Genetic correlation between smoking behaviors and schizophrenia

First author: Sarah M. Hartz

Senior author: Laura J. Bierut

Other authors: Neil E. Caporaso, Li-Shiun Chen, Dana Hancock, Amy Horton, John E. Hokanson, Eric O. Johnson, Carlos Pato, Michele Pato

Word count: 2,019

Submit to *Schizophrenia Research*

Special Issue: *Addictions and Schizophrenia*

Full Length Paper: 2000-3000 words

Abstract (current 188 words, max 250 words)

Nicotine dependence is highly comorbid with schizophrenia, and the etiology of the comorbidity is unknown. To determine whether there is a genetic correlation of smoking behavior with schizophrenia, genome-wide association study (GWAS) meta-analysis results from five smoking phenotypes (ever/never smoker (N=74,035), age of onset of smoking (N=28,647), cigarettes smoked per day (CPD, N=38,860), nicotine dependence (N=10,666), and current/former smoker (N=40,562)) were compared to GWAS meta-analysis results from schizophrenia (N=74,626) using linkage disequilibrium (LD) score regression. First, the GWAS heritability (*h2g*) of each of the smoking phenotypes was computed using LD score regression (ever/never smoker *h2g* =0.08, age of onset of smoking *h2g*=0.06, CPD *h2g*=0.06, nicotine dependence *h2g*=0.15 *,* current/former smoker *h2g*=0.07*,* p<0.001 for all phenotypes). The GWAS heritability for nicotine dependence was statistically higher than the GWAS heritability for the other smoking phenotypes (p<0.0005 for all two-way comparisons). Next, a statistically significant (p<0.05) genetic correlation was observed between schizophrenia and three of the five smoking phenotypes (nicotine dependence *rg*=0.14, cigarettes per day *rg*=0.12, and ever/never smoking *rg*=0.10). These results suggest that there is a component of common genetic variation that is shared between smoking behaviors and schizophrenia.

Introduction

Severe mental illness and nicotine dependence frequently co-occur. Individuals suffering from schizophrenia have much higher rates of smoking than the general population (Hartz et al., 2014). Similarly, smokers are more likely to suffer from schizophrenia (Gage et al., 2014; Myles et al., 2012; Sorensen et al., 2011; Zammit et al., 2003). Furthermore, much of the morbidity and premature mortality in individuals with schizophrenia can be attributed to smoking-related diseases (Brady et al., 1993; Colton and Manderscheid, 2006; Crump et al., 2013; Drake and Wallach, 1989; Olfson et al., 2015; Parks et al., 2006).

Given the severe public health consequences of the comorbidity of schizophrenia with nicotine dependence, understanding the etiology of this comorbidity is clinically important. Currently, schizophrenia is diagnosed treated independently of nicotine dependence. Prognostically, there is already evidence that schizophrenia with comorbid nicotine dependence is more severe and has worse outcomes than schizophrenia without comorbid nicotine dependence (Gage et al., 2014; Sorensen et al., 2011; Tsoi et al., 2013; Zammit et al., 2003). If there is evidence of shared genetic factors between nicotine dependence and schizophrenia, this implies there is a common etiology between the two disorders. The combination of a differential prognosis and evidence of shared etiology suggests that perhaps optimal treatment for schizophrenia differs, depending on whether there is comorbid nicotine dependence.

Genome-wide association studies have identified many distinct genetic variants that contribute to the risk for schizophrenia (Moskvina et al., 2009; Ripke et al., 2013; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The most highly replicated variants associated with schizophrenia are in immune-related genes and neurodevelopmental genes (including the major histocompatibility complex genes, *NRGN,* and *TCF4*). Recently, the Psychiatric Genetics Consortium identified 128 independent loci that contribute to the risk of developing schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Interestingly, one locus recently identified as contributing to schizophrenia is the chromosome 15q24 locus. This locus contains the α5-α3-β4 nicotinic receptor subunit genes and is the strongest genetic contributor to nicotine dependence (TAG, 2010). This finding suggests that there are shared genetic risk factors between schizophrenia and nicotine dependence.

One approach to determining whether shared genetic factors contribute to multiple phenotypes is to estimate the GWAS correlation between the phenotypes using linkage disequilibrium (LD) score regression (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b). Using known LD between single nucleotide polymorphisms (SNPs), the intercept computed from LD score regression can be included in GWAS studies as a powerful correction factor for the inflation of test statistics (Bulik-Sullivan et al., 2015b). In addition, the formula for LD score regression can be permuted to compute the genetic correlation between phenotypes based on GWAS results, termed “GWAS correlation” (Bulik-Sullivan et al., 2015a).

LD score regression has been used to show GWAS correlation between multiple psychiatric phenotypes (Bulik-Sullivan et al., 2015a). To our knowledge, the GWAS correlation between smoking behaviors and schizophrenia has not been fully characterized. In this study, we use LD score regression to evaluate the GWAS correlation between multiple smoking phenotypes and schizophrenia.

**Methods**

Smoking phenotypes: To evaluate the GWAS correlation between smoking phenotypes and schizophrenia, five different smoking phenotypes were used (Table 1). Ever/never smoker was coded as a dichotomous phenotype, with ever smokers typically defined as having smoked 100 cigarettes lifetime (Tobacco and Genetics Consortium, 2010). Age of onset of smoking was a continuous phenotype that was log transformed for analysis, and was defined as the age of onset of regular smoking (Tobacco and Genetics Consortium, 2010). Cigarettes per day (CPD) was coded as a continuous phenotype and is correlated with nicotine dependence (Tobacco and Genetics Consortium, 2010). The phenotype of nicotine dependence was measured only among ever smokers and was defined by the Fagerström Test for Nicotine Dependence (FTND), a six item questionnaire designed to assess the intensity of physical addiction to nicotine, with scores ranging from 0 to 10 (Heatherton et al., 1991). Nicotine dependence was then classified into mild (FTND score 0-3), moderate (FTND score 4-6), or severe (FTND score 7-10), as has been done in previous research (Hancock et al., 2015). Current/former smoker was coded as a dichotomous phenotype, where current smokers reported at interview that they presently smoked and former smokers had quit smoking at least 1 year before interview (Tobacco and Genetics Consortium, 2010). The phenotypes of age of onset, cigarettes per day, nicotine dependence, and current/former smokers included only ever smokers. Schizophrenia was also coded as a dichotomous phenotype based on meeting DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Data: The computation of GWAS correlation in LD score regression uses GWAS results from European ancestry meta-analysis studies for each phenotype (references in Table 1). The GWAS for nicotine dependence included eight studies from a meta-analysis of FTND (Hancock et al., 2015): Environment and Genetics in Lung Cancer Etiology Study (N=3,006, dbGaP accession number phs000093.v2.p2) (Landi et al., 2009; Landi et al., 2008); Collaborative Genetic Study of Nicotine Dependence (COGEND, both recruitment waves, N=2,227, dbGaP accession number phs000092.v1.p1) (Bierut et al., 2007); Chronic Obstructive Pulmonary Disease Gene Study (N=2,211, dbGaP accession number phs000765.v1.p2) (Regan et al., 2010); UW-TTURC (N=1,534, dbGaP accession number phs000404.v1.p1) (Baker et al., 2007); Study of Addiction, Genes and Environment (excluding COGEND participants, N=1,075, dbGaP accession number phs000092.v1.p1) (Rice et al., 2012); GAIN (N=774, dbGaP accession number phs000021.v3.p2) (Manolio et al., 2007); nonGAIN (N=671, dbGaP accession number phs000167.v1.p1) (Manolio et al., 2007); and COHRA1 (N=243, dbGaP accession number phs000095.v2.p1) (Shaffer et al., 2011). Published GWAS results for schizophrenia, and four Tobacco and Genetics (TAG) Consortium analyses of smoking-related behaviors were downloaded from the Psychiatric Genetics Consortium website (<https://www.med.unc.edu/pgc/results-and-downloads>).

LD Score regression: The patterns of LD found across the genome enable genetic correlations between traits to be derived. This is because the observed association for a SNP is a product of both its own contribution toward a phenotype and the association of the SNPs that are in LD with it (Yang et al., 2011). Because SNPs in regions of high LD tag a greater proportion of the genome than SNPs in regions of low LD, SNPs in regions of high LD will have greater association statistics than SNPs found in regions of low LD. Thus, by using the known LD structure of a reference panel of SNPs, the GWAS heritability of a single phenotype or the GWAS correlation of two phenotypes can be computed using LD score regression (Bulik-Sullivan et al., 2015a; Lee et al., 2016).

To estimate GWAS heritability (*h2g*) and GWAS correlation (*rg*), we used the software and protocol from the study by Bulik-Sullivan et al. (2015a) (<http://www.github.com/bulik/ldsc>) and applied it to our datasets. To control for imputation quality, only those SNPs found in the HapMap3 with 1000 Genomes EUR with a minor allele frequency (MAF) > 0.01 were included (integrated\_phase1\_v3.20101123). Next, insertions and deletions (INDELs) and structural variants were removed along with strand-ambiguous SNPs. LD scores and weights for use with the GWAS of European ancestry were downloaded from the Broad institute (<http://www.broadinstitute.org/~bulik/eur_ldscores/>). An unconstrained intercept was used in the regression model.

**Results**

The first step was to estimate the heritability of the smoking phenotypes. The univariate GWAS heritability, the proportion of phenotypic variance explained by GWAS SNPs, was evaluated for each smoking phenotype (Table 2). All the smoking phenotypes have statistically significant GWAS heritability (p<0.001). The phenotype with the highest estimated GWAS heritability is nicotine dependence, which has a GWAS heritability estimate of 15%. This is approximately double the estimated GWAS heritability for the other smoking phenotypes (estimates ranging 6%-8%), suggesting that nicotine dependence, as defined using FTND, has higher GWAS heritability than the other smoking phenotypes (p<0.0005, for all two-way comparisons).

Next, we looked at the genetic correlation between the smoking phenotypes and schizophrenia. The genetic correlation, defined here as the proportion of common genetic variation that is shared by two phenotypes, was evaluated between the smoking phenotypes and schizophrenia. Significant genetic correlation was observed between schizophrenia and three of the five smoking phenotypes (p<0.05): ever/never smoker (rg 0.10), cigarettes per day (rg 0.12), and nicotine dependence (rg 0.14). The values for ever/never smoker and age of onset are slightly different from those published previously because the previous results used earlier schizophrenia GWAS results (Bulik-Sullivan et al., 2015a).

**Discussion**

The results of this study show that (1) common genetic variation explains more phenotypic variance for nicotine dependence relative to other smoking phenotypes (i.e. higher GWAS heritability), and (2) there is a component of common genetic variation that is shared between smoking behaviors and schizophrenia (i.e. nonzero GWAS correlation).

Our findings of higher GWAS heritability for nicotine dependence (as measured by FTND) relative to other smoking phenotypes is consistent with observations of differential GWAS associations for different smoking phenotypes (Chen et al., 2012a; Hancock et al., 2015; Rice et al., 2012). Specifically, variants in the *CHRNA6/CHRNB3* region are more strongly associated with FTND-based nicotine dependence than CPD (Rice et al., 2012). In contrast, FTND-based nicotine dependence and CPD were equally associated with genetic variants in the *CHRNA5/CHRNA3/CHRNB4* region (Chen et al., 2012a). This highlights the complexity of the relationship between smoking behavior and genetics.

The observed GWAS correlation between smoking behaviors and schizophrenia suggests that shared genetic variation contributes to the comorbidity between schizophrenia and smoking behaviors. There are three models of comorbidity that could explain this: (1) a direct model, where the same genetic variation contributes directly to both schizophrenia and smoking behaviors, (2) the smoking medication model, where smoking is inferred to cause schizophrenia, and (3) the schizophrenia mediation model, where schizophrenia is inferred to cause smoking, also often described as the self-medication hypothesis (Kumari and Postma, 2005). It is unlikely that either mediation model explains the majority of shared genetic variation because a significant proportion of individuals with schizophrenia do not smoke (Hartz et al., 2014), limiting the power of the smoking mediation model, and schizophrenia is rare (~1%) in the populations from which most individuals in the smoking studies were sampled (Chen et al., 2012b), limiting the power of the schizophrenia mediation model. It is likely that the observed shared genetic variation is due to a combination of all three models.

LD score regression has identified multiple diseases that have shared genetic factors with schizophrenia (Bulik-Sullivan et al., 2015a). Of these, bipolar disorder (*rg*=0.79) and depression (*rg*=0.51) have the highest genetic correlations. The next tier of genetic correlations include other psychiatric disorders (Attention Deficit Hyperactivity Disorder *rg*=0.23, Anorexia *rg*=0.19, Autism Spectrum Disorders *rg*=0.14) and autoimmune disorders (Crohn's Disease *rg*=0.13, Ulcerative Colitis *rg*=0.13). Our observed genetic correlations between schizophrenia and smoking behaviors fit into this second tier (ranging from 0.14 for nicotine dependence to 0.10 for ever/never smoking). This suggests that smoking behaviors should be included when leveraging other phenotypes to investigate the genetic etiology of schizophrenia.

An inherent limitation of genetic correlation estimates using LD score regression is that they capture only shared *common* genetic variation between two phenotypes. This is due to the fact that these estimates are based on GWAS data, filtered to include only SNPs with minor allele frequency greater than 0.01. In addition, the effects of the SNPs must all be in the same direction; SNPs that contribute to both phenotypes, but have opposite effect sizes will reduce the genetic correlation estimates. These limitations, however, do not bias the methodology, but instead reduce the power of the methodology. Therefore the observed associations are likely sound.

A potential confounder of these analyses is smoking behavior itself: because individuals with schizophrenia are more likely to smoke than controls (Hartz et al., 2014), some of the GWAS associations for schizophrenia may, in fact, be associations with smoking behavior. Because (1) there is a significant proportion of individuals with schizophrenia who do not smoke, and (2) we are looking at composite GWAS results rather than individual SNPs, it is unlikely that this confounder biases the findings.

This study adds to the growing body of literature suggesting that genetic factors contribute to the comorbidity between smoking and schizophrenia (Chen et al., 2016; Gage and Munafo, 2015), highlighting the importance of further research in order to better understand the complex relationship between these two disorders.

**Acknowledgements:**

We thank the many participants of these studies. This work was supported by the National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA) grant number R01 DA035825 and R01DA036583.

The COPDGene® project was supported by award numbers R01 HL089897 and R01 HL089856 from the NHLBI. Research reported in this publication was also supported by the NHLBI award number K01 HL125858. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The COPDGene® project is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer Ingelheim, Novartis, Pfizer, Siemens, Sunovion, and GlaxoSmithKline. The authors acknowledge investigators of the COPDGene® project core units: Administrative (James Crapo [Principal Investigator] and Edwin Silverman [Principal Investigator]), Barry Make, and Elizabeth Regan); Genetic Analysis (Terri Beaty, Nan Laird, Christoph Lange, Michael Cho, Stephanie Santorico, Dawn DeMeo, Nadia Hansel, Craig Hersh, Peter Castaldi, Merry-Lynn McDonald, Emily Wan, Megan Hardin, Jacqueline Hetmanski, Margaret Parker, Marilyn Foreman, Brian Hobbs, Robert Busch, Adel El-Bouiez, Megan Hardin, Dandi Qiao, Elizabeth Regan, Eitan Halper-Stromberg, Ferdouse Begum, Sungho Won); Imaging (David Lynch, Harvey Coxson, MeiLan Han, Eric Hoffman, Stephen Humphries Francine Jacobson, Philip Judy, Ella Kazerooni, John Newell, Jr., Elizabeth Regan, James Ross, Raul San Jose Estepar, Berend Stoel, Juerg Tschirren, Eva van Rikxoort, Bram van Ginneken, George Washko, Carla Wilson, Mustafa Al Qaisi, Teresa Gray, Alex Kluiber, Tanya Mann, Jered Sieren, Douglas Stinson, Joyce Schroeder, Edwin Van Beek); Pulmonary Function Testing Quality Assurance (Robert Jensen); Data Coordinating Center and Biostatistics (Douglas Everett, Anna Faino, Matt Strand, Carla Wilson); and Epidemiology (Jennifer Black-Shinn, Gregory Kinney, Katherine Pratte). The authors also acknowledge the clinical center investigators: Jeffrey Curtis, Carlos Martinez, Perry G. Pernicano, Nicola Hanania, Philip Alapat, Venkata Bandi, Mustafa Atik, Aladin Boriek, Kalpatha Guntupalli, Elizabeth Guy, Amit Parulekar, Arun Nachiappan, Dawn DeMeo, Craig Hersh, George Washko, Francine Jacobson, R. Graham Barr, Byron Thomashow, John Austin, Belinda D’Souza, Gregory D.N. Pearson, Anna Rozenshtein, Neil MacIntyre, Jr., Lacey Washington, H. Page McAdams, Charlene McEvoy, Joseph Tashjian, Robert Wise, Nadia Hansel, Robert Brown, Karen Horton, Nirupama Putcha, Richard Casaburi, Alessandra Adami, Janos Porszasz, Hans Fischer, Matthew Budoff, Dan Cannon, Harry Rossiter, Amir Sharafkhaneh, Charlie Lan, Christine Wendt, Brian Bell, Marilyn Foreman, Gloria Westney, Eugene Berkowitz, Russell Bowler, David Lynch, Richard Rosiello, David Pace, Gerard Criner, David Ciccolella, Francis Cordova, Chandra Dass, Robert D’Alonzo, Parag Desai, Michael Jacobs, Steven Kelsen, Victor Kim, A. James Mamary, Nathaniel Marchetti, Aditti Satti, Kartik Shenoy, Robert M. Steiner, Alex Swift, Irene Swift, Gloria Vega-Sanchez, Mark Dransfield, William Bailey, J. Michael Wells, Surya Bhatt, Hrudaya Nath, Joe Ramsdell, Paul Friedman, Xavier Soler, Andrew Yen, Alejandro Cornellas, John Newell, Jr., Brad Thompson, MeiLan Han, Ella Kazerooni, Fernando Martinez, Joanne Billings, Tadashi Allen, Frank Sciurba, Divay Chandra, Joel Weissfeld, Carl Fuhrman, Jessica Bon, Antonio Anzueto, Sandra Adams, Diego Maselli-Caceres, and Mario Ruiz.

Funding support for the Environment and Genetics in Lung Cancer Etiology (EAGLE) study was provided through the NIH GEI (Z01 CP 010200). The human participants participating in this study and its companion “Prostate, Lung Colon and Ovary Screening Trial” are supported by intramural resources of the NCI. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the GENEVA Coordinating Center (U01 HG004446). Assistance with data cleaning was provided by the National Center for Biotechnology Information. Funding support for genotyping, which was performed at The Johns Hopkins University’s Center for Inherited Disease Research (CIDR), was provided by the NIH GEI (U01 HG004438). The datasets used for the analyses described in this manuscript were obtained from the database of Genotypes and Phenotypes (dbGaP, http://www.ncbi.nlm.nih.gov/gap) through accession number phs000093.vs.p2.

**Table 1:** GWAS meta-analysis results used for computation of LD score regression

|  |  |  |  |
| --- | --- | --- | --- |
|  | N | Coding | Reference |
| Ever/Never smoked | 74,035 | Dichotomous | (Tobacco and Genetics Consortium, 2010) |
| Age of onset of smoking | 28,647 | Continuous, log transform | (Tobacco and Genetics Consortium, 2010) |
| Cigarettes per day (CPD) | 38,860 | Continuous | (Tobacco and Genetics Consortium, 2010) |
| Nicotine Dependence | 10,666 | 3 level: mild, moderate, severe | (Hancock et al., 2015) |
| Current/Former smoker | 40,562 | Dichotomous | (Tobacco and Genetics Consortium, 2010) |
| Schizophrenia | 74,626 | Dichotomous | (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) |

**Table 2:** GWAS heritability of smoking phenotypes and genetic correlation estimates with schizophrenia

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Univariate GWAS Heritability (*h2g*) | | Genetic Correlation with Schizophrenia (*rg*) | |
|  | Estimate  (95% CI) | P | Estimate | P |
| Ever/Never Smoked | 0.08  (0.06-0.09) | 1E-27 | 0.10 | 0.009 |
| Age of onset of smoking | 0.06  (0.03-0.09) | 0.0004 | 0.14 | 0.08 |
| Cigarettes Per Day | 0.06  (0.03-0.09) | 0.0002 | 0.12 | 0.05 |
| Nicotine Dependence | 0.15  (0.07-0.24) | 0.0008 | 0.14 | 0.04 |
| Current/former Smoker | 0.07  (0.05-0.09) | 9E-10 | -0.03 | 0.68 |

References

Baker, T.B., Piper, M.E., McCarthy, D.E., Bolt, D.M., Smith, S.S., Kim, S.Y., Colby, S., Conti, D., Giovino, G.A., Hatsukami, D., Hyland, A., Krishnan-Sarin, S., Niaura, R., Perkins, K.A., Toll, B.A., 2007. Time to first cigarette in the morning as an index of ability to quit smoking: implications for nicotine dependence. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 9 Suppl 4, S555-570.

Bierut, L.J., Madden, P.A., Breslau, N., Johnson, E.O., Hatsukami, D., Pomerleau, O.F., Swan, G.E., Rutter, J., Bertelsen, S., Fox, L., Fugman, D., Goate, A.M., Hinrichs, A.L., Konvicka, K., Martin, N.G., Montgomery, G.W., Saccone, N.L., Saccone, S.F., Wang, J.C., Chase, G.A., Rice, J.P., Ballinger, D.G., 2007. Novel genes identified in a high-density genome wide association study for nicotine dependence. Hum Mol Genet 16(1), 24-35.

Brady, K.T., Killeen, T., Jarrell, P., 1993. Depression in alcoholic schizophrenic patients. Am J Psychiatry 150(8), 1255-1256.

Bulik-Sullivan, B., Finucane, H.K., Anttila, V., Gusev, A., Day, F.R., Loh, P.R., Duncan, L., Perry, J.R., Patterson, N., Robinson, E.B., Daly, M.J., Price, A.L., Neale, B.M., 2015a. An atlas of genetic correlations across human diseases and traits. Nat Genet 47(11), 1236-1241.

Bulik-Sullivan, B.K., Loh, P.R., Finucane, H.K., Ripke, S., Yang, J., Schizophrenia Working Group of the Psychiatric Genomics, C., Patterson, N., Daly, M.J., Price, A.L., Neale, B.M., 2015b. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet 47(3), 291-295.

Chen, J., Bacanu, S.A., Yu, H., Zhao, Z., Jia, P., Kendler, K.S., Kranzler, H.R., Gelernter, J., Farrer, L., Minica, C., Pool, R., Milaneschi, Y., Boomsma, D.I., Penninx, B.W., Tyndale, R.F., Ware, J.J., Vink, J.M., Kaprio, J., Munafo, M., Chen, X., 2016. Genetic Relationship between Schizophrenia and Nicotine Dependence. Scientific reports 6, 25671.

Chen, L.S., Baker, T.B., Grucza, R., Wang, J.C., Johnson, E.O., Breslau, N., Hatsukami, D., Smith, S.S., Saccone, N., Saccone, S., Rice, J.P., Goate, A.M., Bierut, L.J., 2012a. Dissection of the phenotypic and genotypic associations with nicotinic dependence. Nicotine Tob Res 14(4), 425-433.

Chen, L.S., Xian, H., Grucza, R.A., Saccone, N.L., Wang, J.C., Johnson, E.O., Breslau, N., Hatsukami, D., Bierut, L.J., 2012b. Nicotine dependence and comorbid psychiatric disorders: examination of specific genetic variants in the CHRNA5-A3-B4 nicotinic receptor genes. Drug and alcohol dependence 123 Suppl 1, S42-51.

Colton, C.W., Manderscheid, R.W., 2006. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Preventing chronic disease 3(2), A42.

Crump, C., Winkleby, M.A., Sundquist, K., Sundquist, J., 2013. Comorbidities and Mortality in Persons With Schizophrenia: A Swedish National Cohort Study. Am J Psychiatry.

Drake, R.E., Wallach, M.A., 1989. Substance abuse among the chronic mentally ill. Hosp Community Psychiatry 40(10), 1041-1046.

Gage, S.H., Hickman, M., Heron, J., Munafo, M.R., Lewis, G., Macleod, J., Zammit, S., 2014. Associations of cannabis and cigarette use with psychotic experiences at age 18: findings from the Avon Longitudinal Study of Parents and Children. Psychol Med 44(16), 3435-3444.

Gage, S.H., Munafo, M.R., 2015. Smoking as a causal risk factor for schizophrenia. The lancet. Psychiatry 2(9), 778-779.

Hancock, D.B., Reginsson, G.W., Gaddis, N.C., Chen, X., Saccone, N.L., Lutz, S.M., Qaiser, B., Sherva, R., Steinberg, S., Zink, F., Stacey, S.N., Glasheen, C., Chen, J., Gu, F., Frederiksen, B.N., Loukola, A., Gudbjartsson, D.F., Bruske, I., Landi, M.T., Bickeboller, H., Madden, P., Farrer, L., Kaprio, J., Kranzler, H.R., Gelernter, J., Baker, T.B., Kraft, P., Amos, C.I., Caporaso, N.E., Hokanson, J.E., Bierut, L.J., Thorgeirsson, T.E., Johnson, E.O., Stefansson, K., 2015. Genome-wide meta-analysis reveals common splice site acceptor variant in CHRNA4 associated with nicotine dependence. Translational psychiatry 5, e651.

Hartz, S.M., Pato, C.N., Medeiros, H., Cavazos-Rehg, P., Sobell, J.L., Knowles, J.A., Bierut, L.J., Pato, M.T., Consortium, G.P.C., 2014. Comorbidity of Severe Psychotic Disorders With Measures of Substance Use. Jama Psychiatry 71(3), 248-254.

Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Fagerstrom, K.O., 1991. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 86(9), 1119-1127.

Kumari, V., Postma, P., 2005. Nicotine use in schizophrenia: the self medication hypotheses. Neurosci Biobehav Rev 29(6), 1021-1034.

Landi, M.T., Chatterjee, N., Yu, K., Goldin, L.R., Goldstein, A.M., Rotunno, M., Mirabello, L., Jacobs, K., Wheeler, W., Yeager, M., Bergen, A.W., Li, Q., Consonni, D., Pesatori, A.C., Wacholder, S., Thun, M., Diver, R., Oken, M., Virtamo, J., Albanes, D., Wang, Z., Burdette, L., Doheny, K.F., Pugh, E.W., Laurie, C., Brennan, P., Hung, R., Gaborieau, V., McKay, J.D., Lathrop, M., McLaughlin, J., Wang, Y., Tsao, M.-S., Spitz, M.R., Wang, Y., Krokan, H., Vatten, L., Skorpen, F., Arnesen, E., Benhamou, S., Bouchard, C., Metsapalu, A., Vooder, T., Nelis, M., Välk, K., Field, J.K., Chen, C., Goodman, G., Sulem, P., Thorleifsson, G., Rafnar, T., Eisen, T., Sauter, W., Rosenberger, A., Bickeböller, H., Risch, A., Chang-Claude, J., Wichmann, H.E., Stefansson, K., Houlston, R., Amos, C.I., Fraumeni Jr, J.F., Savage, S.A., Bertazzi, P.A., Tucker, M.A., Chanock, S., Caporaso, N.E., 2009. A Genome-wide Association Study of Lung Cancer Identifies a Region of Chromosome 5p15 Associated with Risk for Adenocarcinoma. The American Journal of Human Genetics 85(5), 679-691.

Landi, M.T., Consonni, D., Rotunno, M., Bergen, A.W., Goldstein, A.M., Lubin, J.H., Goldin, L., Alavanja, M., Morgan, G., Subar, A.F., Linnoila, I., Previdi, F., Corno, M., Rubagotti, M., Marinelli, B., Albetti, B., Colombi, A., Tucker, M., Wacholder, S., Pesatori, A.C., Caporaso, N.E., Bertazzi, P.A., 2008. Environment And Genetics in Lung cancer Etiology (EAGLE) study: an integrative population-based case-control study of lung cancer. BMC public health 8, 203.

Lee, P.H., Baker, J.T., Holmes, A.J., Jahanshad, N., Ge, T., Jung, J.Y., Cruz, Y., Manoach, D.S., Hibar, D.P., Faskowitz, J., McMahon, K.L., de Zubicaray, G.I., Martin, N.H., Wright, M.J., Ongur, D., Buckner, R., Roffman, J., Thompson, P.M., Smoller, J.W., 2016. Partitioning heritability analysis reveals a shared genetic basis of brain anatomy and schizophrenia. Molecular psychiatry 21(12), 1680-1689.

Manolio, T.A., Rodriguez, L.L., Brooks, L., Abecasis, G., Ballinger, D., Daly, M., Donnelly, P., Faraone, S.V., Frazer, K., Gabriel, S., Gejman, P., Guttmacher, A., Harris, E.L., Insel, T., Kelsoe, J.R., Lander, E., McCowin, N., Mailman, M.D., Nabel, E., Ostell, J., Pugh, E., Sherry, S., Sullivan, P.F., Thompson, J.F., Warram, J., Wholley, D., Milos, P.M., Collins, F.S., 2007. New models of collaboration in genome-wide association studies: the Genetic Association Information Network. Nat Genet 39(9), 1045-1051.

Moskvina, V., Craddock, N., Holmans, P., Nikolov, I., Pahwa, J.S., Green, E., Wellcome Trust Case Control, C., Owen, M.J., O'Donovan, M.C., 2009. Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk. Molecular psychiatry 14(3), 252-260.

Myles, N., Newall, H.D., Curtis, J., Nielssen, O., Shiers, D., Large, M., 2012. Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. The Journal of clinical psychiatry 73(4), 468-475.

Olfson, M., Gerhard, T., Huang, C., Crystal, S., Stroup, T.S., 2015. Premature Mortality Among Adults With Schizophrenia in the United States. JAMA Psychiatry 72(12), 1172-1181.

Parks, J., Svendsen, D., Singer, P., Foti, M.E., 2006. Morbidity and Mortality in People with Serious Mental Illness. National Association of State Mental Health Program Directors (NASMHPD) Medical Directors Council.

Regan, E.A., Hokanson, J.E., Murphy, J.R., Make, B., Lynch, D.A., Beaty, T.H., Curran-Everett, D., Silverman, E.K., Crapo, J.D., 2010. Genetic epidemiology of COPD (COPDGene) study design. COPD 7(1), 32-43.

Rice, J.P., Hartz, S.M., Agrawal, A., Almasy, L., Bennett, S., Breslau, N., Bucholz, K.K., Doheny, K.F., Edenberg, H.J., Goate, A.M., Hesselbrock, V., Howells, W.B., Johnson, E.O., Kramer, J., Krueger, R.F., Kuperman, S., Laurie, C., Manolio, T.A., Neuman, R.J., Nurnberger, J.I., Porjesz, B., Pugh, E., Ramos, E.M., Saccone, N., Saccone, S., Schuckit, M., Bierut, L.J., Consortium, G., 2012. CHRNB3 is more strongly associated with Fagerstrom test for cigarette dependence-based nicotine dependence than cigarettes per day: phenotype definition changes genome-wide association studies results. Addiction 107(11), 2019-2028.

Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J.L., Kahler, A.K., Akterin, S., Bergen, S.E., Collins, A.L., Crowley, J.J., Fromer, M., Kim, Y., Lee, S.H., Magnusson, P.K., Sanchez, N., Stahl, E.A., Williams, S., Wray, N.R., Xia, K., Bettella, F., Borglum, A.D., Bulik-Sullivan, B.K., Cormican, P., Craddock, N., de Leeuw, C., Durmishi, N., Gill, M., Golimbet, V., Hamshere, M.L., Holmans, P., Hougaard, D.M., Kendler, K.S., Lin, K., Morris, D.W., Mors, O., Mortensen, P.B., Neale, B.M., O'Neill, F.A., Owen, M.J., Milovancevic, M.P., Posthuma, D., Powell, J., Richards, A.L., Riley, B.P., Ruderfer, D., Rujescu, D., Sigurdsson, E., Silagadze, T., Smit, A.B., Stefansson, H., Steinberg, S., Suvisaari, J., Tosato, S., Verhage, M., Walters, J.T., Multicenter Genetic Studies of Schizophrenia, C., Levinson, D.F., Gejman, P.V., Kendler, K.S., Laurent, C., Mowry, B.J., O'Donovan, M.C., Owen, M.J., Pulver, A.E., Riley, B.P., Schwab, S.G., Wildenauer, D.B., Dudbridge, F., Holmans, P., Shi, J., Albus, M., Alexander, M., Campion, D., Cohen, D., Dikeos, D., Duan, J., Eichhammer, P., Godard, S., Hansen, M., Lerer, F.B., Liang, K.Y., Maier, W., Mallet, J., Nertney, D.A., Nestadt, G., Norton, N., O'Neill, F.A., Papadimitriou, G.N., Ribble, R., Sanders, A.R., Silverman, J.M., Walsh, D., Williams, N.M., Wormley, B., Psychosis Endophenotypes International, C., Arranz, M.J., Bakker, S., Bender, S., Bramon, E., Collier, D., Crespo-Facorro, B., Hall, J., Iyegbe, C., Jablensky, A., Kahn, R.S., Kalaydjieva, L., Lawrie, S., Lewis, C.M., Lin, K., Linszen, D.H., Mata, I., McIntosh, A., Murray, R.M., Ophoff, R.A., Powell, J., Rujescu, D., Van Os, J., Walshe, M., Weisbrod, M., Wiersma, D., Wellcome Trust Case Control, C., Donnelly, P., Barroso, I., Blackwell, J.M., Bramon, E., Brown, M.A., Casas, J.P., Corvin, A.P., Deloukas, P., Duncanson, A., Jankowski, J., Markus, H.S., Mathew, C.G., Palmer, C.N., Plomin, R., Rautanen, A., Sawcer, S.J., Trembath, R.C., Viswanathan, A.C., Wood, N.W., Spencer, C.C., Band, G., Bellenguez, C., Freeman, C., Hellenthal, G., Giannoulatou, E., Pirinen, M., Pearson, R.D., Strange, A., Su, Z., Vukcevic, D., Donnelly, P., Langford, C., Hunt, S.E., Edkins, S., Gwilliam, R., Blackburn, H., Bumpstead, S.J., Dronov, S., Gillman, M., Gray, E., Hammond, N., Jayakumar, A., McCann, O.T., Liddle, J., Potter, S.C., Ravindrarajah, R., Ricketts, M., Tashakkori-Ghanbaria, A., Waller, M.J., Weston, P., Widaa, S., Whittaker, P., Barroso, I., Deloukas, P., Mathew, C.G., Blackwell, J.M., Brown, M.A., Corvin, A.P., McCarthy, M.I., Spencer, C.C., Bramon, E., Corvin, A.P., O'Donovan, M.C., Stefansson, K., Scolnick, E., Purcell, S., McCarroll, S.A., Sklar, P., Hultman, C.M., Sullivan, P.F., 2013. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet 45(10), 1150-1159.

Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511(7510), 421-427.

Shaffer, J.R., Wang, X., Feingold, E., Lee, M., Begum, F., Weeks, D.E., Cuenco, K.T., Barmada, M.M., Wendell, S.K., Crosslin, D.R., Laurie, C.C., Doheny, K.F., Pugh, E.W., Zhang, Q., Feenstra, B., Geller, F., Boyd, H.A., Zhang, H., Melbye, M., Murray, J.C., Weyant, R.J., Crout, R., McNeil, D.W., Levy, S.M., Slayton, R.L., Willing, M.C., Broffitt, B., Vieira, A.R., Marazita, M.L., 2011. Genome-wide association scan for childhood caries implicates novel genes. Journal of dental research 90(12), 1457-1462.

Sorensen, H.J., Mortensen, E.L., Reinisch, J.M., Mednick, S.A., 2011. A prospective study of smoking in young women and risk of later psychiatric hospitalization. Nordic journal of psychiatry 65(1), 3-8.

TAG, 2010. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nat Genet 42(5), 441-447.

Tobacco and Genetics Consortium, 2010. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nat Genet 42(5), 441-447.

Tsoi, D.T., Porwal, M., Webster, A.C., 2013. Interventions for smoking cessation and reduction in individuals with schizophrenia. The Cochrane database of systematic reviews(2), Cd007253.

Yang, J., Weedon, M.N., Purcell, S., Lettre, G., Estrada, K., Willer, C.J., Smith, A.V., Ingelsson, E., O'Connell, J.R., Mangino, M., Magi, R., Madden, P.A., Heath, A.C., Nyholt, D.R., Martin, N.G., Montgomery, G.W., Frayling, T.M., Hirschhorn, J.N., McCarthy, M.I., Goddard, M.E., Visscher, P.M., 2011. Genomic inflation factors under polygenic inheritance. European journal of human genetics : EJHG 19(7), 807-812.

Zammit, S., Allebeck, P., Dalman, C., Lundberg, I., Hemmingsson, T., Lewis, G., 2003. Investigating the association between cigarette smoking and schizophrenia in a cohort study. Am J Psychiatry 160(12), 2216-2221.