as a retrospective measure of the risk for alcoholism. *Addiction* **92**, 979-988.

Schunkert H, Konig IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AF, Barbalic M, Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL,

Ardissino D, Ball SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS, Brown MJ, Burnett MS, Buysschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NE, Ellis SG, Elosua R, Engert JC, Epstein SE, de Faire U, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR, Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA, Kaplan LM, Kastelein JJ, Khaw KT, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger T, Melander O, Merlini PA, Mooser V, Morgan T, Muhleisen TW, Muhlestein JB, Munzel T, Musunuru K, Nahrstaedt J, Nelson CP, Nothen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA, Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schafer A, Schillert A, Schreiber S, Schrezenmeir J, Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A, Smith TB, Snoep JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WH, Tennstedt S, Thorgeirsson G, Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann HE, Wild PS, Willenborg C, Witteman JC, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA, Quertermous T, Marz W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR, Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J, Samani NJ (2011). Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nature Genetics* **43**, 333-338.

Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Magi R, Strawbridge RJ, Pers TH, Fischer K, Justice AE, Workalemahu T, Wu JMW, Buchkovich ML, Heard-Costa NL, Roman TS, Drong AW, Song C, Gustafsson S, Day FR, Esko T, Fall T, Kutalik Z, Luan J, Randall JC, Scherag A, Vedantam S, Wood AR, Chen J, Fehrmann R, Karjalainen J, Kahali B, Liu CT, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bragg-Gresham JL, Buyske S, Demirkan A, Ehret GB, Feitosa MF, Goel A, Jackson AU, Johnson T, Kleber ME, Kristiansson K, Mangino M, Leach IM, Medina-Gomez C, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Stancakova A,

787 **Sung YJ, Tanaka T, Teumer A, Van Vliet-Ostaptchouk JV, Yengo L, Zhang W, Albrecht E, Arnlov**
788 **J, Arscott GM, Bandinelli S, Barrett A, Bellis C, Bennett AJ, Berne C, Bluher M, Bohringer S,**
789 **Bonnet F, Bottcher Y, Bruinenberg M, Carba DB, Caspersen IH, Clarke R, Daw EW, Deelen J,**
790 **Deelman E, Delgado G, Doney AS, Eklund N, Erdos MR, Estrada K, Eury E, Friedrich N, Garcia**
791 **ME, Giedraitis V, Gigante B, Go AS, Golay A, Grallert H, Grammer TB, Grassler J, Grewal J,**
792 **Groves CJ, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heikkila K, Herzig KH,**
793 **Helmer Q, Hillege HL, Holmen O, Hunt SC, Isaacs A, Ittermann T, James AL, Johansson I,**
794 **Juliusdottir T, Kalafati IP, Kinnunen L, Koenig W, Kooner IK, Kratzer W, Lamina C, Leander K,**
795 **Lee NR, Lichtner P, Lind L, Lindstrom J, Lobbens S, Lorentzon M, Mach F, Magnusson PK,**
796 **Mahajan A, McArdle WL, Menni C, Merger S, Mihailov E, Milani L, Mills R, Moayyeri A, Monda**
797 **KL, Mooijaart SP, Muhleisen TW, Mulas A, Muller G, Muller-Nurasyid M, Nagaraja R, Nalls MA,**
798 **Narisu N, Glorioso N, Nolte IM, Olden M, Rayner NW, Renstrom F, Ried JS, Robertson NR, Rose**
799 **LM, Sanna S, Scharnagl H, Scholtens S, Sennblad B, Seufferlein T, Sitlani CM, Smith AV, Stirrups**
800 **K, Stringham HM, Sundstrom J, Swertz MA, Swift AJ, Syvanen AC, Tayo BO, Thorand B,**
801 **Thorleifsson G, Tomaschitz A, Troffa C, van Oort FV, Verweij N, Vonk JM, Waite LL, Wennauer**
802 **R, Wilsgaard T, Wojczynski MK, Wong A, Zhang Q, Zhao JH, Brennan EP, Choi M, Eriksson P,**
803 **Folkersen L, Franco-Cereceda A, Gharavi AG, Hedman AK, Hivert MF, Huang J, Kanoni S, Karpe**
804 **F, Keildson S, Kiryluk K, Liang L, Lifton RP, Ma B, McKnight AJ, McPherson R, Metspalu A, Min**
805 **JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Olsson C, Perry JR,**
806 **Reinmaa E, Salem RM, Sandholm N, Schadt EE, Scott RA, Stolk L, Vallejo EE, Westra HJ,**
807 **Zondervan KT, Amouyel P, Arveiler D, Bakker SJ, Beilby J, Bergman RN, Blangero J, Brown MJ,**
808 **Burnier M, Campbell H, Chakravarti A, Chines PS, Claudi-Boehm S, Collins FS, Crawford DC,**
809 **Danesh J, de Faire U, de Geus EJ, Dorr M, Erbel R, Eriksson JG, Farrall M, Ferrannini E, Ferrieres**
810 **J, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gieger C, Gudnason V, Haiman CA,**
811 **Harris TB, Hattersley AT, Heliovaara M, Hicks AA, Hingorani AD, Hoffmann W, Hofman A,**
812 **Homuth G, Humphries SE, Hypponen E, Illig T, Jarvelin MR, Johansen B, Jousilahti P, Jula AM,**
813 **Kaprio J, Kee F, Keinanen-Kiukaanniemi SM, Kooner JS, Kooperberg C, Kovacs P, Kraja AT,**
814 **Kumari M, Kuulasmaa K, Kuusisto J, Lakka TA, Langenberg C, Le Marchand L, Lehtimaki T,**

Lyssenko V, Mannisto S, Marette A, Matise TC, McKenzie CA, McKnight B, Musk AW, Mohlenkamp S, Morris AD, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Palmer LJ, Penninx BW, Peters A, Pramstaller PP, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schwarz PE, Shuldiner AR, Staessen JA, Steinthorsdottir V, Stolk RP, Strauch K, Tonjes A, Tremblay A, Tremoli E, Vohl MC, Volker U, Vollenweider P, Wilson JF, Witteman JC, Adair LS, Bochud M, Boehm BO, Bornstein SR, Bouchard C, Cauchi S, Caulfield MJ, Chambers JC, Chasman DI, Cooper RS, Dedoussis G, Ferrucci L, Froguel P, Grabe HJ, Hamsten A, Hui J, Hveem K, Jockel KH, Kivimaki M, Kuh D, Laakso M, Liu Y, Marz W, Munroe PB, Njolstad I, Oostra BA, Palmer CN, Pedersen NL, Perola M, Perusse L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sinisalo J, Slagboom PE, Snieder H, Spector TD, Stefansson K, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Veronesi G, Walker M, Wareham NJ, Watkins H, Wichmann HE, Abecasis GR, Assimes TL, Berndt SI, Boehnke M, Borecki IB, Deloukas P, Franke L, Frayling TM, Groop LC, Hunter DJ, Kaplan RC, O'Connell JR, Qi L, Schlessinger D, Strachan DP, Thorsteinsdottir U, van Duijn CM, Willer CJ, Visscher PM, Yang J, Hirschhorn JN, Zillikens MC, McCarthy MI, Speliotes EK, North KE, Fox CS, Barroso I, Franks PW, Ingelsson E, Heid IM, Loos RJ, Cupples LA, Morris AP, Lindgren CM, Mohlke KL (2015). New genetic loci link adipose and insulin biology to body fat distribution. *Nature* **518**, 187-196.

Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, Li Y, Kurreeman FA, Zhernakova A, Hinks A, Guiducci C, Chen R, Alfredsson L, Amos CI, Ardlie KG, Barton A, Bowes J, Brouwer E, Burtt NP, Catanese JJ, Coblyn J, Coenen MJ, Costenbader KH, Criswell LA, Crusius JB, Cui J, de Bakker PI, De Jager PL, Ding B, Emery P, Flynn E, Harrison P, Hocking LJ, Huizinga TW, Kastner DL, Ke X, Lee AT, Liu X, Martin P, Morgan AW, Padyukov L, Posthumus MD, Radstake TR, Reid DM, Seielstad M, Seldin MF, Shadick NA, Steer S, Tak PP, Thomson W, van der Helm-van Mil AH, van der Horst-Bruinsma IE, van der Schoot CE, van Riel PL, Weinblatt ME, Wilson AG, Wolbink GJ, Wordsworth BP, Wijmenga C, Karlson EW, Toes RE, de Vries N, Begovich AB, Worthington J, Siminovitch KA, Gregersen PK, Klareskog L, Plenge RM (2010). Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nature Genetics* **42**, 508-514.

Steinberg L, Lamborn SD, Dornbusch SM, Darling N (1992). Impact of parenting practices on adolescent achievement: Authoritative parenting, school involvement, and encouragement to succeed. *Child Development* **63**, 1266-1281.

Taal HR, Pourcain BS, Thiering E, Das S, Mook-Kanamori DO, Warrington NM, Kaakinen M, Kreiner-Moller E, Bradfield JP, Freathy RM, Geller F, Guxens M, Cousminer DL, Kerkhof M, Timpson NJ, Ikram MA, Beilin LJ, Bonnelykke K, Buxton JL, Charoen P, Chawes BLK, Eriksson J, Evans DM, Hofman A, Kemp JP, Kim CE, Klopp N, Lahti J, Lye SJ, McMahon G, Mentch FD, Muller M, O'Reilly PF, Prokopenko I, Rivadeneira F, Steegers EAP, Sunyer J, Tiesler C, Yaghootkar H, Breteler MMB, Debette S, Fornage M, Gudnason V, Launer LJ, van der Lugt A, Mosley TH, Seshadri S, Smith AV, Vernooij MW, Blakemore AI, Chiavacci RM, Feenstra B, Fernandez-Benet J, Grant SFA, Hartikainen AL, van der Heijden AJ, Iniguez C, Lathrop M, McArdle WL, Molgaard A, Newnham JP, Palmer LJ, Palotie A, Pouta A, Ring SM, Sovio U, Standl M, Uitterlinden AG, Wichmann HE, Vissing NH, DeCarli C, van Duijn CM, McCarthy MI, Koppelman GH, Estivill X, Hattersley AT, Melbye M, Bisgaard H, Pennell CE, Widen E, Hakonarson H, Smith GD, Heinrich J, Jarvelin MR, Jaddoe VWV (2012). Common variants at 12q15 and 12q24 are associated with infant head circumference. *Nature Genetics* **44**, 532-538.

Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, Pirruccello JP, Ripatti S, Chasman DI, Willer CJ, Johansen CT, Fouchier SW, Isaacs A, Peloso GM, Barbalic M, Ricketts SL, Bis JC, Aulchenko YS, Thorleifsson G, Feitosa MF, Chambers J, Orho-Melander M, Melander O, Johnson T, Li X, Guo X, Li M, Shin Cho Y, Jin Go M, Jin Kim Y, Lee JY, Park T, Kim K, Sim X, Twee-Hee Ong R, Croteau-Chonka DC, Lange LA, Smith JD, Song K, Hua Zhao J, Yuan X, Luan J, Lamina C, Ziegler A, Zhang W, Zee RY, Wright AF, Witteman JC, Wilson JF, Willemsen G, Wichmann HE, Whitfield JB, Waterworth DM, Wareham NJ, Waeber G, Vollenweider P, Voight BF, Vitart V, Uitterlinden AG, Uda M, Tuomilehto J, Thompson JR, Tanaka T, Surakka I, Stringham HM, Spector TD, Soranzo N, Smit JH, Sinisalo J, Silander K, Sijbrands EJ, Scuteri A, Scott J, Schlessinger D, Sanna S, Salomaa V, Saharinen J, Sabatti C, Ruokonen A, Rudan I, Rose LM, Roberts R, Rieder M, Psaty BM, Pramstaller PP, Pichler I, Perola M, Penninx BW, Pedersen NL, Pattaro C, Parker AN, Pare G, Oostra BA, O'Donnell CJ, Nieminen MS, Nickerson DA,

Montgomery GW, Meitinger T, McPherson R, McCarthy MI, McArdle W, Masson D, Martin NG, Marroni F, Mangino M, Magnusson PK, Lucas G, Luben R, Loos RJ, Lokki ML, Lettre G, Langenberg C, Launer LJ, Lakatta EG, Laaksonen R, Kyvik KO, Kronenberg F, Konig IR, Khaw KT, Kaprio J, Kaplan LM, Johansson A, Jarvelin MR, Janssens AC, Ingelsson E, Igl W, Kees Hovingh G, Hottenga JJ, Hofman A, Hicks AA, Hengstenberg C, Heid IM, Hayward C, Havulinna AS, Hastie ND, Harris TB, Haritunians T, Hall AS, Gyllensten U, Guiducci C, Groop LC, Gonzalez E, Gieger C, Freimer NB, Ferrucci L, Erdmann J, Elliott P, Ejebe KG, Doring A, Dominiczak AF, Demissie S, Deloukas P, de Geus EJ, de Faire U, Crawford G, Collins FS, Chen YD, Caulfield MJ, Campbell H, Burtt NP, Bonnycastle LL, Boomsma DI, Boekholdt SM, Bergman RN, Barroso I, Bandinelli S, Ballantyne CM, Assimes TL, Quertermous T, Altshuler D, Seielstad M, Wong TY, Tai ES, Feranil AB, Kuzawa CW, Adair LS, Taylor HA, Jr., Borecki IB, Gabriel SB, Wilson JG, Holm H, Thorsteinsdottir U, Gudnason V, Krauss RM, Mohlke KL, Ordovas JM, Munroe PB, Kooner JS, Tall AR, Hegele RA, Kastelein JJ, Schadt EE, Rotter JI, Boerwinkle E, Strachan DP, Mooser V, Stefansson K, Reilly MP, Samani NJ, Schunkert H, Cupples LA, Sandhu MS, Ridker PM, Rader DJ, van Duijn CM, Peltonen L, Abecasis GR, Boehnke M, Kathiresan S (2010). Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **466**, 707-713.

Tobacco and Genetics Consortium (2010). Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nature Genetics* **42**, 441-447.

van der Valk RJ, Kreiner-Moller E, Kooijman MN, Guxens M, Stergiakouli E, Saaf A, Bradfield JP, Geller F, Hayes MG, Cousminer DL, Korner A, Thiering E, Curtin JA, Myhre R, Huikari V, Joro R, Kerkhof M, Warrington NM, Pitkanen N, Ntalla I, Horikoshi M, Veijola R, Freathy RM, Teo YY, Barton SJ, Evans DM, Kemp JP, St Pourcain B, Ring SM, Davey Smith G, Bergstrom A, Kull I, Hakonarson H, Mentch FD, Bisgaard H, Chawes B, Stokholm J, Waage J, Eriksen P, Sevelsted A, Melbye M, van Duijn CM, Medina-Gomez C, Hofman A, de Jongste JC, Taal HR, Uitterlinden AG, Armstrong LL, Eriksson J, Palotie A, Bustamante M, Estivill X, Gonzalez JR, Llop S, Kiess W, Mahajan A, Flexeder C, Tiesler CM, Murray CS, Simpson A, Magnus P, Sengpiel V, Hartikainen AL, Keinanen-Kiukaanniemi S, Lewin A, Da Silva Couto Alves A, Blakemore AI, Buxton JL, Kaakinen M, Rodriguez A, Sebert S, Vaarasmaki M, Lakka T, Lindi V, Gehring U, Postma DS, Ang

W, Newnham JP, Lyytikainen LP, Pahkala K, Raitakari OT, Panoutsopoulou K, Zeggini E, Boomsma DI, Groen-Blokhuis M, Ilonen J, Franke L, Hirschhorn JN, Pers TH, Liang L, Huang J, Hocher B, Knip M, Saw SM, Holloway JW, Melen E, Grant SF, Feenstra B, Lowe WL, Widen E, Sergeyev E, Grallert H, Custovic A, Jacobsson B, Jarvelin MR, Atalay M, Koppelman GH, Pennell CE, Niinikoski H, Dedoussis GV, McCarthy MI, Frayling TM, Sunyer J, Timpson NJ, Rivadeneira F, Bonnelykke K, Jaddoe VW (2015). A novel common variant in DCST2 is associated with length in early life and height in adulthood. *Human Molecular Genetics* **24**, 1155-1168.

van den Berg SM, de Moor MH, Verweij KJ, Krueger RF, Luciano M, Arias Vasquez A, Matteson LK, Derringer J, Esko T, Amin N, Gordon SD, Hansell NK, Hart AB, Seppala I, Huffman JE, Konte B, Lahti J, Lee M, Miller M, Nutile T, Tanaka T, Teumer A, Viktorin A, Wedenoja J, Abdellaoui A, Abecasis GR, Adkins DE, Agrawal A, Allik J, Appel K, Bigdeli TB, Busonero F, Campbell H, Costa PT, Smith GD, Davies G, de Wit H, Ding J, Engelhardt BE, Eriksson JG, Fedko IO, Ferrucci L, Franke B, Giegling I, Grucza R, Hartmann AM, Heath AC, Heinonen K, Henders AK, Homuth G, Hottenga JJ, Iacono WG, Janzing J, Jokela M, Karlsson R, Kemp JP, Kirkpatrick MG, Latvala A, Lehtimaki T, Liewald DC, Madden PA, Magri C, Magnusson PK, Marten J, Maschio A, Mbarek H, Medland SE, Mihailov E, Milaneschi Y, Montgomery GW, Nauck M, Nivard MG, Ouwens KG, Palotie A, Pettersson E, Polasek O, Qian Y, Pulkki-Raback L, Raitakari OT, Realo A, Rose RJ, Ruggiero D, Schmidt CO, Slutske WS, Sorice R, Starr JM, St Pourcain B, Sutin AR, Timpson NJ, Trochet H, Vermeulen S, Vuoksimaa E, Widen E, Wouda J, Wright MJ, Zgaga L, Porteous D, Minelli A, Palmer AA, Rujescu D, Ciullo M, Hayward C, Rudan I, Metspalu A, Kaprio J, Deary IJ, Raikkonen K, Wilson JF, Keltikangas-Jarvinen L, Bierut LJ, Hettema JM, Grabe HJ, Penninx BW, van Duijn CM, Evans DM, Schlessinger D, Pedersen NL, Terracciano A, McGue M, Martin NG, Boomsma DI (2016). Meta-analysis of genome-wide association studies for extraversion: Findings from the genetics of personality consortium. *Behavior Genetics* **46**, 170-182.

Vilhjalmsson BJ, Yang J, Finucane HK, Gusev A, Lindstrom S, Ripke S, Genovese G, Loh PR, Bhatia G, Do R, Hayeck T, Won HH, Kathiresan S, Pato M, Pato C, Tamimi R, Stahl E, Zaitlen N, Pasaniuc B, Belbin G, Kenny EE, Schierup MH, De Jager P, Patsopoulos NA, McCarroll S, Daly M, Purcell S, Chasman D, Neale B, Goddard M, Visscher PM, Kraft P, Patterson N, Price AL (2015). Modeling

linkage disequilibrium increases accuracy of polygenic risk scores. *American Journal of Human Genetics* **97**, 576-592.

Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, Frayling TM (2014). Defining the role of common variation in the genomic and biological architecture of adult human height. *Nature Genetics* **46**, 1173-1186.