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Running Head: Genetic analyses of smoking behaviors among schizophrenia cases

Genome-wide analyses of smoking behaviors in schizophrenia: findings from the Psychiatric Genomics Consortium

Roseann E Peterson, PhD[1,‡]; Tim B Bigdeli, PhD[1,2,‡]; Stephan Ripke, MD, PhD[3,4]; Silviu-Alin Bacanu, PhD[1]; Pablo V Gejman, MD[5,6]; Douglas F Levinson, MD[7]; Qingqin S Li, PhD[8]; Dan Rujescu, MD, PhD[10,9]; Marcella Rietschel, MD, PhD[11]; Daniel R Weinberger, MD[12,13]; Richard E Straub, PhD[12]; James TR Walters, MD, PhD[14]; Michael J Owen, MBChB, PhD[14]; Michael C O'Donovan, MBChB, PhD[14]; Bryan J Mowry, MD, FRANZCP [15,16]; Roel A Ophoff, PhD[17,18,19]; Ole A Andreassen, MD, PhD[20,21]; Tõnu Esko, PhD[22,23,24,25]; Tracey L Petryshen, PhD[26,27,28]; Kenneth S Kendler, MD[1]; Schizophrenia Working Group of the Psychiatric Genomics Consortium[a]; Ayman H Fanous, MD[1,2,29*]

[1]Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, VA, USA
[2]Department of Psychiatry and Behavioral Sciences, State University of New York Downstate Medical Center, Brooklyn, NY, USA
[3]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA
[4]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA
[5]Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, IL, USA
[6]Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA
[7]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA
[8]Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Raritan, NJ, USA
[9]Department of Psychiatry, University of Halle, Halle, Germany
[10]Department of Psychiatry, University of Munich, Munich, Germany
[11]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany
[12]Lieber Institute for Brain Development, Baltimore, MD, USA
[13]Departments of Psychiatry, Neurology, Neuroscience and Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, MD
[14]MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK
[15]Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
[16]Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, Australia
[17]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, USA
[18]Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, CA, USA
[19]Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands
[20]NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[21]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[22]Estonian Genome Center, University of Tartu, Tartu, Estonia
[23]Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA, USA
[24]Department of Genetics, Harvard Medical School, Boston, MA, USA
[25]Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, MA, USA
[26]Center for Human Genetic Research and Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
[27]Department of Psychiatry, Harvard Medical School, Boston, MA, USA
[28]The Broad Institute of MIT and Harvard, Boston MA
[29]VA New York Harbor Healthcare System, Brooklyn NY, USA

*Corresponding author
Department of Psychiatry and Behavioral Sciences
SUNY Downstate Medical Center
450 Clarkson Ave
Brooklyn, NY 11203

‡These authors contributed equally to this work
[a]Full list of consortium members appears in the supplement.

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Abstract

While 17% of US adults use tobacco regularly, smoking rates among persons with schizophrenia are upwards of 60%. Research supports a shared etiological basis for smoking and schizophrenia, including findings from genome-wide association studies (GWAS). However, few studies have directly tested whether the same or distinct genetic variants also influence smoking behavior among schizophrenia cases. Using data from the Psychiatric Genomics Consortium (PGC) study of schizophrenia (35476 cases, 46839 controls), we estimated genetic correlations between these traits and tested whether polygenic risk scores (PRS) constructed from the results of smoking behaviors GWAS were associated with schizophrenia risk or smoking behaviors among schizophrenia cases. Results indicated significant genetic correlations of schizophrenia with smoking initiation (r_g=0.159; P=5.05×10^{-10}), cigarettes-smoked-per-day (r_g=0.094; P=0.006), and age-of-onset of smoking (r_g=0.10; P=0.009). Comparing smoking behaviors among schizophrenia cases to the general population, we observe positive genetic correlations for smoking initiation (r_g=0.624, P=0.002) and cigarettes-smoked-per-day (r_g=0.689, P=0.120). Similarly, TAG-based PRS for smoking initiation and cigarettes-smoked-per-day were significantly associated with smoking initiation (P=3.49×10^{-5}) and cigarettes-smoked-per-day (P=0.007) among schizophrenia cases. We performed the first GWAS of smoking behavior among schizophrenia cases and identified a novel association with cigarettes-smoked-per-day upstream of the *TMEM106B* gene on chromosome 7p21.3 (rs148253479, P=3.18×10^{-8}, n=3520). Results provide evidence of a partially shared genetic basis for schizophrenia and smoking behaviors. Additionally, genetic risk factors for smoking behaviors were largely shared across schizophrenia and non-schizophrenia populations. Future research should address mechanisms underlying these associations to aid both schizophrenia and smoking treatment and prevention efforts.

Key Words: schizophrenia, genetics, GWAS, smoking initiation, cigarettes per day, pleiotropy.

Introduction

Schizophrenia is a chronic mental illness affecting nearly 1% of the world's population and is associated with considerable morbidity and mortality(McGrath et al., 2008; Simeone et al., 2015). Affected persons are at markedly increased risk for substance use disorders, particularly nicotine dependence(Hartz et al., 2014; Volkow, 2009). Currently, 17% of US adults and upwards of 60% of schizophrenia spectrum cases smoke tobacco regularly(de Leon and Diaz, 2005; Jamal et al., 2015; Volkow, 2009). Furthermore, patients tend to smoke a greater number of cigarettes, extract more nicotine per cigarette, and experience greater withdrawal symptoms than smokers in the general population(Centers for Disease Control and Prevention (CDC), 2013; Strand and Nybäck, 2005; Tidey et al., 2014), thereby increasing their risk of nicotine dependence and associated adverse medical conditions including cardiovascular disease and cancers(Olfson et al., 2015).

Decades of twin and family studies have demonstrated that schizophrenia is highly heritable (~80%)(Sullivan et al., 2003). Common genetic variants captured by genome-wide single-nucleotide polymorphism (SNP) arrays account for at least one third of variance in risk(International Schizophrenia Consortium et al., 2009; Ripke et al., 2013). A landmark genome-wide association study (GWAS) meta-analysis of schizophrenia identified 108 robustly associated loci(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), one of which resides in a gene cluster encoding neuronal nicotinic acetylcholine receptors (nAChR) on chromosome 15q25, which has previously been shown to be associated with heaviness of smoking in the general population(Tobacco and Genetics Consortium, 2010).

Similarly, twin and family studies have consistently shown a significant genetic component to the liability of smoking behavior, with estimated heritabilities on the order of 0.50-

0.70 for smoking initiation and 0.60 for nicotine dependence among European ancestry populations(Maes et al., 2004; Vink et al., 2005). Large, population-based GWAS of smoking-related traits have yielded several putative risk variants, including an association between smoking initiation and *BDNF* on 11p14.1(Tobacco and Genetics Consortium, 2010) and several associations for smoking quantity, most notably the previously reported 15q25 locus harboring three genes encoding nAChR subunits *CHRNA5-CHRNA3-CHRNA4,* a second locus encoding nAChRs on 8p11 in and near *CHRNB3-CHRNA6*, and variants in and near *CYP2A6-CYP2B6* on 19q13 encoding nicotine metabolizing enzymes(Thorgeirsson et al., 2010; Tobacco and Genetics Consortium, 2010).

Mechanisms underlying the schizophrenia-smoking association are not completely understood. Several mechanisms have been proposed to explain elevated tobacco use in those with schizophrenia including: 1) the self-medication hypothesis, 2) that smoking causes schizophrenia, and 3) a shared liability underlying both traits. The self-medication hypothesis posits that smoking is used as a strategy to alleviate adverse positive or negative symptoms of schizophrenia, cognitive impairments, or medication side-effects(Kumari and Postma, 2005). The shared vulnerability hypothesis postulates that factors common to both disorders (i.e. genetic, environmental) drive their co-occurrence. For example, dysfunction in nAChRs represents a common substrate for various symptoms of schizophrenia and comorbid nicotine use(Parikh et al., 2016; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Tobacco and Genetics Consortium, 2010). It has been suggested that reduced expression of the α7-nicotinic receptor in schizophrenia(Guillozet-Bongaarts et al., 2014; Severance and Yolken, 2008) results in reduced sensory gating inhibition as measured by paradigms such as P50 auditory-evoked potentials, prepulse inhibition, and mismatch negativity(Freedman, 2014).

Such deficits could conceivably diminish an individual's ability to keep extraneous stimuli from awareness, possibly giving rise to hallucinations and delusions(Howes and Kapur, 2009). Additional research supports mechanisms 2 and 3(Chen et al., 2016; Gurillo et al., 2015; Kendler et al., 2015). For example, in a population-based Swedish cohort it was found that smoking prospectively predicted risk for schizophrenia in a dose-response relationship and shared familial/genetic factors accounted for a portion of the comorbidity between smoking and schizophrenia(Kendler et al., 2015).

Recent findings support a molecular genetic component underlying schizophrenia-smoking associations(Chen et al., 2016; Hartz et al., 2018, 2017) but has not been demonstrated conclusively(Brainstorm Consortium et al., 2018; B. Bulik-Sullivan et al., 2015; Gage et al., 2017; Gage and Munafò, 2015; Zheng et al., 2017). Therefore, in this study, we sought to advance the understanding of schizophrenia-smoking associations in the context of available smoking data in schizophrenia cases from the Psychiatric Genomics Consortium (PGC) study of schizophrenia (see Table 1 for study overview)(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). First, we leverage summary statistics from genome-wide findings to estimate genetic correlations between smoking behaviors and schizophrenia. Next, using available phenotypic data on smoking initiation and smoking quantity for >5000 schizophrenia cases from 10 participating studies, we consider whether polygenic risk scores (PRS) constructed from results of the Tobacco and Genetics (TAG) consortium study of smoking behaviors(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Tobacco and Genetics Consortium, 2010) can predict these same behaviors among schizophrenia cases. We perform the largest GWAS of smoking behaviors among schizophrenia cases to date. Finally, we consider whether smoking patterns among schizophrenia cases and genetic risk

factors for smoking are related to the clinical presentation of schizophrenia including age-of-onset and symptom-based positive, negative, manic, and depressive factor scores.

Methods

Ascertainment and assessment

The subsamples included in this study comprise 10 constituent sites from Stage 2 of the PGC study of schizophrenia (Table 2). Ascertainment, diagnostic assessment, genotyping, and genotype quality control have been previously described(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Briefly, 52 samples from the US, Europe, and Australia comprising 34,241 cases, 45,604 controls, and 1,235 parent affected-offspring trios were genotyped using a number of commercial SNP genotyping platforms. These data were processed using the stringent PGC quality control procedures, followed by imputation of SNPs and insertion-deletions using the 1000 Genomes Project reference panel (UCSC hg19/NCBI 37)(1000 Genomes Project Consortium et al., 2012; Sachidanandam et al., 2010) using IMPUTE2(Howie et al., 2011, 2009), resulting in nearly 9.5*M* markers for GWAS analysis.

Smoking behavior and clinical phenotypes

Smoking behavior variables were harmonized across sites. Smoking initiation was coded as positive if any of the following were endorsed: ever smoked, ever regular smoker, smoked 100 cigarettes, current smoker, former smoker, smoke 1 or more cigarettes-per-day, or nicotine dependence. Since smoking quantity data varied by site, cigarettes-smoked-per-day was centered and scaled for each cohort. To account for initiation, only those who endorsed ever smoked were included in genetic analyses of cigarettes-smoked-per-day. A summary of individual sites, their

sample sizes, and smoking measures available are presented in Table 2 and Supplementary Figures S1 and S2.

We assessed whether age-of-onset of schizophrenia or symptom-based factor scores representing dimensions of illness were associated with smoking behaviors among cases. Age-of-onset was determined retrospectively and defined the age at first diagnosis or hospitalization. Symptoms averaged over the course of illness were assessed using the Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT), Positive and Negative Syndrome Scale (PANSS), Lifetime Dimensions of Psychosis Scale (LDPS), Schedules for Clinical Assessment in Neuropsychiatry (SCAN), Structured Clinical Interview for DSM (SCID), and Comprehensive Assessment of Symptoms and History (CASH). Factor analyses of constituent PGC studies identified positive, negative, manic, and depressive symptom dimensions and methodological details can be found in Ruderfer et al(Ruderfer et al., 2014). Association between smoking initiation or cigarettes-smoked-per-day and each clinical measure was assessed by logistic and linear regression, respectively, including sex, age-at-interview, and a study site indicator as covariates.

Estimation of SNP-based heritability and genetic correlation

We obtained estimates of SNP-based heritability (h^2) and genetic correlation (r_g) using the LD-score regression approach, as previously described(B. K. Bulik-Sullivan et al., 2015). Genome-wide summary statistics for schizophrenia and TAG smoking-related traits (ever-smoked, cigarettes-per-day, smoking cessation "former vs current", log-transformed age-of-onset of smoking, logOnset) were filtered using default parameters (INFO>0.9, MAF>1%). Reference LD-scores estimated for European populations in the 1000 Genomes Project were used;

regression weights were based on common SNPs present in Hapmap Phase 3, as suggested by the developers of this approach(B. K. Bulik-Sullivan et al., 2015). We reduced potential bias in heritability estimation by reanalyzing the PGC schizophrenia with overlapping TAG samples omitted, and constraining regression intercepts to one and zero when estimating univariate heritability and genetic correlation, respectively. For the schizophrenia case-only binary trait of smoking initiation, we assumed population prevalence estimates (K) equal to the observed sample prevalence (Supplemental Table S1).

Replication of the observed r_g between schizophrenia risk and TAG traits utilized meta-analysis summary statistics for three East-Asian studies from the PGC(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and the *popcorn* method for estimating cross-ancestry correlations(Brown et al., 2016). We compared estimates based on European and East-Asian schizophrenia samples by assuming an approximately normal distribution for r_g and obtaining a Z-score for the difference in values.

Polygenic scoring analyses

To test for polygenic effects on smoking behaviors or schizophrenia risk, we performed risk score profiling as previously described(Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). We constructed scores based on TAG results for smoking behaviors(Tobacco and Genetics Consortium, 2010). Given differences in the imputation reference panels between the TAG and PGC2 studies, we considered only overlapping SNPs with imputation INFO greater than 0.9 and minor allele frequency (MAF) greater than 1% in PGC2. Schizophrenia risk scores were generated for each study site in the PGC2 study of schizophrenia, using every other study as the training set in an iterative, "leave-one-out"

procedure. This approach ensured no overlap in training and testing samples, while offering improved power compared to subdividing the full cohort into approximate halves. For both PGC-schizophrenia and TAG-based analyses, we computed several scores based on varying *P*-value threshold signifying the proportion of SNPs with smaller *P*-values in the training set; *P*-value thresholds (*P*t) ranged between 0.0001 and 1.0. We tested for association between smoking behaviors and schizophrenia-PRS by linear regression, adjusting for sex, age, study-site and 10 associated ancestry principal components (PCs). Association between schizophrenia risk and TAG-based scores was assessed by logistic regression, adjusting for study-site and all covariates used in the primary PGC-schizophrenia association analysis. Because controls subjects from the Molecular Genetics of Schizophrenia (MGS) study were included in the TAG study, we excluded MGS from our case-control analyses of schizophrenia; in the context of genetic correlation estimation from summary statistics, this permitted us to constrain the intercept.

Genome-wide association and replication sample

For each trait, associated ancestry PCs were identified for the full cohort by backwards-stepwise regression ($P<0.159$), after adjusting for study site. We tested for association between SNPs and each trait by either linear or logistic regression, as implemented in PLINK v1.07 (http://pngu.mgh.harvard.edu/~purcell/plink/)(Purcell et al., 2007), using allelic dosages and adjusting for significant covariates including sex, age, and ancestry PCs. We performed GWAS of each trait separately for individual study sites, combining summary statistics in subsequent random-effects meta-analyses using METAL(Willer et al., 2010). We excluded all SNPs with MAF less than 0.01, average statistical imputation information (INFO) less than 0.6, absent from

more than half of total number of sub-studies, or displayed evidence of excessive heterogeneity (Cochran's test *P*-value < 0.05).

For replication efforts, a total of 1802 European-ancestry cases with complete phenotypic information from four independent "waves" were made available by Janssen Pharmaceuticals(Li et al., 2017; Metspalu et al., 2004). We identified independent (pairwise linkage disequilibrium $r^2 < 0.1$ within 500kb based on European 1000 Genomes Project samples), significant SNPs ($P < 10^{-5}$) from the random-effects meta-analyses of each smoking behavior phenotype considered. We tested these SNPs for association by linear or logistic regression, using ancestry PCs, sex, age, and study site indicator as covariates. Subsequent, joint meta-analyses of the combined discovery and replication samples were performed using METAL.

Results

I. Genetic correlations between schizophrenia and smoking behaviors

We first estimated the genetic correlation (r_g) between schizophrenia (35,476 cases, 46,839 controls) and each smoking-related trait from TAG (Table 3). The estimated genetic correlation between schizophrenia and smoking initiation in the general population was positive and highly significant (r_g=0.159, 95% CI:[0.108,0.210]; $P=5.05\times10^{-10}$); significant positive relationships between schizophrenia and both cigarettes-smoked-per-day (r_g=0.094, 95% CI:[0.027,0.161]; *P*=0.006) and age-of-onset of smoking (r_g=0.100, 95% CI:[0.026,0.174]; *P*=0.009) were also seen; a nominal association between schizophrenia and smoking cessation was found (r_g=-0.076, 95% CI:[-0.145,-0.007]; *P*= 0.032). We sought to replicate the observed genetic correlations using an independent cohort of East-Asian schizophrenia cases (*n*=1836) and controls (*n*=3383). No statistically significant cross-ancestry correlations were observed (Table 3) but confidence

intervals overlapped with the results from the European ancestry cohorts. Results for the East-Asian cohort should be considered tentative until replication can be performed.

II. Association of smoking behavior polygenic risk scores with schizophrenia risk

We evaluated the predictive ability of polygenic scores based on TAG results for smoking behaviors as applied to the PGC study of schizophrenia (35,476 cases, 46,839 controls, Figure 1). Genome-wide scores for smoking initiation ("ever/never smoked") were higher among cases ($P_T < 0.3$, β=0.014, 95%CI:[0.010, 0.017], P=4.94×10^{-15}), explaining 0.14% of the variance in schizophrenia risk. Scores based on independent SNPs significant at $P_T < 10^{-5}$ in TAG for cigarettes-smoked-per-day were also significantly higher among schizophrenia cases compared to controls (β=0.026, 95%CI:[0.014, 0.038], P=3.58×10^{-5}), explaining 0.04% of the variance in schizophrenia risk. Although, this effect was attenuated at more inclusive P-value thresholds. Genome-wide scores based on TAG results for age-of-initiation of smoking were not associated with schizophrenia status (P>0.056). Scores based on TAG results for smoking cessation ("former vs current") were significant, though only for $P_T < 10^{-4}$ and were in the expected negative direction of effect ($P_T < 10^{-5}$, β=-0.130, 95%CI:[-0.222, -0.038], P=0.006).

We further investigated significant polygenic score associations in order to determine if they were driven by the chromosome 15q25 locus that has been independently associated with both schizophrenia risk and smoking quantity in the general population. SNPs from the 15q25 locus were removed from TAG polygenic scores (up to 171 SNPs depending on P_T) and were re-tested for association. Results remained robust for TAG-smoking initiation polygenic scores predicting schizophrenia ($P_T < 0.3$, β=0.014, 95%CI:[0.010, 0.017], P=1.13×10^{-13}) but associations with schizophrenia were attenuated for TAG-cigarettes-smoked-per-day ($P_T < 10^{-}$

^{5},β=0.015, 95%CI:[-0.025, 0.054], *P*=0.469), and smoking cessation ($P_T < 10^{-5}$, β=-0.086, 95%CI:[-0.182, 0.011], *P*=0.081). These results suggest that the association seen between TAG-smoking initiation polygenic scores and schizophrenia were not due to confounding with the 15q25. However, associations of TAG-cigarettes-smoked-per-day and TAG-Cessation scores with schizophrenia were largely driven by this locus.

III. Smoking behavior among schizophrenia cases

The average smoking initiation rate across all cohorts was 72.9% and ranged from 52.6 to 77.3% (Table 2, Figure S1). Among schizophrenia cases that smoke 29.5% smoked more than a pack per day. Figure S2 displays prevalence of smoking quantity by cohort.

III.1 Heritability of smoking behavior among schizophrenia cases

We applied the LD-score regression method to directly estimate SNP-based heritability (SNP-h^2) from GWAS summary statistics for smoking behaviors among schizophrenia cases. For neither smoking initiation nor cigarettes-smoked-per-day did observed inflation of genome-wide test statistics indicate confounding by population stratification, as indicated by regression intercept values close to one (0.998 and 0.999). Among schizophrenia cases, the SNP-based heritability of smoking initiation was estimated as 0.219 (95% CI:[-0.001,0.439]; *P*=0.051; *n*=5255); the corresponding estimate for cigarettes-smoked-per-day was 0.0917 (95% CI:[-0.096,0.280]; *P*=0.340; *n*=3370). That neither estimate was robustly statistically significant likely reflects the modest sample size. Although the SNP-based heritability point estimates for smoking behavior among schizophrenia cases were larger than the general population, their confidence intervals were overlapping (general population: smoking initiation SNP-h^2=0.075 (95% CI:[0.063,0.088], cigarettes-smoked-per-day SNP-h^2=0.056 (95% CI:[0.030,0.083]).[33]

III.2 Genetic correlations between smoking behaviors among schizophrenia cases and the general population

We estimated the r_g to determine the magnitude of genetic overlap of smoking behaviors between schizophrenia cases ($n_{\text{smoking initiation}}$=5255, $n_{\text{cigarettes-smoked-per-day}}$=3370) and the general population (TAG). We observed a significant positive genetic correlation for smoking initiation (r_g=0.624, 95% CI: [0.228,1.020]; P=0.002). Though, a positive relationship for cigarettes-smoked-per-day was not statistically significant (r_g=0.689, 95% CI: [-0.179, 1.557]; P=0.120). Given the small sample size schizophrenia cases with data on smoking behaviors, these analyses are considered exploratory and require replication.

III.3 Association of smoking behavior polygenic risk scores with smoking behavior among schizophrenia cases

We considered whether TAG scores for smoking initiation and cigarettes-smoked-per-day could predict smoking behaviors among schizophrenia subjects (Figure 1). TAG-based scores for smoking initiation significantly predicted initiation among schizophrenia cases ($P_T < 0.01$, β=0.087, 95%CI:[0.049, 0.126], P=9.57×10^{-6}, n=5255) accounting for 0.6% of the variance and results remained robust when SNPs from the 15q25 locus were removed from scores ($P_T < 0.01$, β=0.083, 95%CI:[0.042, 0.125], P=8.12×10^{-5}, Nagelkerke's pseudo-R^2=0.0046). The scores based on TAG results for cigarettes-smoked-per-day also significantly predicted cigarettes-smoked-per-day among schizophrenia cases ($P_T < 0.01$, β=0.005, 95%CI:[0.002, 0.008], P=8.57×10^{-4}, n=3370) accounting for 0.35% of the variance and results remained robust when SNPs from the 15q25 locus were removed from scores ($P_T < 0.01$, β=0.006, 95%CI:[0.003,

0.009], P=4.42×10^{-4}, R^2=0.0039). For both smoking behaviors, the direction of the observed effect in schizophrenia was the same as that observed in the general population.

Next, we asked whether aggregate genetic risk of schizophrenia, as indexed by PGC2-based polygenic scores, was significantly associated with smoking behavior among schizophrenia cases (Figure S3). Neither smoking behaviors (smoking initiation, cigarettes-smoked-per-day) among schizophrenia-cases showed association with schizophrenia risk scores (P>0.1). Complete results for polygenic scoring analyses are reported in Tables S2-S7.

Finally, we estimated SNP-h^2 from GWAS summary statistics for schizophrenia stratified by smoking status. Among schizophrenia smokers (3832 schizophrenia-cases, 8518 controls), the heritability of schizophrenia was estimated as 0.237 (95% CI:[0.169,0.304]) and among schizophrenia non-smokers (1423 schizophrenia-cases, 8518 controls) was 0.133 (95% CI:[0.017,0.249]). The estimated genetic correlation between these groups (schizophrenia smokers and schizophrenia non-smokers) was 0.860 (95% CI: [0.497,1.224]) and was significantly different from 0 (P=3.52×10^{-6}) but not from 1. These results suggest that the genetic risk for schizophrenia is largely overlapping between smoking and non-smoking schizophrenia patients.

III.4 Genome-wide association of smoking behaviors among schizophrenia cases

Genomic inflation factors (λ) were 1.017 and 1.005 for smoking initiation (n=5255) and cigarettes-smoked-per-day (n=3370), respectively. The discovery GWAS did not yield SNP associations significant at established genome-wide criteria (5.0×10^{-8}). The strongest evidence of SNP-based association was observed for cigarettes-smoked-per-day, upstream of the *CBWD2* gene at chromosome 2q13 (rs1900325; P=1.01×10^{-7}). Subsequent follow-up of suggestively associated SNPs (P < 10^{-6}) in an independent European-ancestry cohort (n=1802) yielded a

significant finding between cigarettes-smoked-per-day and rs148253479 upstream of the *TMEM106B* gene at 7p21.3 (Table 4, discovery $P=1\times10^{-6}$, replication $P=0.011$, combined $P=3.18\times10^{-8}$). Regional association and forest plots for top associations are provided in the accompanying supplemental information (Figures S7-8). Notably, none of the previously identified smoking behavior-associated SNPs were detected at genome-wide significant thresholds in our GWAS of smoking behaviors within schizophrenia cases, likely due in part to the limited power to detect small SNP effects in our modest sample size (Table S12).

IV. Phenotypic and polygenic associations between smoking behavior and schizophrenia symptom dimensions

We considered whether smoking patterns among schizophrenia cases and genetic risk factors for smoking were related to the clinical presentation of schizophrenia. For sex, age, and each clinical variable considered, Table 5 gives the estimated effect and significance from logistic or linear regression. Age-of-onset of schizophrenia was found to have a nominal association with smoking initiation ($P=0.018$) indicating higher rates of initiation in cases with earlier onset. The positive symptom factor score showed a positive association with smoking initiation ($P=3.21\times10^{-5}$) and cigarettes-smoked-per-day ($P=0.015$). Depressive symptoms were also nominally associated with cigarettes-smoked-per-day ($P=0.014$) indicating that those with higher depression scores endorsed smoking more cigarettes. No significant phenotypic associations were found between smoking behaviors and the negative and mania factor scores.

We followed-up phenotypic associations by examining the relationship between symptom dimensions and TAG-based polygenic scores for smoking behaviors (Tables S8-S11, Figure S4). Both the TAG-smoking initiation and TAG-cigarettes-smoked-per-day scores were

associated with positive symptoms at nominal levels of significance (P=0.023, P=0.006 respectively).

Discussion

Despite conspicuous epidemiological and molecular genetic evidence supporting a link between smoking behavior and schizophrenia, the biological basis of this relationship is not well understood. Given the availability of subject-level clinical data from the PGC study of schizophrenia, we were able to characterize smoking patterns among >5000 schizophrenia cases. Using polygenic risk score methodology and genome-wide summary statistics, we not only provide confirmatory evidence of aggregate genetic effects contributing to both smoking initiation and risk of schizophrenia, but demonstrate also that risk factors influencing smoking initiation and quantity are at least partially shared between schizophrenia patients and the general population.

Of particular importance, we have successfully demonstrated shared genetic liabilities to schizophrenia and smoking behaviors in European populations. While polygenic scores based on TAG results for smoking initiation and cigarettes-smoked-per-day were both strongly associated with increased risk of schizophrenia, the association with cigarettes-smoked-per-day was largely driven by the 15q25 locus. Although the results support a polygenic overlap between smoking behavior in the general population and schizophrenia risk, we cannot definitively rule out the possibility that some identified schizophrenia genetic variants may be in fact indexing liability to smoking behavior (rather than having a pleiotropic effect on both traits) because of the high prevalence of nicotine use among affected persons. Future research is needed to disentangle this

confounded relationship by collecting smoking behavior information for both schizophrenia cases *and* control subjects.

Polygenic scores for smoking initiation also significantly predicted initiation among schizophrenia cases. Taken together with an estimated genetic correlation of ~0.624, this suggests that genetic factors influencing smoking behavior are at least partially shared between schizophrenia and non-schizophrenia populations. We could rule out the possibility that they are entirely independent, but better powered studies are needed to more precisely estimate the degree of overlap. Similarly, polygenic scores for smoking quantity were also significantly predictive of smoking quantity among schizophrenia patients, albeit to a lesser degree of statistical significance.

By contrast, polygenic scores based on PGC results for schizophrenia were not predictive of smoking behavior among schizophrenia patients. Our results suggest a shared genetic liability to smoking behavior and schizophrenia, and that genetic liability to smoking is shared between the general population and schizophrenia patients, while liability to schizophrenia is *not* associated with smoking behavior among schizophrenia-affected individuals. The latter could be partially due to power and the restricted range of the smoking liability distribution among the selected schizophrenia population, as recent studies have found schizophrenia-PRS to be associated with smoking behavior in substance use enriched samples(Chen et al., 2016; Hartz et al., 2017).

Exploratory GWAS of smoking initiation and cigarettes-smoked-per-day among schizophrenia cases did not yield genome-wide significant evidence of association in the discovery stages. The top association was observed for cigarettes-smoked-per-day (rs1900325; P=1.01×10^{-7}) was upstream of *CBWD2*, which has been previously implicated in sleep and

metabolic traits(Doherty et al., 2018; Hammerschlag et al., 2017). In the replication phase, a single genome-wide significant association was observed between cigarettes-smoked-per-day and SNPs upstream of the *TMEM106B* gene, a much studied risk locus for frontotemporal lobar degeneration (FTLD)(Van Deerlin et al., 2010) that encodes a trans-membrane protein involved in lysosomal trafficking and dendritic branching(Brady et al., 2013; Schwenk et al., 2014). In addition to FTLD, the *TMEM106B* gene has demonstrated associations with the clinical presentation of Alzheimer disease(Rutherford et al., 2012), the volume of left-sided temporal lobe and interhemispheric structures(Adams et al., 2014), and amphetamine response(Hart et al., 2012). Although not genome-wide significant, our results support an association between the *CHRNA3/CHRNA5* locus (rs16969968) and cigarettes-smoked-per-day among schizophrenia cases (replication P=0.0001, Table S12). Interestingly, analysis of schizophrenia stratified by case smoking status revealed elevated odds ratio (and higher allele frequencies) for this SNP among schizophrenia cases that have ever smoked (Figure S9). Also notable is the lack of genome-wide significant associations between TAG-associated variants and smoking behaviors among schizophrenia cases, which could reflect our limited power to detect individual SNP effects in our current sample size (<35%; Table S12).

Consistent with the literature, schizophrenia cases had elevated smoking rates and smoked more cigarettes per day than smokers in the general population (>30 cigarettes: 16.5 versus 6.9% respectively)(de Leon and Diaz, 2005; Jamal et al., 2015). Earlier age of schizophrenia onset was associated with higher rates of smoking initiation. When examining clinical features of schizophrenia, the positive symptom factor score was associated with smoking behavior indicating that those endorsing hallucinations and delusions were more likely to initiate smoking and smoke more cigarettes. This is broadly consistent with the self-

medication hypothesis, by itself does not tell against other etiological hypotheses, as it might represent a process by which symptoms might be reduced, irrespective of etiology. Pharmacological upregulation of nicotinic acetylcholinergic transmission using either acetylcholinesterase inhibitors or positive allosteric modulators (PAMs) have been shown to ameliorate symptoms of schizophrenia(Wallace and Bertrand, 2015). The clinical dimensions for which the literature most strongly supports a role for such treatments are negative and cognitive symptoms(Singh et al., 2012). However, animal models also support a potential role in positive symptom-like features of ketamine-induced psychosis as well(Nikiforuk et al., 2016). Additionally, a nominal association was found between cigarettes-smoked-per-day and the depressive symptom dimension adding support for the role of nicotine on mood in schizophrenia patients. This might be consistent with an improvement in mood concomitant with an amelioration of symptoms of the illness overall. It might also represent an inherent antidepressant effect of agonizing nicotinic transmission, as has been suggested by studies using the forced swim test in rodents(Marcus et al., 2016; Onajole et al., 2016; Shang et al., 2016; Zhang et al., 2016).

The major limitation of this study was the number of available schizophrenia cases with detailed clinical and smoking-related data. Despite attaining a modest sample size for smoking analyses within schizophrenia cases, our power was limited to detect single-SNP associations with smoking initiation or cigarettes-smoked-per-day (Table S12). Another limitation was the use of self-report data to index smoking behavior among schizophrenia cases. Future research should incorporate objective nicotine metabolite biomarkers such as cotinine levels. The age of schizophrenia onset was determined retrospectively in some cases and since the duration of untreated psychosis can vary, the precision of the true onset is unknown. Also, because smoking

data on control subjects was not available for the majority of participating studies, we were limited in our ability to relate findings from the smoking analyses within schizophrenia cases to variation in the general population. Recently, a large-scale GWAS from the GSCAN consortium reported 55, 378, and 99 associated genetic variants with cigarettes-smoked-per-day, smoking initiation, and alcohol drinks per week respectively(Liu et al., 2019). Forthcoming research needs to examine shared genetic risk of schizophrenia across substances as well as gender and diverse populations. As available sample sizes and phenotypic data grow(Pardiñas et al., 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2020) it will be possible to apply alternative methods such as Mendelian Randomization to assess causal processes between these phenotypes. Nonetheless, findings suggest a portion of the schizophrenia-smoking association is due to shared genetic etiology, as we were able to demonstrate partial overlap between genetic liability to smoking behavior in the general population and (1) schizophrenia risk, and (2) smoking behavior among schizophrenia patients. In addition to supporting genome-wide pleiotropic effects, our smoking GWAS within schizophrenia cases highlighted a schizophrenia-specific genetic liability for smoking quantity. Future research needs to address mechanisms underlying associations between these traits (e.g., Mendelian randomization, pharmacogenetics) to aid both schizophrenia and smoking treatment and prevention efforts.

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Disclosures

Q.S.L. is an employee of Janssen Research and Development, LLC. The other authors declare no conflict of interest.

Contributions

Authors R. Peterson, T. Bigdeli, and A. Fanous designed the study and wrote the first draft of the manuscript. R. Peterson, T. Bigdeli, and S. Ripke undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Tables

Table 1. Conceptual overview of analyses of schizophrenia and smoking behaviors.

Research Question	Cohorts & Sample Sizes	Analysis
Question 1: Are there genetic correlations between schizophrenia and smoking behaviors?	*Primary* - PGC-Schizophrenia European ancestry: 35,476 cases, 46,839 controls; TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181, cessation 41,278, age of smoking onset 24,114	genetic correlation (LD score regression)
	Replication - PGC-Schizophrenia East-Asian ancestry: 1,836 cases, 3,383 controls	trans-ethnic genetic correlation (popcorn)
Question 2: Do polygenic risk scores for smoking behaviors also predict schizophrenia case status?	*Training Set* - TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181, cessation 41,278, age of smoking onset 24,114	polygenic risk scores (cross-trait association)
	Testing Set - PGC-Schizophrenia: 35,476 cases, 46,839 controls	
Question 3: What is the genetic architecture of smoking behavior among schizophrenia patients?		
3.1 What is the SNP-based heritability of smoking behaviors among schizophrenia cases?	PGC-Schizophrenia Phenotype Working Group - 10 study sites: smoking initiation 5,255, cigarettes-per-day 3,370	SNP-based heritability (LD score regression)
3.2 Are genetic factors for smoking behaviors shared between populations with and without schizophrenia?	PGC-Schizophrenia: smoking initiation 5,255, cigarettes-per-day 3,370; TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181	genetic correlation (LD score regression)
3.3 Do polygenic risk scores for smoking behaviors also predict these behaviors in schizophrenia patients?	*Training Set* - TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181	polygenic risk scores (within-trait across-cohort association)
	Testing Set - PGC-Schizophrenia: smoking initiation 5,255, cigarettes-per-day 3,370	
3.4 Are there schizophrenia-specific genetic risk variants for smoking behaviors?	*Primary* - PGC-Schizophrenia: smoking initiation 5,255, cigarettes-per-day 3,370	genome-wide association study meta-analysis of smoking behaviors among schizophrenia cases
	Replication - Janssen Pharmaceuticals: smoking initiation 1802, cigarettes-per-day 1802	
Question 4: Are there associations between smoking behaviors and clinical features of schizophrenia?		
4.1 Are smoking behaviors among schizophrenia cases associated with clinical presentation of schizophrenia?	PGC-Schizophrenia: smoking initiation 5,255, cigarettes-per-day 3,370, age-schizophrenia-onset 4,658; symptom dimension factor scores: positive 3,846, negative 3,845, manic 3,740, depression 3,740	phenotypic associations (linear/logistic regression)
4.2 Do polygenic risk scores for smoking behaviors predict schizophrenia symptom dimensions?	*Training Set* - TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181	polygenic risk scores (across-trait across-cohort association)
	Testing Set - PGC-Schizophrenia: age-schizophrenia-onset 11,600; symptom dimension factor scores: positive 8,330, negative 8,427, manic 6,965, depression 6,964	

PGC is Psychiatric Genomics Consortium, TAG is Tobacco and Genetics consortium, LD is linkage disequilibrium, SNP is single nucleotide polymorphism.

Table 2. Sample characteristics for each PGC2-schizophrenia cohort.

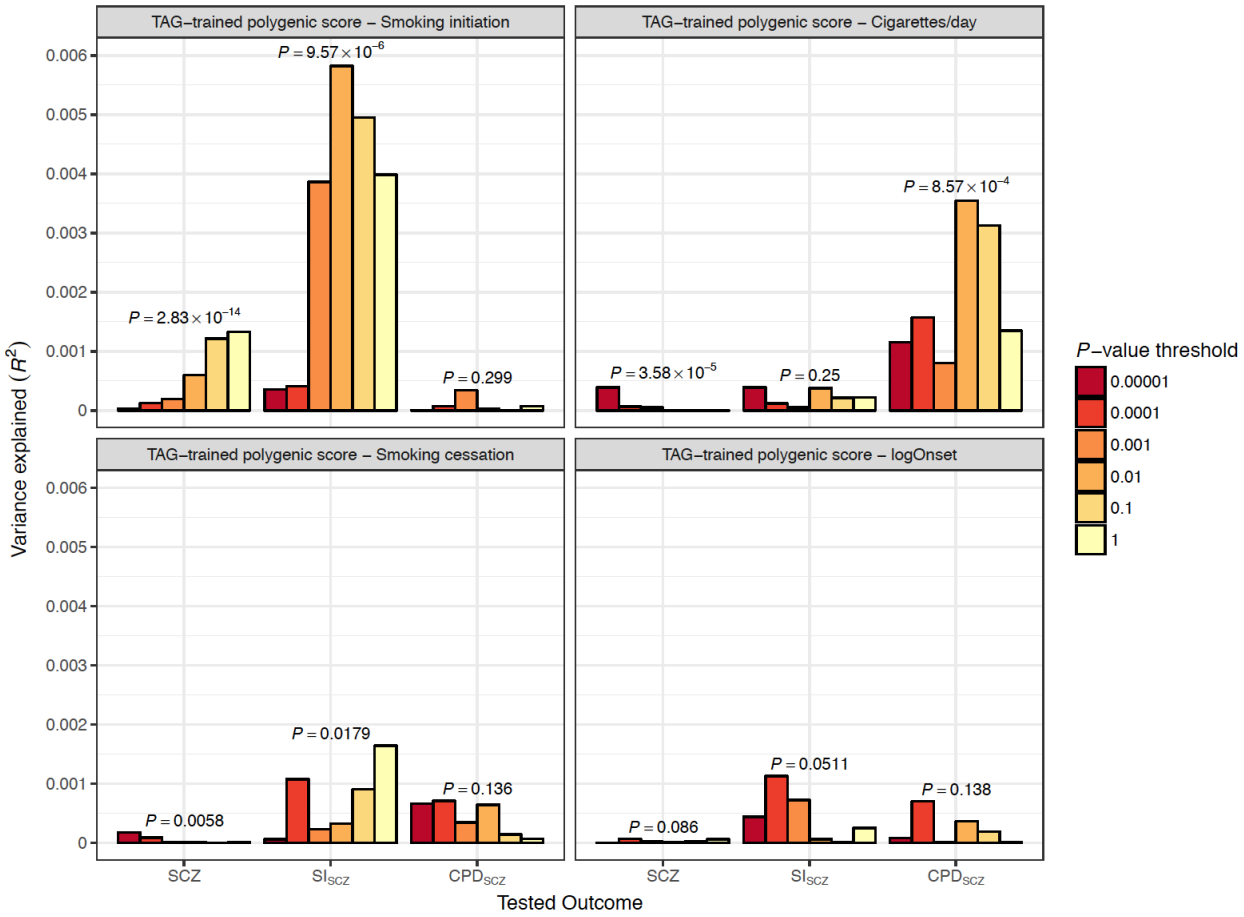
Table 3. Genetic correlations between TAG and PGC-schizophrenia phenotypes.

Table 4. Association results for top SNP associations.

Table 5. Association of smoking variables with clinical features in schizophrenia.

Figure legends

Figure 1. Association of TAG-based polygene scores with schizophrenia risk and smoking behaviors. For polygenic scores based on analyses of smoking behaviors described by TAG, the variance explained for selected outcomes in PGC-schizophrenia is shown on the *y*-axis, in terms of Nagelkerke's pseudo-R^2(schizophrenia and smoking initiation) or R^2 (cigarettes-smoked-per-day); scores based on varying SNP *P*-value inclusion thresholds are displayed as colored bars. *logOnset* is log-transformed age-of-onset (see Methods).



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Genome-wide analyses of smoking behaviors in schizophrenia: findings from the Psychiatric Genomics Consortium

Roseann E Peterson, PhD[1,‡]; Tim B Bigdeli, PhD[1,2,‡]; Stephan Ripke, MD, PhD[3,4]; Silviu-Alin Bacanu, PhD[1]; Pablo V Gejman, MD[5,6]; Douglas F Levinson, MD[7]; Qingqin S Li, PhD[8]; Dai Wang, PhD[8]; Dan Rujescu, MD, PhD[10,9]; Marcella Rietschel, MD, PhD[11]; Daniel R Weinberger, MD[12,13]; Richard E Straub, PhD[12]; James TR Walters, MD, PhD[14]; Bryan J Mowry, MD, FRANZCP [15,16]; Roel A Ophoff, PhD[17,18,19]; Ole A Andreassen, MD, PhD[20,21]; Tõnu Esko, PhD[22,23,24,25]; Tracey L Petryshen, PhD[26,27,28]; Kenneth S Kendler, MD[1]; Schizophrenia Working Group of the Psychiatric Genomics Consortium[a]; Ayman H Fanous, MD[1,2,29*]

[1]Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, VA, USA
[2]Department of Psychiatry and Behavioral Sciences, State University of New York Downstate Medical Center, Brooklyn, NY, USA
[3]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA
[4]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA
[5]Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, IL, USA
[6]Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA
[7]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA
[8]Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Raritan, NJ, USA
[9]Department of Psychiatry, University of Halle, Halle, Germany
[10]Department of Psychiatry, University of Munich, Munich, Germany
[11]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany
[12]Lieber Institute for Brain Development, Baltimore, MD, USA
[13]Departments of Psychiatry, Neurology, Neuroscience and Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, MD
[14]MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK
[15]Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia
[16]Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, Australia
[17]Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, USA
[18]Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, CA, USA
[19]Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands
[20]NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[21]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[22]Estonian Genome Center, University of Tartu, Tartu, Estonia
[23]Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA, USA
[24]Department of Genetics, Harvard Medical School, Boston, MA, USA
[25]Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, MA, USA
[26]Center for Human Genetic Research and Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
[27]Department of Psychiatry, Harvard Medical School, Boston, MA, USA
[28]The Broad Institute of MIT and Harvard, Boston MA
[29]Mental Health Service Line, Washington VA Medical Center, Washington DC, USA

*Corresponding author
Department of Psychiatry and Behavioral Sciences
SUNY Downstate Medical Center
450 Clarkson Ave
Brooklyn, NY 11203
‡These authors contributed equally to this work
[a]Full list of consortium members appears at the end of this Supplement.

Study descriptions

For participating studies, ascertainment and diagnosis has been described previously (1), and are reproduced here in brief. For each study, the first line gives the name of the principal investigator(s) name, PubMed ID for citations describing the sample in detail, the country of origin or study name, and the study identifier used herein.

Discovery studies (SCZ smoking behaviors)

Rietschel/Rujescu | 19571808 | Bonn/Mannheim, Germany | boco
Rujescu, D | 19571808 | Munich, Germany | munc
These German samples were collected by separate groups from Bonn/Mannheim and the University of Munich. For the PGC analyses, the samples were combined by chip and ancestry.
In Bonn/Mannheim, cases were ascertained as previously described (2). Controls were drawn from three population-based epidemiological studies (PopGen) (3), the Cooperative Health Research in the Region of Augsburg (KORA) study (4), and the Heinz Nixdorf Recall (HNR) study (5). All participants gave written informed consent and the local ethics committees approved the human subjects protocols.

Cases were ascertained from the Munich area of Germany, as described previously (2). The controls were unrelated volunteers randomly selected from the general population of Munich. All were screened to exclude a history of psychosis/central neurological disease either personally or in a first-degree relative. All participants gave written informed consent and the local ethics committees approved the human subjects protocols.

Petryshen, T | Not Published | Boston, US (CIDAR) | cims
Cases were recruited from inpatient and outpatient settings in the Boston area by clinician referral, through review of medical records, or through advertisements in local media. Cases were diagnosed with DSM-IV schizophrenia through a structured clinical interview (SCID) by trained interviewers with review of medical records and a best estimate diagnostic procedure including reliability trials across interviewers. A psychiatrist or a PhD-level mental health professional made the final diagnostic determination. Controls were ascertained through local advertisements from the same geographical area. Ethical approval was provided by local ethics committees and all participants gave written informed consent.

Walters, J | 21850710 | Cardiff, UK (CogUK) | cou3
Cases were recruited from community mental health teams in Wales and England on the basis of a clinical diagnosis of schizophrenia or schizoaffective disorder (depressed sub-type) as described previously (6). Diagnosis was confirmed following a SCAN (7) interview and review of case notes followed by consensus diagnosis according to DSM-IV (8) criteria. The samples were genotyped at the Broad Institute. The UK Multicentre Research Ethics Committee (MREC) approved the study and all participants provided valid informed consent.

Esko, T | 15133739 | Estonia (EGCUT) | egcu
The Estonian cohort comes from the population-based biobank of the Estonian Genome Project of University of Tartu (EGCUT) (9). The project was conducted according to the Estonian Gene Research Act and all participants provided informed consent (www.biobank.ee). In total, 52,000 individuals aged 18 years or older participated in this cohort (33% men, 67% women). The population distributions of the cohort reflect those of the Estonian population (83% Estonians, 14% Russians and 3% other). General practitioners (GP) and physicians in the hospitals randomly recruited the participants. A Computer-

Assisted Personal interview was conducted over 1-2 ours at doctors' offices. Data on demographics, genealogy, educational and occupational history, lifestyle and anthropometric and physiological data were assessed. Schizophrenia was diagnosed prior to the recruitment by a psychiatrist according to ICD-10 criteria and identified from the Estonian Biobank phenotype database. Controls were drawn from a larger pool of genotyped biobank samples by matching on gender, age and genetic ancestry. All the controls were population-based and have not been sampled for any specific disease.

Weinberger, D | 11381111 | NIMH CBDB | lie2, lie5
Subjects were recruited from the Clinical Brain Disorders Branch of the NIMH 'Sibling Study' as previously described (10). In brief, cases and controls gave informed consent and only participants of European ancestry were included in the current analysis. Cases completed a structured clinical interview and were diagnosed with schizophrenia-spectrum disorders. Samples were genotyped at the NIMH.

Gejman, P | 19571809 | US, Australia (MGS) | mgs2
European ancestry case samples were collected by the Molecular Genetics of Schizophrenia (MGS) collaboration across multiple sites in the USA and Australia as described in detail elsewhere (11). Cases gave written informed consent, and IRBs at each collecting site approved the human subjects protocol. A survey company (Knowledge Networks, under MGS guidance) collected the European ancestry control sample and ascertainment is described in detail elsewhere (12). DNA samples were genotyped at the Broad Institute.

Andreassen, O | 19571808 | Norway (TOP) | top8
In the TOP study (Tematisk omrade psykoser), cases of European ancestry, born in Norway, were recruited from psychiatric hospitals in the Oslo region. Patients were diagnosed according to SCID and further ascertainment details have been reported (13). Healthy control subjects were randomly selected from statistical records of persons from the same catchment area as the patient groups. All participants provided written informed consent and the human subjects protocol was approved by the Norwegian Scientific-Ethical Committee and the Norwegian Data Protection Agency.

Ophoff, R | 19571808 | Netherlands | ucla
The case sample consisted of inpatients and outpatients recruited through psychiatric hospitals and institutions throughout the Netherlands. Cases with DSM-IV schizophrenia were included in the analysis. Further details on ascertainment are provided elsewhere (2). Controls came from the University Medical Centre Utrecht and were volunteers with no psychiatric history. Ethical approval was provided by local ethics committees and all participants gave written informed consent.

Replication studies (SCZ case-control)

Iwata, N | 20832056 | Japan | scz_jpn1_asn
Case and control participants were recruited from the Tokai area of mainland Japan and self-identified as Japanese. Full details on sample ascertainment and ethical approval have been reported previously (14).

Liu, J | NP | Singapore (STCRP) | scz_tcr1_asn
The Singapore Translational and Clinical Research in Psychosis (STCRP) Study sample consisted of schizophrenia patients and healthy controls of Chinese ancestry. All patients were recruited from the Institute of Mental Health in Singapore from 2005-2008 and were aged 18-83 years. Diagnosis of schizophrenia was made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Research Version, Patient Edition (SCID-I/P) by trained raters. The controls were from the Singapore Prospective Study Program(15) and were randomly sampled from the Singapore population and approximately matched for age and sex to cases.

Sham, P | 24043878 | China | scz_hok2_asn
The case sample include patients with DSM-IV schizophrenia recruited in Hong Kong and Sichuan China described previously (16). The control group was a convenience sample gathered from several sources - subjects from a GWAS on bone mineral density (17), the control subjects from a GWAS on hypertension (18), and on liver cancer (19), and healthy control subjects recruited from Sichuan and Taiwan. All cases and controls gave written consent to participate. The was approved by the Institutional Review Boards of the University of Hong Kong and the West China Hospital at Sichuan University. Genotyping was performed at deCODE Genetics.

Replication studies (SCZ smoking behaviors)

Esko, T; Wang, D | 15133739 | J&J cases, EGCUT controls | jr3a, jr3b, jri6, jrsa
Cases were collected by Johnson and Johnson (J&J) as part of clinical collaborations with hospitals and outpatient centers in Eastern Europe. Cases were diagnosed according to DSM-IV criteria, following a structured clinical interview, with medical record review by a trained psychiatrist. There were reliability trials across centers. Most of the cases were from Estonian and Russia (>100) with intermediate numbers from Austria, the Czech Republic, Latvia, Lithuania, and Spain (50-100). There were smaller collections from Bulgaria, Hungary, and Poland (<50). Most of the Eastern European controls were from the Estonian Biobank project (EGCUT) (9) and were ancestrally matched with cases from the J&J sample.

Supplemental Tables

Supplemental Table S1. SNP-based heritability estimates for SI and CPD among PGC-SCZ cases. For each trait, LD-score regression summary output is displayed.

Study	Trait	K_{pop}	K_{sample}	β_0 (SE)	λ_{GC}	$h^2_{intercept}$ (SE)	$h^2_{constrain}$ (SE)
TAG	SI	0.350	0.562	1.003 (0.007)	1.093	0.116 (0.011)	0.120 (0.007)
	CPD	·	·	1.010 (0.007)	1.056	0.054 (0.016)	0.067 (0.012)
PGC	SI_{SCZ}	0.725	0.725	0.987 (0.006)	1.020	0.464 (0.158)	0.219 (0.112)
	CPD_{SCZ}	·	·	0.999 (0.006)	1.005	0.107 (0.138)	0.092 (0.096)

K_{pop} and K_{sample} are the assumed population and calculated sample prevalence, respectively. For each trait, λ_{GC} and β_0, are the estimated genomic control factor (λ) and regression intercept, respectively. Estimates of heritability, h^2, are reported on the liability scale for SI and the observed scale for CPD, for analyses in which the intercept was unconstrained ($h^2_{intercept}$) or constrained to 1 ($h^2_{constrain}$).

Supplemental Table S2. Association of TAG-SI polygenic scores with SCZ. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained in terms of Nagelkerke's R^2; β and SE are the beta regression coefficient and standard error from logistic regression; P_{het} is the significance of Cochran's test for heterogeneity.

P_T	R^2	β	SE	*Z*	*P*-value	P_{het}
1.00E-05	2.52E-05	0.104	0.099	1.049	0.294	0.629
1.00E-04	0.000128	0.091	0.038	2.364	0.018	0.740
0.001	0.000191	0.036	0.012	2.889	0.004	0.079
0.01	0.000602	0.027	0.005	5.122	3.03E-07	0.078
0.1	0.00122	0.016	0.002	7.280	3.38E-13	0.013
1	0.00133	0.012	0.002	7.608	2.83E-14	0.016

Supplemental Table S3. Association of TAG-CPD polygenic scores with SCZ. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained in terms of Nagelkerke's R^2; β and SE are the beta regression coefficient and standard error from logistic regression; P_{het} is the significance of Cochran's test for heterogeneity.

P_T	R^2	β	SE	*Z*	*P*-value	P_{het}
1.00E-05	0.000391	0.0260	0.0063	4.1334	3.58E-05	0.125
1.00E-04	6.62E-05	0.0077	0.0045	1.6997	0.089	0.126
0.001	5.01E-05	0.0027	0.0018	1.4794	0.139	0.228
0.01	5.97E-06	0.0004	0.0008	0.5104	0.610	0.831
0.1	1.72E-06	0.0001	0.0003	0.2736	0.784	0.533
1	1.61E-07	0.0000	0.0002	0.0838	0.933	0.435

Supplemental Table S4. Association of TAG-SI polygenic scores with SCZ-SI. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained in terms of Nagelkerke's R^2; β and SE are the beta regression coefficient and standard error from logistic regression; P_{het} is the significance of Cochran's test for heterogeneity.

P_T	R^2	β	SE	*Z*	*P*-value	P_{het}
1.00E-05	0.0004	0.4182	0.3797	1.1014	2.71E-01	0.442
1.00E-04	0.0004	0.1718	0.1460	1.1766	2.39E-01	0.794
0.001	0.0039	0.1717	0.0475	3.6168	3.01E-04	0.952
0.01	0.0058	0.0873	0.0197	4.4314	9.57E-06	0.463
0.1	0.0050	0.0345	0.0085	4.0873	4.44E-05	0.452
1	0.0040	0.0219	0.0060	3.6658	2.49E-04	0.629

Table S5. Association of TAG-CPD polygenic scores with SCZ-CPD. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained; β and SE are the beta regression coefficient and standard error from linear regression; P_{het} is the significance of Cochran's test for heterogeneity.

P_T	R^2	β	SE	*Z*	*P*-value	P_{het}
1.00E-05	0.0012	0.0241	0.0127	1.9026	5.72E-02	0.838
1.00E-04	0.0016	0.0202	0.0091	2.2170	2.67E-02	0.648
0.001	0.0008	0.0058	0.0037	1.5811	1.14E-01	0.378
0.01	0.0035	0.0052	0.0016	3.3370	8.57E-04	0.747
0.1	0.0031	0.0022	0.0007	3.1336	1.74E-03	0.541
1	0.0013	0.0009	0.0005	2.0533	4.01E-02	0.088

Table S6. Association of PGC-SCZ polygenic scores with SCZ-SI. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained in terms of Nagelkerke's R^2; β and SE are the beta regression coefficient and standard error from logistic regression; P_{het} is the significance of Cochran's test for heterogeneity.

P_T	R^2	β	SE	*Z*	*P*-value	P_{het}
1.00E-04	9.59E-05	-0.0288	0.0506	-0.5698	0.569	0.495
0.001	3.11E-05	-0.0108	0.0332	-0.3245	0.746	0.634
0.01	1.49E-05	0.0047	0.0209	0.2247	0.822	0.394
0.1	0.0002	0.0122	0.0133	0.9170	0.359	0.412
1	0.0004	0.0128	0.0109	1.1752	0.240	0.662

Table S7. Association of PGC-SCZ polygenic scores with SCZ-CPD. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained; β and SE are the beta regression coefficient and standard error from linear regression; P_{het} is the significance of Cochran's test for heterogeneity.

P_T	R^2	β	SE	*Z*	*P*-value	P_{het}
1.00E-04	0.0007	0.0389	0.0269	1.4419	0.149	0.362
0.001	0.0005	0.0226	0.0176	1.2879	0.198	0.168
0.01	0.0005	0.0137	0.0112	1.2231	0.221	0.149
0.1	0.0004	0.0079	0.0072	1.1025	0.270	0.155
1	0.0001	0.0036	0.0059	0.6110	0.541	0.437

Table S8. Association of TAG-SI polygenic scores with age-of-onset. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained; β and SE are the beta regression coefficient and standard error from linear regression; P_{het} is the significance of Cochran's test for heterogeneity.

P_T	R^2	β	SE	*t*-statistic	*P*-value	P_{het}
1.00E-05	1.03E-05	-0.034	0.14	-0.247	0.805	0.589
1.00E-04	5.93E-06	0.01	0.054	0.187	0.852	0.388
0.001	2.73E-05	-0.007	0.018	-0.4	0.689	0.391
0.01	2.68E-07	0	0.007	0.04	0.968	0.529
0.1	2.68E-06	0	0.003	0.126	0.9	0.0308
1	9.58E-06	-0.001	0.002	-0.237	0.812	0.0014

Table S9. Association of TAG-SI polygenic scores with positive symptoms. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained; β and SE are the beta regression coefficient and standard error from linear regression; P_{het} is the significance of Cochran's test for heterogeneity.

P_T	R^2	β	SE	*t*-statistic	*P*-value	P_{het}
1.00E-05	6.00E-04	-0.27	0.158	-1.707	0.0878	0.982
1.00E-04	0.00107	-0.141	0.062	-2.279	0.0227	0.643
0.001	2.13E-05	0.006	0.02	0.322	0.748	0.508
0.01	1.59E-05	0.002	0.008	0.278	0.781	0.852
0.1	1.85E-05	0.001	0.003	0.3	0.764	0.97
1	0.000136	0.002	0.002	0.813	0.416	0.907

Table S10. Association of TAG-CPD polygenic scores with positive symptoms. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained; β and SE are the beta regression coefficient and standard error from linear regression; P_{het} is the significance of Cochran's test for heterogeneity.

P_T	R^2	β	SE	*t*-statistic	*P*-value	P_{het}
1.00E-05	2.15E-05	0.003	0.01	0.323	0.747	0.159
1.00E-04	3.40E-05	0.003	0.007	0.406	0.685	0.457
0.001	0.00044	0.004	0.003	1.461	0.144	0.85
0.01	0.000569	0.002	0.001	1.662	0.0965	0.792
0.1	0.00115	0.001	0.001	2.368	0.0179	0.828
1	0.00155	0.001	0	2.748	0.00602	0.986

Table S11. Association of TAG-CPD polygenic scores with depression symptoms. For scores based on varying *P*-value thresholds (P_T), R^2 is the variance explained; β and SE are the beta regression coefficient and standard error from linear regression; P_{het} is the significance of Cochran's test for heterogeneity.

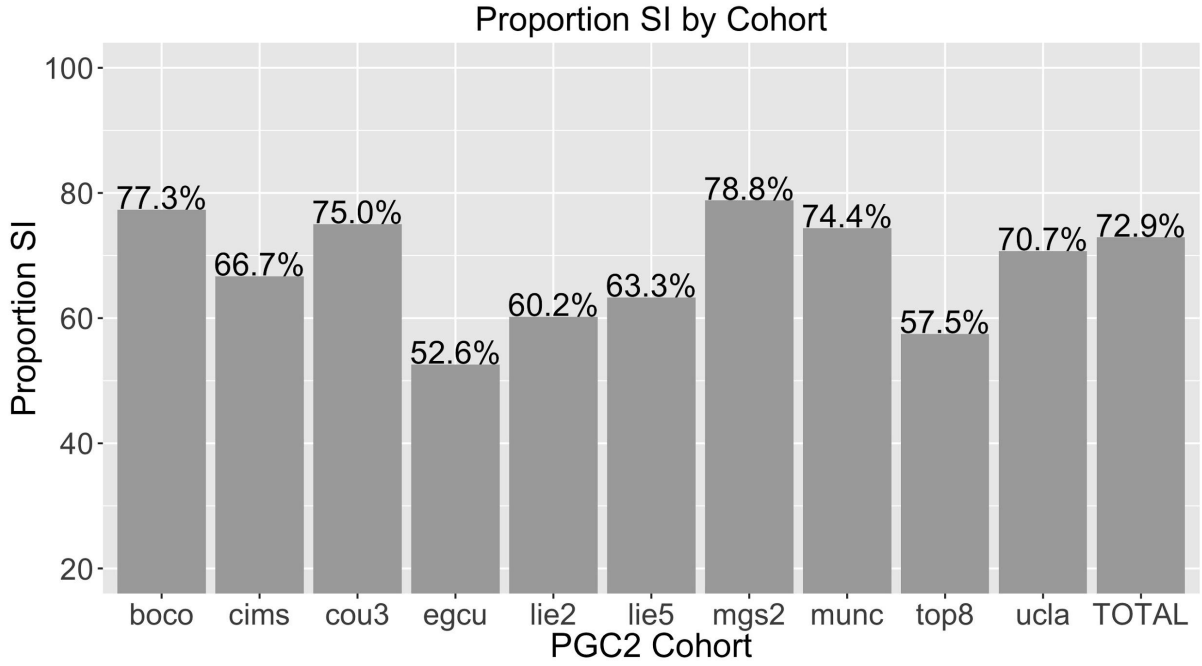
P_T	R^2	β	SE	*t*-statistic	*P*-value	P_{het}
1.00E-05	0.000244	0.011	0.011	1.066	0.286	0.449
1.00E-04	2.75E-05	0.003	0.008	0.358	0.721	0.512
0.001	4.49E-06	0	0.003	0.145	0.885	0.532
0.01	3.98E-07	0	0.001	0.043	0.966	0.00209
0.1	0.000115	0	0.001	0.732	0.464	0.0242
1	0.000132	0	0	0.786	0.432	0.0452

Table S12. *Post-hoc* power analyses for top associated SNPs from TAG. For genomewide-significant SNPs in the TAG study of smoking behaviors (20) the statistical power to detect these associations in the PGC-SCZ study is shown, Chr is chromosome, SNP is single-nucleotide polymorphism, Frq is effect allele frequency, *β* and SE are the beta regression coefficient and standard error from linear/logistic regression, P is P-value, N is sample size, CPD is cigarettes-per-day, SI is smoking initiation, Cessation is smoking cessation. The "GeneticsDesign" package in Bioconductor was used to estimate the power to detect SNP effects for quantitative traits (CPD) (https://www.bioconductor.org/packages/devel/bioc/manuals/GeneticsDesign/) and CaTS Power Calculator (http://csg.sph.umich.edu//abecasis/CaTS/gas_power_calculator/index.html) (21) was used for binary traits (SI, Cessation).

Marker		**TAG Meta-Analysis**				**PGC-SCZ Results**			
Chr	**SNP** **Gene**	**A1/A2** **A1 Frq.**	**Trait** ***N***	***β*** ***SE***	***P***	***N***	***β*** ***SE***	***P***	**Power**
15	rs16969968 *CHRNA3*	G/A 0.65	CPD 73853	-1.00 0.06	$2.8x10^{-72}$	3344	-0.09 0.03	$8.0x10^{-4}$	0.376
10	rs1329650 *LOC100188947*	T/G 0.28	CPD 73853	-0.37 0.06	$5.7x10^{-10}$	3344	-0.02 0.03	0.421	0.087
9	rs3733829 *CYP2A6*	G/A 0.36	CPD 73853	0.33 0.06	$1.0x10^{-8}$	3344	-0.004 0.03	0.891	0.083
11	rs6265 *BDNF*	T/C 0.21	SI 143023	-0.06 0.01	$1.8x10^{-8}$	4991	-0.02 0.06	0.761	0.050
9	rs3025343 *DBH*	G/A 0.84	Cessation 64924	0.12 0.02	$3.6x10^{-8}$	2742	NA	NA	0.135

Supplemental Figures

Figure S1. **Proportion of smoking initiation by PGC2 schizophrenia cohort.** The percent of each PGC2-SCZ cohort endorsing ever smoked a cigarette, SI is smoking initiation.



Cohort	SI Definition
boco	Smoking ever, 100 cigarettes, CPD ≥ 1
cims	100 cigarettes, CPD ≥ 1, Nicotine Dependence
cou3	Ever regular smoker, current smoker, age started smoking, years smoking, CPD ≥ 1
egcu	Never/current/former smoker, CPD ≥ 1
lie2	Current smoker, past smoker, packs per day > 0
lie5	Current smoker, past smoker, packs per day > 0
mgs2	Ever smoked on a daily basis, packs per day > 0
munc	Ever smoked, CPD ≥ 1
top8	Lifetime smoker, smoking years > 0
ucla	Smoking ever, 100 cigarettes, CPD ≥ 1

Figure S2. Smoking quantity by PGC2 schizophrenia cohort. The proportion of each cohort endorsing each smoking quantity category.

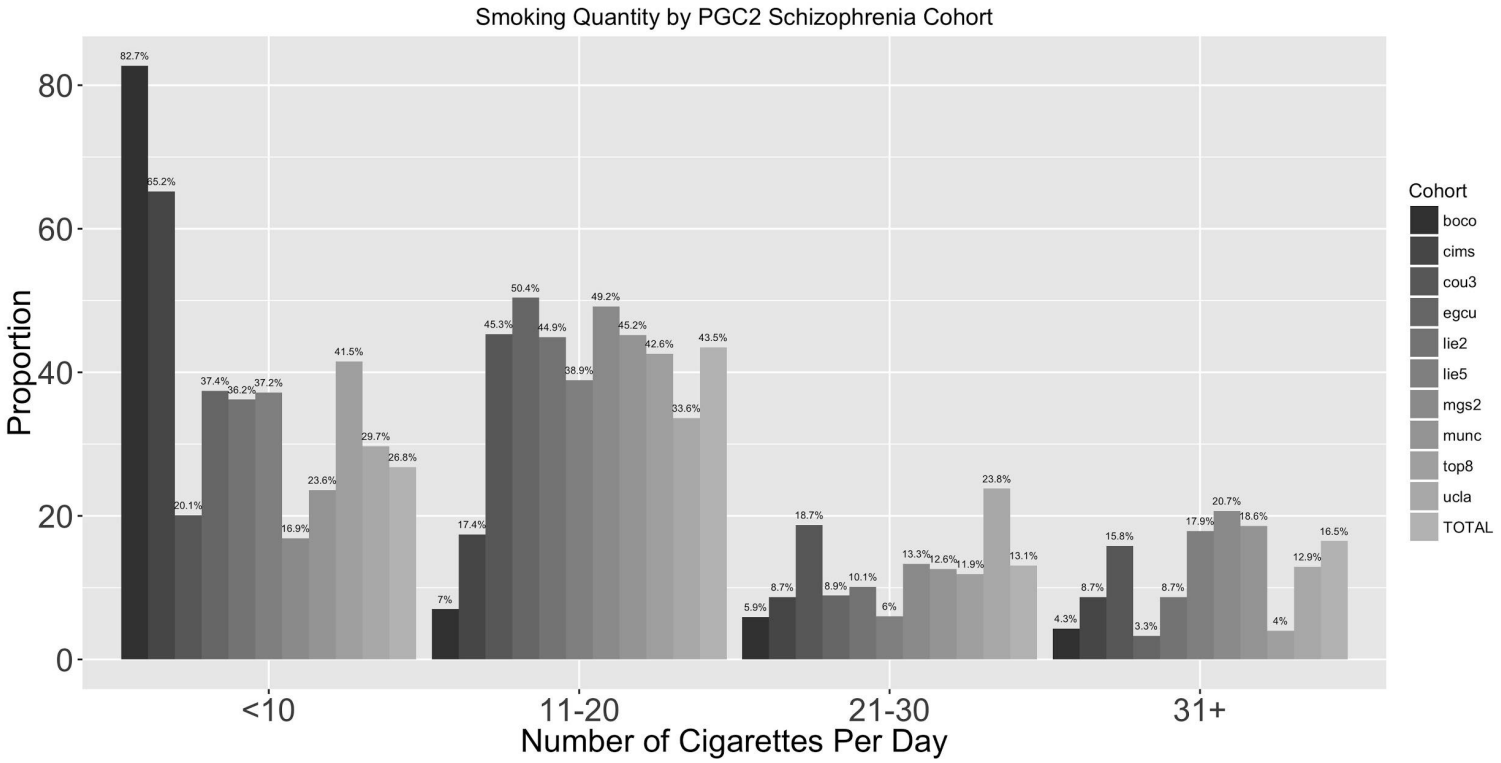

Smoking Quantity by PGC2 Schizophrenia Cohort
Proportion
0
20
40
60
80
<10
11-20
21-30
31+
Number of Cigarettes Per Day
Cohort
boco
cims
cou3
egcu
lie2
lie5
mgs2
munc
top8
ucla
TOTAL
82.7%
65.2%
20.1%
37.4%
36.2%
37.2%
16.9%
23.6%
41.5%
29.7%
26.8%
7%
17.4%
45.3%
50.4%
44.9%
38.9%
49.2%
45.2%
42.6%
33.6%
43.5%
5.9%
8.7%
18.7%
8.9%
10.1%
6%
13.3%
12.6%
11.9%
23.8%
13.1%
4.3%
8.7%
15.8%
3.3%
8.7%
17.9%
20.7%
18.6%
4%
12.9%
16.5%

Figure S3. Association of PGC-SCZ with smoking behaviors among cases. For polygenic scores based on PGC-SCZ results, the variance explained for smoking behaviors is shown on the *y*-axis, in terms of Nagelkerke's pseudo-R^2 (SI) or R^2 (CPD); scores based on varying SNP *P*-value inclusion thresholds are displayed as colored bars.

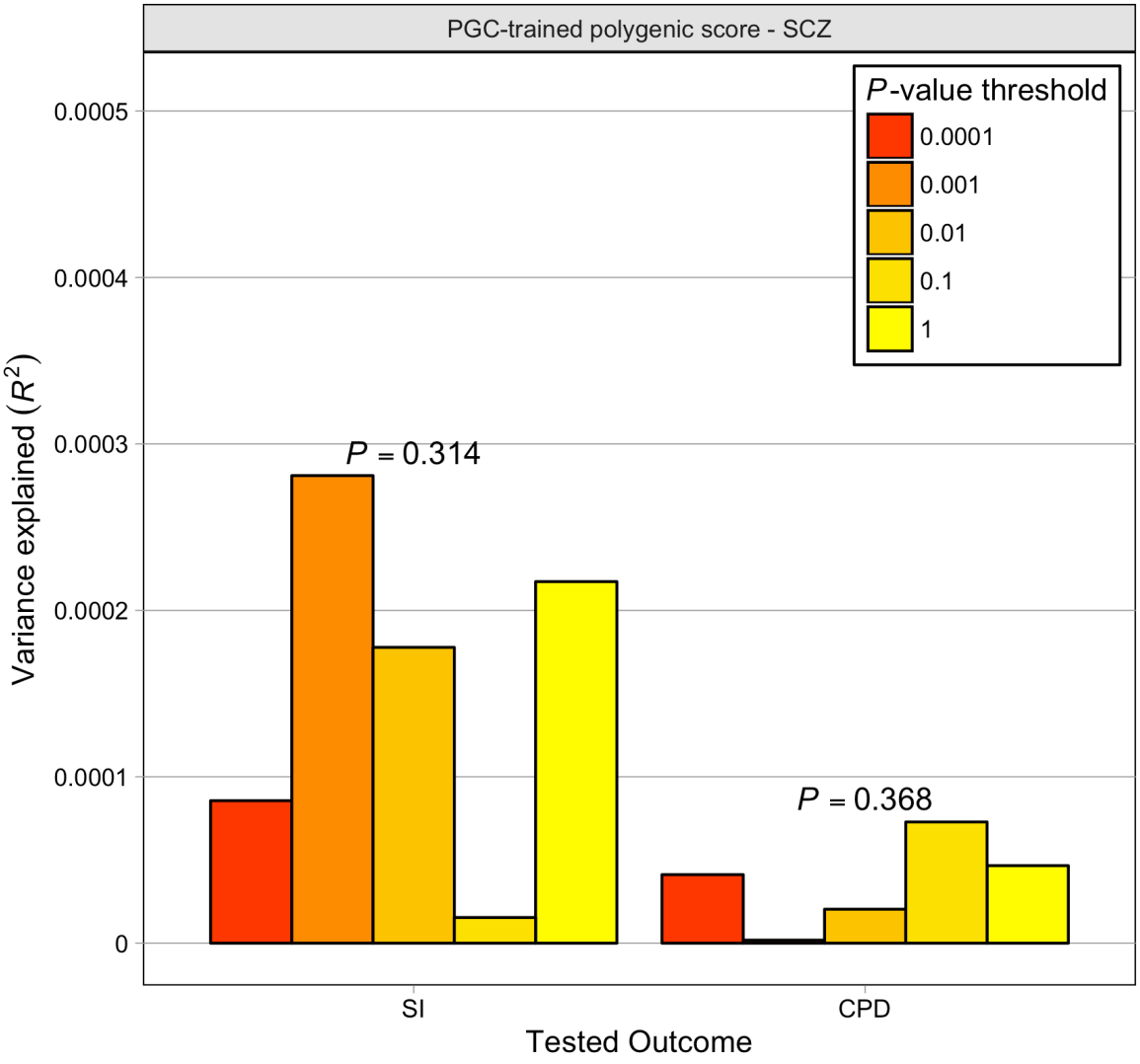


Figure S4. Association of TAG-based polygene scores with SCZ clinical features. For polygenic scores based on analyses of smoking behaviors described by TAG , the variance explained for selected clinical features in PGC-SCZ is shown on the *y*-axis, in terms of R^2; scores based on varying SNP *P*-value inclusion thresholds are displayed as colored bars.

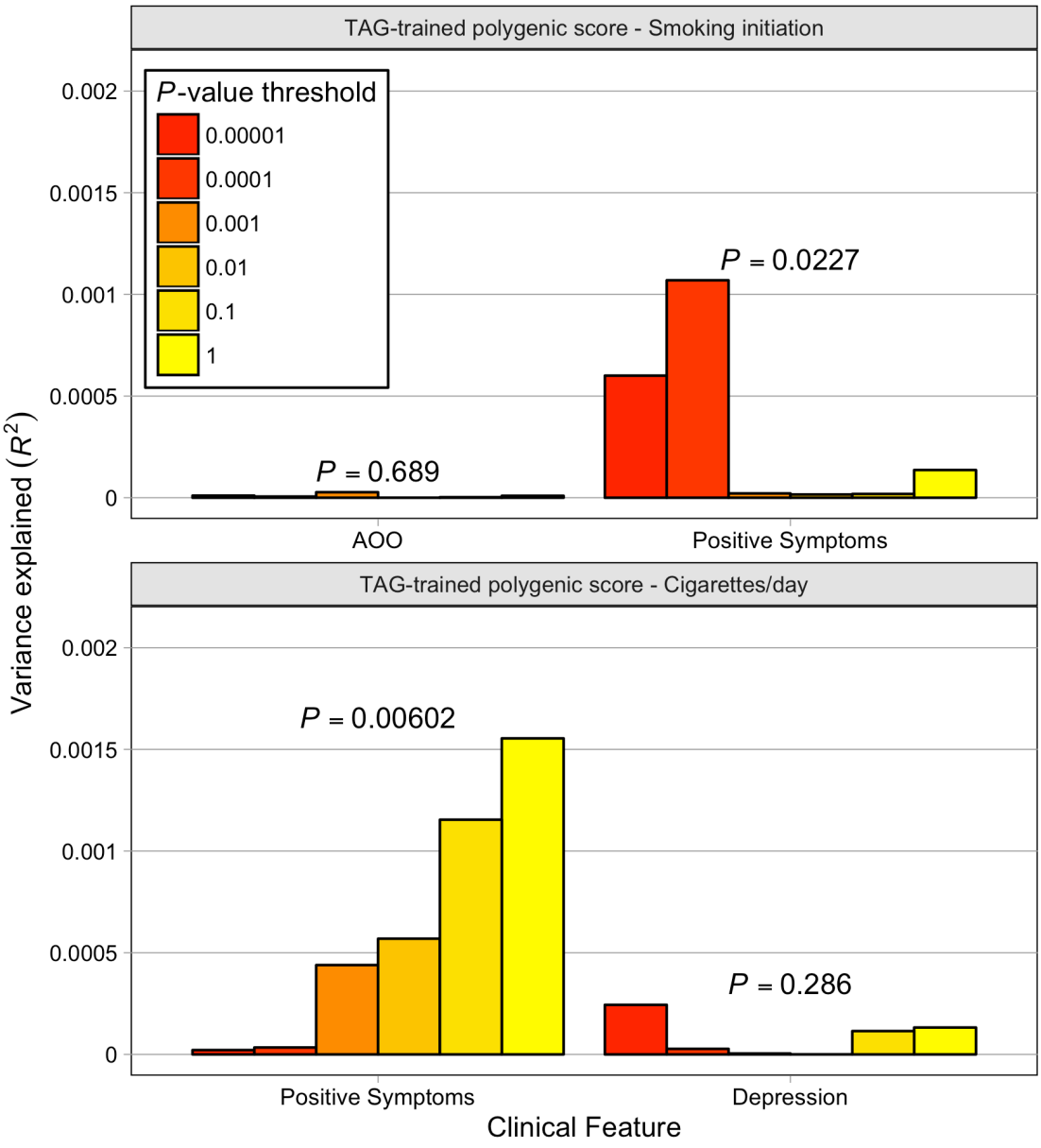


Figure S5. Manhattan plots for random-effects meta-analyses of CPD and SI in SCZ. Red and blue lines indicate thresholds for genome-wide significance ($P<5\times10^{-8}$) and replication follow-up ($P<10^{-6}$). For regions significant at the latter, the most significant "independent" SNP within a 500kb region is displayed as a blue diamond; nearby SNPs in linkage disequilibrium ($r^2 > 0.1$) are highlighted.

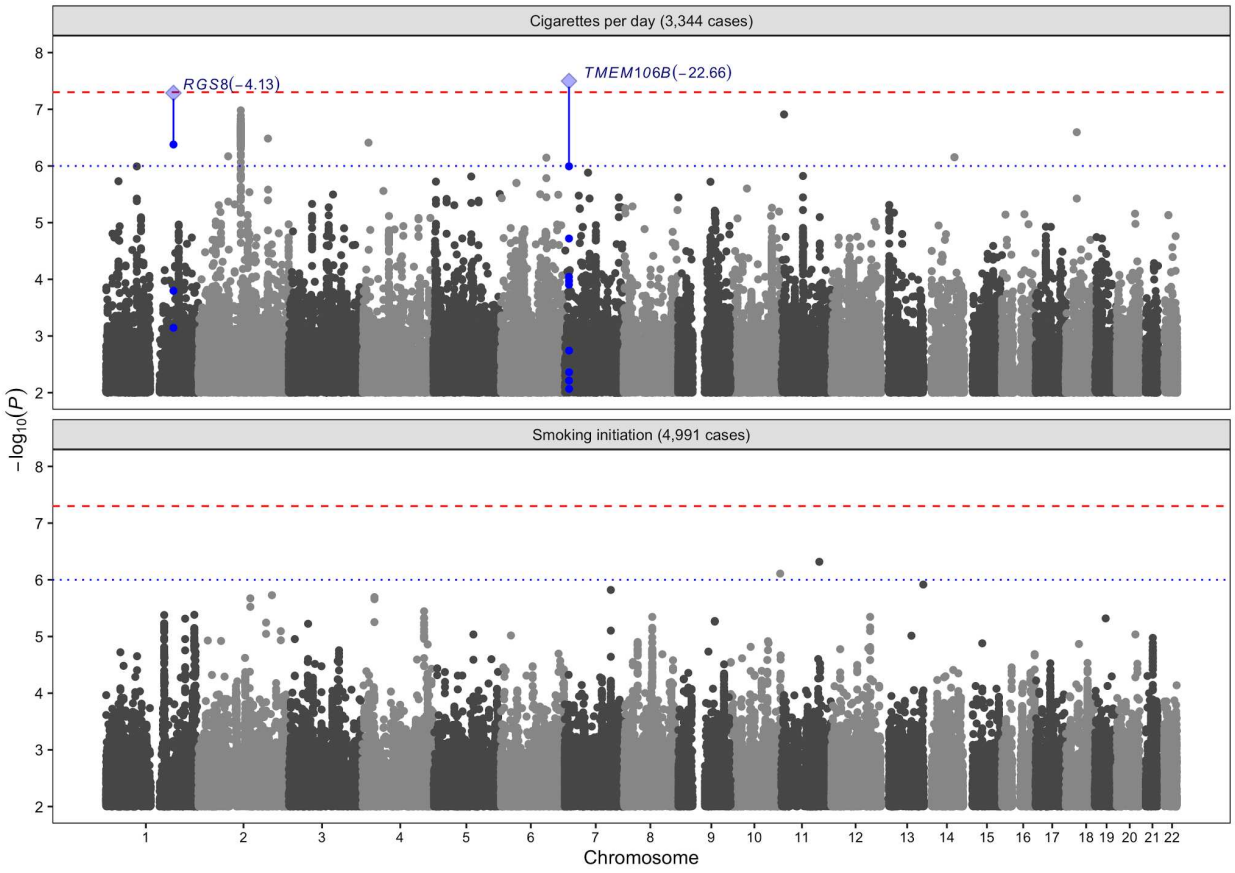
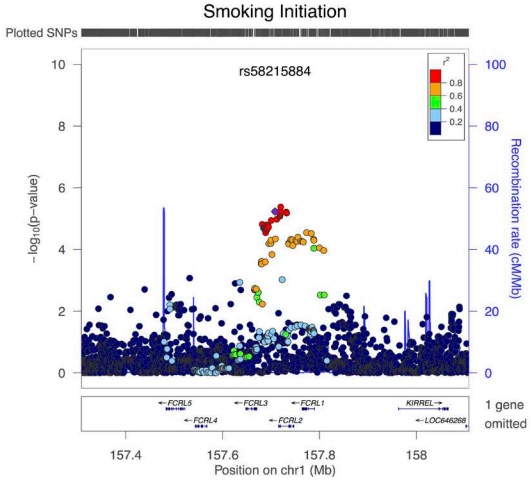
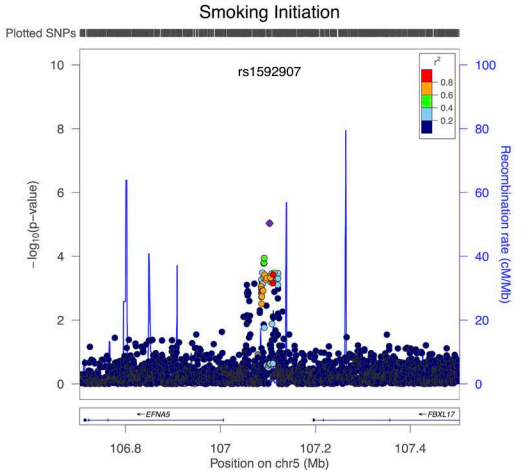


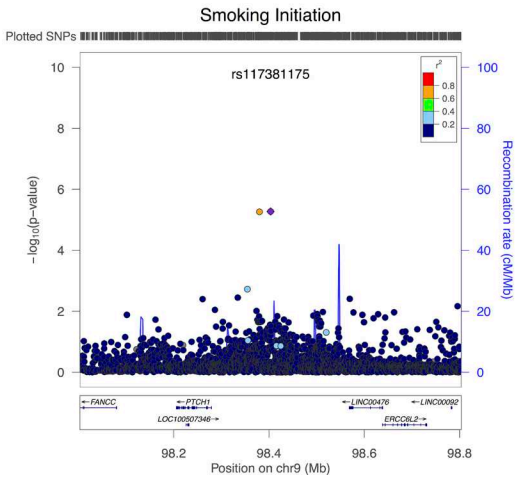
Figure S7. Regional association and forest plots for SI associations. *(left)* Regional association plot created using LocusZoom (22). LD of each SNP with the "index" SNP, displayed as a large purple diamond, is indicated by its color. *(right) Study* abbreviation "repli" is the replication sample; all other study indicators are as given above; *HetP* is the *P*-value for Cochran's test of heterogeneity.



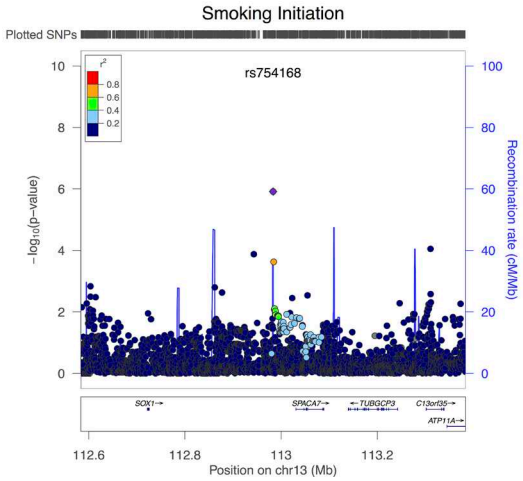
rs58215884				SI		chr1:157708335:T/G	
						hetPval:0.3493	
study	**freq**	**info**	**or**	**se**	**pval**	**n**
boco	0.159	1.026	1.187	0.208	0.409	308
cims	0.136	0.84	3.866	1.46	0.354	33
cou3	0.194	0.963	1.242	0.199	0.276	501
egcu	0.123	1.023	2.272	0.318	0.00977	234
lie2	0.15	1.057	1.073	0.36	0.846	128
lie5	0.147	1.002	1.8	0.214	0.00598	479
mgs2	0.163	0.96	1.262	0.107	0.0303	2194
munc	0.162	0.997	1.986	0.261	0.00854	406
top8	0.151	1.038	1.596	0.237	0.0486	319
ucla	0.168	0.886	0.836	0.224	0.424	389
meta	**0.162**	**0.975**	**1.339**	**0.066**	**5.91e−06**	**4991**
repli			1.281	0.118	0.0353	1776
joint			**1.326**	**0.058**	**6.75e−07**	**6767**



rs1592907				SI		chr5:107103563:A/G	
						hetPval:0.8086	
study	**freq**	**info**	**or**	**se**	**pval**	**n**
boco	0.464	1.059	0.811	0.147	0.155	308
cims	0.519	0.753	2.243	1.042	0.438	33
cou3	0.429	0.98	0.702	0.154	0.0213	501
egcu	0.59	0.953	0.788	0.205	0.246	234
lie2	0.463	0.978	0.789	0.277	0.393	128
lie5	0.432	1.012	0.769	0.14	0.0603	479
mgs2	0.448	0.992	0.857	0.074	0.0384	2194
munc	0.459	0.923	0.802	0.177	0.213	406
top8	0.444	0.916	0.813	0.172	0.228	319
ucla	0.444	0.989	0.787	0.162	0.139	389
meta	**0.454**	**0.982**	**0.811**	**0.046**	**9.21e−06**	**4991**
repli			0.839	0.08	0.0298	1760
joint			**0.818**	**0.04**	**8.54e−07**	**6751**



rs117381175				SI		chr9:98403220:T/C	
						hetPval:0.911	
study	**freq**	**info**	**or**	**se**	**pval**	**n**
boco	0.03	0.793	0.713	0.448	0.449	308
cims	0.047	0.742	0.101	2.593	0.376	33
cou3	0.03	0.78	0.578	0.46	0.233	501
egcu	0.029	0.747	1.105	0.671	0.882	234
lie2	0.029	0.742	0.812	0.912	0.819	128
lie5	0.038	0.734	0.553	0.408	0.147	479
mgs2	0.034	0.815	0.508	0.201	0.000724	2194
munc	0.033	0.762	0.369	0.484	0.0397	406
top8	0.016	0.877	0.62	0.682	0.483	319
ucla	0.025	0.75	0.415	0.54	0.104	389
meta	**0.031**	**0.792**	**0.539**	**0.136**	**5.33e−06**	**4991**
repli			0.502	0.301	0.0396	1746
joint			**0.533**	**0.124**	**6.86e−07**	**6737**



rs754168 **SI** **chr13:112983288:A/C**

hetPval:0.5736

study	freq	info	or	se	pval	n
boco	0.351	0.706	0.61	0.183	0.007	308
cims	0.333	0.98	0.956	0.744	0.952	33
cou3	0.34	0.882	0.677	0.165	0.018	501
egcu	0.347	0.874	1.186	0.219	0.435	234
lie2	0.377	0.848	1.002	0.297	0.994	128
lie5	0.344	0.746	0.92	0.168	0.616	479
mgs2	0.365	0.75	0.751	0.088	0.0011	2194
munc	0.334	0.746	0.84	0.204	0.392	406
top8	0.332	0.699	0.74	0.208	0.148	319
ucla	0.334	0.753	0.628	0.194	0.0163	389
meta	**0.352**	**0.767**	**0.769**	**0.054**	**1.21e−06**	**4991**
repli			0.85	0.104	0.115	1277
joint			**0.785**	**0.048**	**4.58e−07**	**6268**

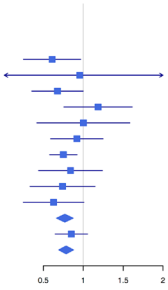
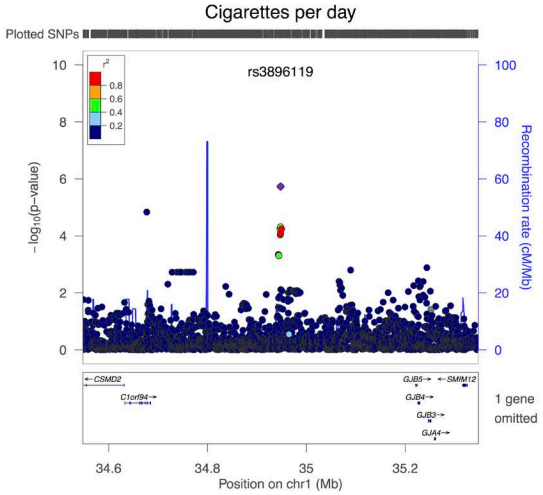
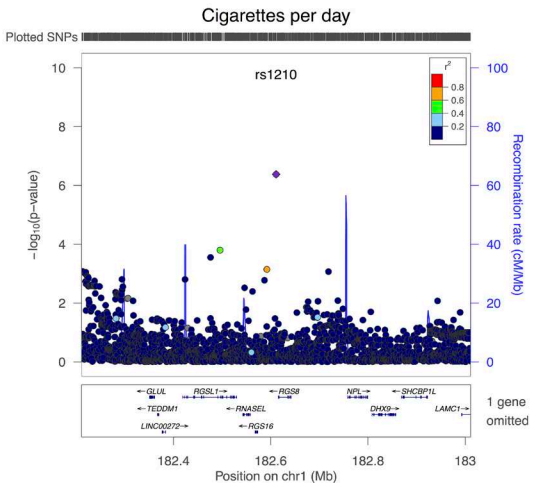


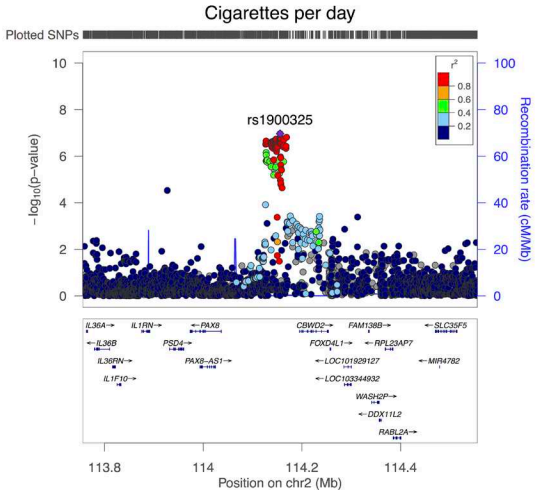
Figure S8. Regional association and forest plots for CPD associations. *(left)* Regional association plot created using LocusZoom(22). LD of each SNP with the "index" SNP, displayed as a large purple diamond, is indicated by its color. *(right) Study* abbreviation "repli" is the replication sample; all other study indicators are as given above; *HetP* is the *P*-value for Cochran's test of heterogeneity.



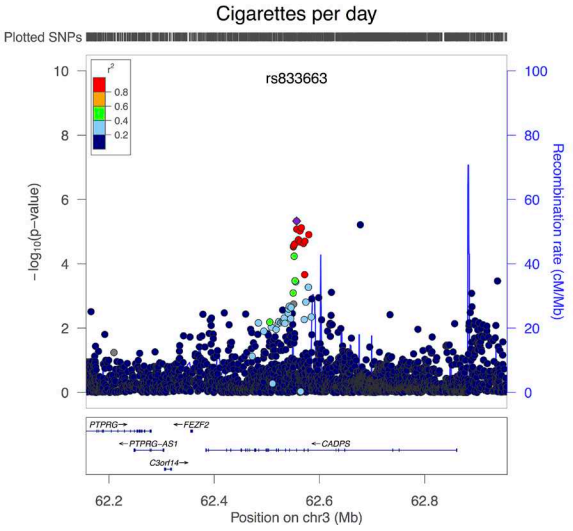
rs3896119			CPD_ZI		chr1:34947725:A/G	
					hetPval:0.2172	
study	**freq**	**info**	**beta**	**se**	**pval**	**n**
boco	0.026	0.749	1.121	0.366	0.00254	185
cims	0.008	0.145				23
cou3	0.011	0.644	0.046	0.504	0.927	278
egcu	0.019	0.691	9.905	4.858	0.0438	123
lie2	0.024	0.71	1.625	0.698	0.0233	69
lie5	0.022	0.746	0.515	0.337	0.128	285
mgs2	0.016	0.926	0.262	0.14	0.0621	1648
munc	0.028	0.761	0.415	0.284	0.144	301
top8	0.019	0.912	0.797	0.409	0.0528	176
ucla	0.012	0.775	1.12	0.462	0.016	256
meta	**0.018**	**0.832**	**0.472**	**0.102**	**1.86e−06**	**3321**
repli			0.255	0.176	0.074	1078
joint			**0.417**	**0.088**	**4.98e−07**	**4399**



rs1210			CPD_ZI		chr1:182611109:T/C	
					hetPval:0.4343	
study	**freq**	**info**	**beta**	**se**	**pval**	**n**
boco	0.035	0.754	0.058	0.325	0.859	185
cims	0.001	0.032				23
cou3	0.045	0.856	0.297	0.221	0.18	278
egcu	0.027	0.707	2.538	4.017	0.529	123
lie2	0.041	0.822	−0.652	0.523	0.217	69
lie5	0.021	0.701	1.017	0.346	0.00357	285
mgs2	0.026	0.781	0.527	0.121	1.5e−05	1648
munc	0.029	0.617	0.735	0.31	0.0183	301
top8	0.026	0.653	−0.112	0.416	0.788	176
ucla	0.027	0.712	0.157	0.321	0.625	256
meta	**0.028**	**0.745**	**0.421**	**0.086**	**4.19e−07**	**3321**
repli			0.405	0.191	0.0347	1052
joint			**0.418**	**0.078**	**5.16e−08**	**4373**

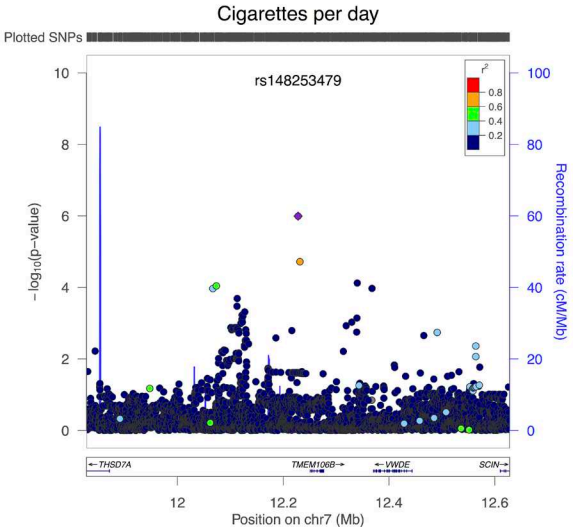


rs1900325			CPD_ZI		chr2:114155795:T/C	
					hetPval:0.6951	
study	**freq**	**info**	**beta**	**se**	**pval**	**n**
boco	0.442	0.968	0.13	0.107	0.225	185
cims	0.43	0.897	0.314	0.488	0.532	23
cou3	0.487	0.834	0.223	0.093	0.0169	278
egcu	0.452	0.843	0.21	1.228	0.864	123
lie2	0.408	0.856	0.301	0.193	0.124	69
lie5	0.474	0.952	0.008	0.088	0.925	285
mgs2	0.483	0.927	0.115	0.036	0.00131	1648
munc	0.504	1.018	0.226	0.08	0.00503	301
top8	0.438	0.928	0.21	0.112	0.0625	176
ucla	0.513	0.881	0.167	0.094	0.0789	256
meta	**0.479**		**0.164**	**0.176**	**1.08e−07**	**3344**
repli			0.008	0.041	0.853	1011
joint			**0.102**	**0.022**	**2.04e−06**	**4355**



rs833663 **CPD_ZI** **chr3:62556622:A/G**
hetPval:0.4928

study	freq	info	beta	se	pval	n
boco	0.041	0.957	0.063	0.273	0.817	185
cims	0.108	0.869	−0.34	0.707	0.639	23
cou3	0.049	0.949	0.298	0.202	0.142	278
egcu	0.024	0.973	4.502	3.587	0.212	123
lie2	0.044	1.292	0.804	0.386	0.0418	69
lie5	0.049	1.022	−0.089	0.192	0.644	285
mgs2	0.034	0.979	0.376	0.094	7.12e−05	1648
munc	0.037	0.968	0.145	0.223	0.517	301
top8	0.023	0.97	0.146	0.369	0.692	176
ucla	0.039	0.96	0.557	0.229	0.0156	256
meta	**0.038**	**0.982**	**0.291**	**0.066**	**4.68e−06**	**3344**
repli			0.209	0.101	0.0318	1097
joint			**0.266**	**0.055**	**4.65e−07**	**4441**



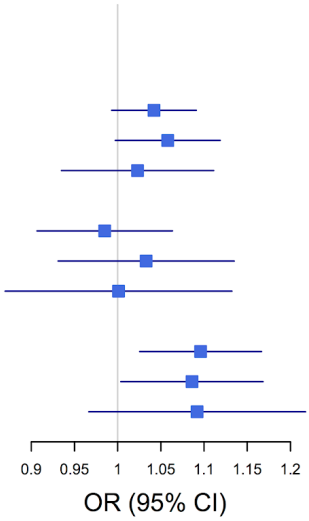
rs148253479 **CPD_ZI** **chr7:12228202:A/C**
hetPval:0.3226

study	freq	info	beta	se	pval	n
boco	0.979	0.888	−0.2	0.387	0.606	185
cims	0.977	0.854	−0.415	1.332	0.761	23
cou3	0.991	0.598				278
egcu	0.998	0.259				123
lie2	0.991	0.777				69
lie5	0.988	0.588	−0.475	0.504	0.348	285
mgs2	0.989	0.746	−0.712	0.191	0.000205	1648
munc	0.987	0.792	−1.546	0.398	0.000126	301
top8	0.995	0.63				176
ucla	0.991	0.545				256
meta	**0.988**	**0.694**	**−0.728**	**0.149**	**1.01e−06**	**2442**
repli			−0.704	0.278	0.00836	1078
joint			**−0.723**	**0.132**	**3.18e−08**	**3520**

Figure S9. Association of rs16969968 with SCZ stratified by smoking status (SI). For analyses of SCZ in the 10 studies contributing smoking data on case subjects, the forest plot displays frequencies and association summary statistics for comparisons of cases versus controls, SI cases that smoke versus controls, and non-SI cases versus controls, overall and further stratified by sex.

Smoking Initiation

Group	SI	Cont.freq	Case.freq	OR	SE	P	Direction	Controls	Cases	HetP
							rs16969968 chr15:78882925:A/G			
All Cases	Any	0.33	0.345	1.042	0.025	0.097	++++++++++	8518	7370	0.097
	Yes	0.33	0.359	1.058	0.031	0.067	+++++++++-	8518	3832	0.067
	No	0.33	0.338	1.023	0.045	0.614	--+++-++++	8518	1423	0.614
Females	Any	0.354	0.346	0.985	0.04	0.704	--+-++--+-	4159	2621	0.704
	Yes	0.354	0.372	1.033	0.052	0.526	++--++-+--	4159	1189	0.526
	No	0.354	0.351	1.001	0.067	0.989	-?+-++--+-	4159	625	0.989
Males	Any	0.311	0.35	1.096	0.036	0.011	-+++++++++	3434	4716	0.011
	Yes	0.311	0.362	1.086	0.042	0.051	-++++++-+	3434	2643	0.051
	No	0.311	0.338	1.092	0.064	0.168	-+-+++++++	3434	798	0.168



[a]Full list of PGC contributors

Stephan Ripke [1,2], Benjamin M Neale [1,2,3,4], Aiden Corvin [5], James TR Walters [6], Kai-How Farh [1], Peter A Holmans [6,7], Phil Lee [1,2,4], Brendan Bulik-Sullivan [1,2], David A Collier [8,9], Hailiang Huang [1,3], Tune H Pers [3,10,11], Ingrid Agartz [12,13,14], Esben Agerbo [15,16,17], Margot Albus [18], Madeline Alexander [19], Farooq Amin [20,21], Silviu A Bacanu [22], Martin Begemann [23], Richard A Belliveau Jr [2], Judit Bene [24,25], Sarah E Bergen [2,26], Elizabeth Bevilacqua [2], Tim B Bigdeli [22], Donald W Black [27], Richard Bruggeman [28], Nancy G Buccola [29], Randy L Buckner [30,31,32], William Byerley [33], Wiepke Cahn [34], Guiqing Cai [35,36], Dominique Campion [37], Rita M Cantor [38], Vaughan J Carr [39,40], Noa Carrera [6], Stanley V Catts [39,41], Kimberley D Chambert [2], Raymond CK Chan [42], Ronald YL Chan [43], Eric YH Chen [44], Wei Cheng [45], Eric FC Cheung [46], Siow Ann Chong [47], C Robert Cloninger [48], David Cohen [49], Nadine Cohen [50], Paul Cormican [5], Nick Craddock [6,7], James J Crowley [51], David Curtis [52,53], Michael Davidson [54], Kenneth L Davis [36], Franziska Degenhardt [55,56], Jurgen Del Favero [57], Ditte Demontis [17,58,59], Dimitris Dikeos [60], Timothy Dinan [61], Srdjan Djurovic [14,62], Gary Donohoe [5,63], Elodie Drapeau [36], Jubao Duan [64,65], Frank Dudbridge [66], Naser Durmishi [67], Peter Eichhammer [68], Johan Eriksson [69,70,71], Valentina Escott-Price [6], Laurent Essioux [72], Ayman H Fanous [73,74,75,76], Martilias S Farrell [51], Josef Frank [77], Lude Franke [78], Robert Freedman [79], Nelson B Freimer [80], Marion Friedl [81], Joseph I Friedman [36], Menachem Fromer [1,2,4,82], Giulio Genovese [2], Lyudmila Georgieva [6], Ina Giegling [81,83], Paola Giusti-Rodríguez [51], Stephanie Godard [84], Jacqueline I Goldstein [1,3], Vera Golimbet [85], Srihari Gopal [86], Jacob Gratten [87], Lieuwe de Haan [88], Christian Hammer [23], Marian L Hamshere [6], Mark Hansen [89], Thomas Hansen [17,90], Vahram Haroutunian [36,91,92], Annette M Hartmann [81], Frans A Henskens [39,93,94], Stefan Herms [55,56,95], Joel N Hirschhorn [3,11,96], Per Hoffmann [55,56,95], Andrea Hofman [55,56], Mads V Hollegaard [97], Masashi Ikeda [98], Inge Joa [99], Antonio Julià [100], René S Kahn [101], Luba Kalaydjieva [102,103], Sena Karachanak-Yankova [104], Juha Karjalainen [78], David Kavanagh [6], Matthew C Keller [105], James L Kennedy [106,107,108], Andrey Khrunin [109], Yunjung Kim [51], Janis Klovins [110], James A Knowles [111], Bettina Konte [81], Vaidutis Kucinskas [112], Zita Ausrele Kucinskiene [112], Hana Kuzelova-Ptackova [113,114], Anna K Kähler [26], Claudine Laurent [19,115], Jimmy Lee [47,116], S Hong Lee [87], Sophie E Legge [6], Bernard Lerer [117], Miaoxin Li [118], Tao Li [119], Kung-Yee Liang [120], Jeffrey Lieberman [121], Svetlana Limborska [109], Carmel M Loughland [39,122], Jan Lubinski [123], Jouko Lönnqvist [124], Milan Macek [113,114], Patrik

KE Magnusson [26], Brion S Maher [125], Wolfgang Maier [126], Jacques Mallet [127], Sara Marsal [100], Manuel Mattheisen [17,58,59,128], Morten Mattingsdal [14,129], Robert W McCarley [130,131], Colm McDonald [132], Andrew M McIntosh [133,134], Sandra Meier [77], Carin J Meijer [88], Bela Melegh [24,25], Ingrid Melle [14,135], Raquelle I Mesholam-Gately [130,136], Andres Metspalu [137], Patricia T Michie [39,138], Lili Milani [137], Vihra Milanova [139], Younes Mokrab [8], Derek W Morris [5,63], Ole Mors [17,58,140], Kieran C Murphy [141], Robin M Murray [142], Inez Myin-Germeys [143], Bertram Müller-Myhsok [144,145,146], Mari Nelis [137], Igor Nenadic [147], Deborah A Nertney [148], Gerald Nestadt [149], Kristin K Nicodemus [150], Liene Nikitina-Zake [110], Laura Nisenbaum [151], Annelie Nordin [152], Eadbhard O'Callaghan [153], Colm O'Dushlaine [2], F Anthony O'Neill [154], Sang-Yun Oh [155], Ann Olincy [79], Line Olsen [17,90], Jim Van Os [143,156], Christos Pantelis [39,157], George N Papadimitriou [60], Sergi Papiol [23], Elena Parkhomenko [36], Michele T Pato [111], Tiina Paunio [158,159], Milica Pejovic-Milovancevic [160], Diana O Perkins [161], Olli Pietiläinen [159,162], Jonathan Pimm [53], Andrew J Pocklington [6], Danielle Posthuma [163,164,165], John Powell [142], Alkes Price [166], Ann E Pulver [149], Shaun Purcell [82], Digby Quested [167], Henrik B Rasmussen [17,90], Abraham Reichenberg [36], Mark A Reimers [168], Alexander L Richards [6,7], Joshua L Roffman [30,32], Panos Roussos [82,169], Douglas M Ruderfer [82], Veikko Salomaa [71], Alan R Sanders [64,65], Ulrich Schall [39,122], Christian R Schubert [170], Thomas G Schulze [77,171], Sibylle G Schwab [172], Edward M Scolnick [2], Rodney J Scott [39,173,174], Larry J Seidman [130,136], Jianxin Shi [175], Engilbert Sigurdsson [176], Teimuraz Silagadze [177], Jeremy M Silverman [36,178], Kang Sim [47], Petr Slominsky [109], Jordan W Smoller [2,4], Hon-Cheong So [43], Chris C A Spencer [179], Eli A Stahl [3,82], Hreinn Stefansson [180], Stacy Steinberg [180], Elisabeth Stogmann [181], Richard E Straub [182], Eric Strengman [183,184], Jana Strohmaier [77], T Scott Stroup [121], Mythily Subramaniam [47], Jaana Suvisaari [124], Dragan M Svrakic [48], Jin P Szatkiewicz [51], Erik Söderman [12], Srinivas Thirumalai [185], Draga Toncheva [104], Sarah Tosato [186], Juha Veijola [187], Peter M Visscher [87], John Waddington [188], Dermot Walsh [189], Dai Wang [86], Qiang Wang [119], Bradley T Webb [22], Mark Weiser [54], Durk Wiersma [190], Dieter B Wildenauer [191], Nigel M Williams [192], Stephanie Williams [51], Stephanie H Witt [77], Aaron R Wolen [168], Emily HM Wong [43], Brandon K Wormley [22], Hualin Simon Xi [193], Clement C Zai [106,107], Xuebin Zheng [194], Fritz Zimprich [181], Naomi R Wray [87], Kari Stefansson [180], Wellcome Trust Case-Control Consortium 2 [195], Rolf Adolfsson [152], Ole A Andreassen [14,135], Douglas HR Blackwood [134], Elvira Bramon [196], Joseph D Buxbaum [35,36,91,197], Anders D Børglum [17,58,59,140], Sven Cichon [55,56,95,198], Ariel Darvasi [199], Enrico Domenici [200], Hannelore Ehrenreich [23], Tõnu Esko [3,11,96,137],

Pablo V Gejman [64,65], Michael Gill [5], Hugh Gurling [53], Christina M Hultman [26], Nakao Iwata [98], Assen V Jablensky [39,201,202,203], Erik G Jönsson [12], Kenneth S Kendler [204], George Kirov [6], Jo Knight [106,107,108], Todd Lencz [205,206,207], Douglas F Levinson [19], Qingqin S Li [86], Jianjun Liu [194,208], Anil K Malhotra [205,206,207], Steven A McCarroll [2,96], Andrew McQuillin [53], Jennifer L Moran [2], Preben B Mortensen [15,16,17], Bryan J Mowry [87,209], Markus M Nöthen [55,56], Roel A Ophoff [38,80,210], Michael J Owen [6,7], Psychosis Endophenotypes International Consortium [211], Aarno Palotie [4,162,212], Carlos N Pato [111], Tracey L Petryshen [130,212,213], Marcella Rietschel [77], Brien P Riley [204], Dan Rujescu [81,83], Pak C Sham [214], Pamela Sklar [82,91,169], David St Clair [215], Daniel R Weinberger [182,216], Jens R Wendland [170], Thomas Werge [17,90,217], Mark J Daly [1], Patrick F Sullivan [26,51,161], Michael C O'Donovan [6,7].

[1] Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. [2] Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA. [3] Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, MA, USA. [4] Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, USA. [5] Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Ireland. [6] MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK. [7] National Centre for Mental Health, Cardiff University, Cardiff, Wales. [8] Eli Lilly and Company Limited, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, UK. [9] Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK. [10] Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark, Lyngby, Denmark. [11] Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children's Hospital, Boston, MA, USA. [12] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. [13] Department of Psychiatry, Diakonhjemmet Hospital, Oslo, Norway. [14] NORMENT, KG Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [15] Centre for Integrative Register-based Research, CIRRAU, Aarhus University, Aarhus, Denmark. [16] National Centre for Register-based Research, Aarhus University, Aarhus, Denmark. [17] The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark. [18] State Mental Hospital, Haar, Germany. [19]

Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA. [20] Department of Psychiatry and Behavioral Sciences, Atlanta Veterans Affairs Medical Center, Atlanta, GA, USA. [21] Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, USA. [22] Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA. [23] Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen, Germany. [24] Department of Medical Genetics, University of Pécs, Pécs, Hungary. [25] Szentagothai Research Center, University of Pécs, Pécs, Hungary. [26] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [27] Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA. [28] University Medical Center Groningen, Department of Psychiatry, University of Groningen, The Netherlands. [29] School of Nursing, Louisiana State University Health Sciences Center, New Orleans, LA, USA. [30] Athinoula A. Martinos Center, Massachusetts General Hospital, Boston, MA, USA. [31] Center for Brain Science, Harvard University, Cambridge MA, USA. [32] Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. [33] Department of Psychiatry, University of California at San Francisco, San Francisco, CA, USA. [34] University Medical Center Utrecht, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, The Netherlands. [35] Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [36] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [37] Centre Hospitalier du Rouvray and INSERM U1079 Faculty of Medicine, Rouen, France. [38] Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, CA, USA. [39] Schizophrenia Research Institute, Sydney, Australia. [40] School of Psychiatry, University of New South Wales, Sydney, Australia. [41] Royal Brisbane and Women's Hospital, University of Queensland, Brisbane, Australia. [42] Institute of Psychology, Chinese Academy of Science, Beijing, PR China. [43] Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, PR China. [44] Department of Psychiatry and State Ket Laboratory for Brain and Cognitive Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, PR China. [45] Department of Computer Science, University of North Carolina, Chapel Hill, NC, USA. [46] Castle Peak Hospital, Hong Kong SAR, PR China. [47] Institute of Mental Health, Singapore. [48] Department of Psychiatry, Washington University, St. Louis, MO, USA. [49] Department of Child and Adolescent

Psychiatry, Pierre and Marie Curie Faculty of Medicine and Brain and Spinal Cord Institute (ICM), Paris, France. [50] Formerly of Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Raritan, NJ, USA. [51] Department of Genetics, University of North Carolina, Chapel Hill, NC, USA. [52] Department of Psychological Medicine, Queen Mary University of London, UK. [53] Molecular Psychiatry Laboratory, Division of Psychiatry, University College London, UK. [54] Sheba Medical Center, Tel Hashomer, Israel. [55] Department of Genomics, Life and Brain Center, Bonn, Germany. [56] Institute of Human Genetics, University of Bonn, Bonn, Germany. [57] Applied Molecular Genomics Unit, VIB Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium. [58] Centre for Integrative Sequencing, iSEQ, Aarhus University, Aarhus, Denmark. [59] Department of Biomedicine, Aarhus University, Aarhus, Denmark. [60] First Department of Psychiatry, University of Athens Medical School, Athens, Greece. [61] Department of Psychiatry, University College Cork, Ireland. [62] Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. [63] Cognitive Genetics and Therapy Group, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Ireland. [64] Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, USA. [65] Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, IL, USA. [66] Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK. [67] Department of Child and Adolescent Psychiatry, University Clinic of Psychiatry, Skopje, Republic of Macedonia. [68] Department of Psychiatry, University of Regensburg, Regensburg, Germany. [69] Department of General Practice, Helsinki University Central Hospital, Helsinki, Finland. [70] Folkhälsan Research Center, Helsinki, Finland. [71] National Institute for Health and Welfare, Helsinki, Finland. [72] Translational Technologies and Bioinformatics, Pharma Research and Early Development, F.Hoffman-La Roche, Basel, Switzerland. [73] Department of Psychiatry, Georgetown University School of Medicine, Washington DC, USA. [74] Department of Psychiatry, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA. [75] Department of Psychiatry, Virginia Commonwealth University School of Medicine, Richmond, VA, USA. [76] Mental Health Service Line, Washington VA Medical Center, Washington DC, USA. [77] Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany. [78] Department of Genetics, University of Groningen, University Medical Centre Groningen, The Netherlands.

[79] Department of Psychiatry, University of Colorado Denver, Aurora, CO, USA. [80] Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, USA. [81] Department of Psychiatry, University of Halle, Halle, Germany. [82] Division of Psychiatric Genomics, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [83] Department of Psychiatry, University of Munich, Munich, Germany. [84] Departments of Psychiatry and Human and Molecular Genetics, INSERM, Institut de Myologie, Hôpital de la Pitiè-Salpêtrière, Paris, France. [85] Mental Health Research Centre, Russian Academy of Medical Sciences, Moscow, Russia. [86] Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Raritan, NJ, USA. [87] Queensland Brain Institute, The University of Queensland, Brisbane, Queensland, Australia. [88] Academic Medical Centre University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands. [89] Illumina, Inc., La Jolla, CA, USA. [90] Institute of Biological Psychiatry, MHC Sct. Hans, Mental Health Services Copenhagen, Denmark. [91] Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [92] JJ Peters VA Medical Center, Bronx, NY, USA. [93] Priority Research Centre for Health Behaviour, University of Newcastle, Newcastle, Australia. [94] School of Electrical Engineering and Computer Science, University of Newcastle, Newcastle, Australia. [95] Division of Medical Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland. [96] Department of Genetics, Harvard Medical School, Boston, MA, USA. [97] Section of Neonatal Screening and Hormones, Department of Clinical Biochemistry, Immunology and Genetics, Statens Serum Institut, Copenhagen, Denmark. [98] Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, Japan. [99] Regional Centre for Clinical Research in Psychosis, Department of Psychiatry, Stavanger University Hospital, Stavanger, Norway. [100] Rheumatology Research Group, Vall d'Hebron Research Institute, Barcelona, Spain. [101] Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, The Netherlands. [102] Centre for Medical Research, The University of Western Australia, Perth, Western Australia, Australia. [103] Perkins Institute for Medical Research, The University of Western Australia, Perth, Western Australia, Australia. [104] Department of Medical Genetics, Medical University, Sofia, Bulgaria. [105] Department of Psychology, University of Colorado Boulder, Boulder, CO, USA. [106] Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada. [107] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. [108]

Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada. [109] Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, Russia. [110] Latvian Biomedical Research and Study Centre, Riga, Latvia. [111] Department of Psychiatry and Zilkha Neurogenetics Institute, Keck School of Medicine at University of Southern California, Los Angeles, CA, USA. [112] Faculty of Medicine, Vilnius University, Vilnius, Lithuania. [113] 2nd Faculty of Medicine and University Hospital Motol, Prague, Czech Republic. [114] Department of Biology and Medical Genetics, Charles University Prague, Prague, Czech Republic. [115] Pierre and Marie Curie Faculty of Medicine, Paris, France. [116] Duke-NUS Graduate Medical School, Singapore. [117] Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel. [118] Centre for Genomic Sciences and Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, PR China. [119] Mental Health Centre and Psychiatric Laboratory, West China Hospital, Sichuan University, Chendu, Sichuan, PR China. [120] Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA. [121] Department of Psychiatry, Columbia University, New York, NY, USA. [122] Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia. [123] Department of Genetics and Pathology, International Hereditary Cancer Center, Pomeranian Medical University in Szczecin, Szczecin, Poland. [124] Department of Mental Health and Substance Abuse Services; National Institute for Health and Welfare, Helsinki, Finland. [125] Department of Mental Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA. [126] Department of Psychiatry, University of Bonn, Bonn, Germany. [127] Centre National de la Recherche Scientifique, Laboratoire de Génétique Moléculaire de la Neurotransmission et des Processus Neurodégénératifs, Hôpital de la Pitié Salpêtrière, Paris, France. [128] Department of Genomics Mathematics, University of Bonn, Bonn, Germany. [129] Research Unit, Sørlandet Hospital, Kristiansand, Norway. [130] Department of Psychiatry, Harvard Medical School, Boston, MA, USA. [131] VA Boston Health Care System, Brockton, MA, USA. [132] Department of Psychiatry, National University of Ireland Galway, Ireland. [133] Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, UK. [134] Division of Psychiatry, University of Edinburgh, Edinburgh, UK. [135] Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. [136] Massachusetts Mental Health Center Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Boston, MA, USA. [137] Estonian Genome Center, University of Tartu, Tartu, Estonia. [138]

School of Psychology, University of Newcastle, Newcastle, Australia. [139] First Psychiatric Clinic, Medical University, Sofia, Bulgaria. [140] Department P, Aarhus University Hospital, Risskov, Denmark. [141] Department of Psychiatry, Royal College of Surgeons in Ireland, Ireland. [142] King's College London, UK. [143] Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht, The Netherlands. [144] Institute of Translational Medicine, University Liverpool, UK. [145] Max Planck Institute of Psychiatry, Munich, Germany. [146] Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. [147] Department of Psychiatry and Psychotherapy, Jena University Hospital, Jena, Germany. [148] Department of Psychiatry, Queensland Brain Institute and Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, Australia. [149] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. [150] Department of Psychiatry, Trinity College Dublin, Ireland. [151] Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA. [152] Department of Clinical Sciences, Psychiatry, Umeå University, Umeå, Sweden. [153] DETECT Early Intervention Service for Psychosis, Blackrock, Dublin, Ireland. [154] Centre for Public Health, Institute of Clinical Sciences, Queens University Belfast, Belfast, UK. [155] Lawrence Berkeley National Laboratory, University of California at Berkeley, Berkeley, CA, USA. [156] Institute of Psychiatry at King's College London, London, UK. [157] Melbourne Neuropsychiatry Centre, University of Melbourne & Melbourne Health, Melbourne, Australia. [158] Department of Psychiatry, University of Helsinki, Finland. [159] Public Health Genomics Unit, National Institute for Health and Welfare, Helsinki, Finland. [160] Medical Faculty, University of Belgrade, Belgrade, Serbia. [161] Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA. [162] Institute for Molecular Medicine Finland, FIMM, Helsinki, Finland. [163] Department of Child and Adolescent Psychiatry, Erasmus University Medical Centre, Rotterdam, The Netherlands. [164] Department of Complex Trait Genetics, Neuroscience Campus Amsterdam, VU University Medical Center Amsterdam, Amsterdam, The Netherlands. [165] Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VU University, Amsterdam, The Netherlands. [166] Department of Epidemiology, Harvard University, Boston, MA, USA. [167] Department of Psychiatry, University of Oxford, Oxford, UK. [168] Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA. [169] Institute for Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY,

USA. [170] PharmaTherapeutics Clinical Research, Pfizer Worldwide Research and Development, Cambridge, MA, USA. [171] Department of Psychiatry and Psychotherapy, University of Gottingen, Göttingen, Germany. [172] Psychiatry and Psychotherapy Clinic, University of Erlangen, Germany. [173] Hunter New England Health Service, Newcastle, Australia. [174] School of Biomedical Sciences, University of Newcastle, Newcastle, Australia. [175] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA. [176] University of Iceland, Landspitali, National University Hospital, Reykjavik, Iceland. [177] Department of Psychiatry and Drug Addiction, Tbilisi State Medical University (TSMU), Tbilisi, Georgia. [178] Research and Development, Bronx Veterans Affairs Medical Center, New York, NY, USA. [179] Wellcome Trust Centre for Human Genetics, Oxford, UK. [180] deCODE Genetics, Reykjavik, Iceland. [181] Department of Clinical Neurology, Medical University of Vienna, Austria. [182] Lieber Institute for Brain Development, Baltimore, MD, USA. [183] Department of Medical Genetics, University Medical Centre, Utrecht, The Netherlands. [184] Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, The Netherlands. [185] Berkshire Healthcare NHS Foundation Trust, Bracknell, UK. [186] Section of Psychiatry, University of Verona, Verona, Italy. [187] Department of Psychiatry, University of Oulu, Finland. [188] Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland. [189] Health Research Board, Dublin, Ireland. [190] Department of Psychiatry, University Medical Center Groningen, University of Groningen, The Netherlands. [191] Department of Psychiatry and Clinical Neurosciences, School of Psychiatry and Clinical Neurosciences, Queen Elizabeth II Medical Centre, Perth, Western Australia, Australia. [192] Department of Psychological Medicine and Neurology, MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Cardiff, Wales, UK. [193] Computational Sciences CoE, Pfizer Worldwide Research and Development, Cambridge, MA, USA. [194] Human Genetics, Genome Institute of Singapore, A*STAR, Singapore. [195] WTCCC2. [196] University College London, UK. [197] Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [198] Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, Germany. [199] Department of Genetics, The Hebrew University of Jerusalem, Jerusalem, Israel. [200] Neuroscience Discovery and Translational Area, Pharma Research and Early Development, F.Hoffman-La Roche, Basel, Switzerland. [201] School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth, Australia. [202] The Perkins Institute of Medical Research, Perth, Australia. [203]

UWA Centre for Clinical Research in Neuropsychiatry. [204] Virginia Institute for Psychiatric and Behavioral Genetics, Departments of Psychiatry and Human and Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA. [205] The Feinstein Institute for Medical Research, Manhasset, NY, USA. [206] The Hofstra NS-LIJ School of Medicine, Hempstead, NY, USA. [207] The Zucker Hillside Hospital, Glen Oaks, NY, USA. [208] Saw Swee Hock School of Public Health, National University of Singapore, Singapore. [209] Queensland Centre for Mental Health Research, University of Queensland, Brisbane, Queensland, Australia. [210] Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, The Netherlands. [211] PEIC. [212] The Broad Institute of MIT and Harvard, Cambridge, MA, USA. [213] Center for Human Genetic Research and Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA. [214] Centre for Genomic Sciences, State Ket Laboratory for Brain and Cognitive Sciences, and Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, PR China. [215] University of Aberdeen, Institute of Medical Sciences, Aberdeen, Scotland, UK. [216] Departments of Psychiatry, Neurology, Neuroscience and Institute of Genetic Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA. [217] Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.

Wellcome Trust Case-Control Consortium 2

Management Committee: Peter Donnelly [179,218], Ines Barroso [219], Jenefer M Blackwell [220,221], Elvira Bramon [196], Matthew A Brown [222], Juan P Casas [223,224], Aiden Corvin [5], Panos Deloukas [219], Audrey Duncanson [225], Janusz Jankowski [226], Hugh S Markus [227], Christopher G Mathew [228], Colin N A Palmer [229], Robert Plomin [9], Anna Rautanen [179], Stephen J Sawcer [230], Richard C Trembath [228], Ananth C Viswanathan [231,232], Nicholas W Wood [233].

Data and Analysis Group: Chris C A Spencer [179], Gavin Band [179], Céline Bellenguez [179], Peter Donnelly [179,218], Colin Freeman [179], Eleni Giannoulatou [179], Garrett Hellenthal [179], Richard Pearson [179], Matti Pirinen [179], Amy Strange [179], Zhan Su [179], Damjan Vukcevic [179].

DNA, Genotyping, Data QC, and Informatics: Cordelia Langford [219], Ines Barroso [219], Hannah Blackburn

[219], Suzannah J Bumpstead [219], Panos Deloukas [219], Serge Dronov [219], Sarah Edkins [219], Matthew Gillman [219], Emma Gray [219], Rhian Gwilliam [219], Naomi Hammond [219], Sarah E Hunt [219], Alagurevathi Jayakumar [219], Jennifer Liddle [219], Owen T McCann [219], Simon C Potter [219], Radhi Ravindrarajah [219], Michelle Ricketts [219], Avazeh Tashakkori-Ghanbaria [219], Matthew Waller [219], Paul Weston [219], Pamela Whittaker [219], Sara Widaa [219].

Publications Committee: Christopher G Mathew [228], Jenefer M Blackwell [220,221], Matthew A Brown [222], Aiden Corvin [5], Mark I McCarthy [234], Chris C A Spencer [179].

Psychosis Endophenotype International Consortium

Maria J Arranz [156,235], Steven Bakker [101], Stephan Bender [236,237], Elvira Bramon [156,238,239], David A Collier [8,9], Benedicto Crespo-Facorro [240,241], Jeremy Hall [134], Conrad Iyegbe [156], Assen V Jablensky [242], René S Kahn [101], Luba Kalaydjieva [102,243], Stephen Lawrie [134], Cathryn M Lewis [156], Kuang Lin [156], Don H Linszen [244], Ignacio Mata [240,241], Andrew M McIntosh [134], Robin M Murray [142], Roel A Ophoff [80], Jim Van Os [143,156], John Powell [156], Dan Rujescu [81,83], Muriel Walshe [156], Matthias Weisbrod [237], Durk Wiersma [190].

[218] Department of Statistics, University of Oxford, Oxford, UK. [219] Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK. [220] Cambridge Institute for Medical Research, University of Cambridge School of Clinical Medicine, Cambridge, UK. [221] Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Subiaco, Western Australia, Australia. [222] Diamantina Institute of Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Brisbane, Queensland, Australia. [223] Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK. [224] Department of Epidemiology and Public Health, University College London, London, UK. [225] Molecular and Physiological Sciences, The Wellcome Trust, London, UK. [226] Peninsula School of Medicine and Dentistry, Plymouth University, Plymouth, UK. [227] Clinical Neurosciences, St George's University of London, London, UK. [228] Department of Medical and Molecular Genetics, School of Medicine, King's College London, Guy's Hospital, London, UK. [229] Biomedical Research Centre, Ninewells Hospital and

Medical School, Dundee, UK. [230] Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK. [231] Institute of Ophthalmology, University College London, London, UK. [232] National Institute for Health Research, Biomedical Research Centre at Moorfields Eye Hospital, National Health Service Foundation Trust, London, UK. [233] Department of Molecular Neuroscience, Institute of Neurology, London, UK. [234] Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK. [235] Fundació de Docència i Recerca Mútua de Terrassa, Universitat de Barcelona, Spain. [236] Child and Adolescent Psychiatry, University of Technology Dresden, Dresden, Germany. [237] Section for Experimental Psychopathology, General Psychiatry, Heidelberg, Germany. [238] Institute of Cognitive Neuroscience, University College London, London, UK. [239] Mental Health Sciences Unit, University College London, London, UK. [240] Centro Investigación Biomédica en Red Salud Mental, Madrid, Spain. [241] University Hospital Marqués de Valdecilla, Instituto de Formación e Investigación Marqués de Valdecilla, University of Cantabria, Santander, Spain. [242] Centre for Clinical Research in Neuropsychiatry, The University of Western Australia, Perth, Western Australia, Australia. [243] Western Australian Institute for Medical Research, The University of Western Australia, Perth, Western Australia, Australia. [244] Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

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Table 1. Conceptual overview of analyses of schizophrenia and smoking behaviors. PGC is Psychiatric Genomics Consortium, TAG is Tobacco and Genetics consortium, LD is linkage disequilibrium, SNP is single nucleotide polymorphism.

Research Question	Cohorts & Sample Sizes	Analysis
Question 1: Are there genetic correlations between schizophrenia and smoking behaviors?	*Primary* - PGC-Schizophrenia European ancestry: 35,476 cases, 46,839 controls; TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181, cessation 41,278, age of smoking onset 24,114	genetic correlation (LD score regression)
	Replication - PGC-Schizophrenia East-Asian ancestry: 1,836 cases, 3,383 controls	trans-ethnic genetic correlation (popcorn)
Question 2: Do polygenic risk scores for smoking behaviors also predict schizophrenia case status?	*Training Set* - TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181, cessation 41,278, age of smoking onset 24,114	polygenic risk scores (cross-trait association)
	Testing Set - PGC-Schizophrenia: 35,476 cases, 46,839 controls	
Question 3: What is the genetic architecture of smoking behavior among schizophrenia patients?		
3.1 What is the SNP-based heritability of smoking behaviors among schizophrenia cases?	PGC-Schizophrenia Phenotype Working Group - 10 study sites: smoking initiation 5,255, cigarettes-per-day 3,370	SNP-based heritability (LD score regression)
3.2 Are genetic factors for smoking behaviors shared between populations with and without schizophrenia?	PGC-Schizophrenia: smoking initiation 5,255, cigarettes-per-day 3,370; TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181	genetic correlation (LD score regression)
3.3 Do polygenic risk scores for smoking behaviors also predict these behaviors in schizophrenia patients?	*Training Set* - TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181	polygenic risk scores (within-trait across-cohort association)
	Testing Set - PGC-Schizophrenia: smoking initiation 5,255, cigarettes-per-day 3,370	
3.4 Are there schizophrenia-specific genetic risk variants for smoking behaviors?	*Primary* - PGC-Schizophrenia: smoking initiation 5,255, cigarettes-per-day 3,370	genome-wide association study meta-analysis of smoking behaviors among schizophrenia cases
	Replication - Janssen Pharmaceuticals: smoking initiation 1802, cigarettes-per-day 1802	

Question 4: Are there associations between smoking behaviors and clinical features of schizophrenia?		
4.1 Are smoking behaviors among schizophrenia cases associated with clinical presentation of schizophrenia?	PGC-Schizophrenia: smoking initiation 5,255, cigarettes-per-day 3,370, age-schizophrenia-onset 4,658; symptom dimension factor scores: positive 3,846, negative 3,845, manic 3,740, depression 3,740	phenotypic associations (linear/logistic regression)
4.2 Do polygenic risk scores for smoking behaviors predict schizophrenia symptom dimensions?	*Training Set* - TAG-Smoking behaviors: smoking initiation 74,035, cigarettes-per-day 38,181	polygenic risk scores (across-trait across-cohort association)
	Testing Set - PGC-Schizophrenia: age-schizophrenia-onset 11,600; symptom dimension factor scores: positive 8,330, negative 8,427, manic 6,965, depression 6,964	

Tables

Table 2. Sample characteristics for each PGC2-SCZ cohort.

Cohort	*N SCZ-cases*	*Sex % female*	Age (mean)	*N* % SI	*N CPD*
boco	756	43.5%	36.7	538 77.3%	185
cims	37	16.2%	33.3	33 66.7%	23
cou3	513	39.2%	44.2	501 75.0%	278
egcu	234	26.9%	46.5	234 52.6%	123
lie2	133	28.6%	36.9	128 60.2%	69
lie5	497	25.7%	36.6	479 63.3%	285
mgs2	2348	30.5%	43.5	2227 78.8%	1674
munc	420	36.4%	37.9	406 74.4%	301
top8	344	43.6%	33.0	320 57.5%	176
ucla	450	23.8%	34.7	389 70.7%	256
TOTAL	6183	6183	6132	5255	3370

Note: PGC = Psychiatric Genomics Consortium, SCZ - schizophrenia, Age = age at assessment, SI = smoking initiation, CPD = cigarettes per day.

Table 3. Genetic correlations between TAG and PGC-SCZ phenotypes.

Trait 1	*Discovery*			*Replication*		
	Trait 2	***r_g* (se)**	***P***	***Trait 2***	***r_g* (se)**	***P'***
SI_{TAG}	SCZ_{EUR}	0.159 (0.026)	5.05×10^{-10}	SCZ_{EAS}	0.040 (0.124)	0.744
CPD_{TAG}	SCZ_{EUR}	0.094 (0.034)	0.006	SCZ_{EAS}	-0.080 (0.161)	0.619
$logOnset_{TAG}$	SCZ_{EUR}	0.100 (0.038)	0.009	SCZ_{EAS}	0.463 (0.251)	0.064
$Cessation_{TAG}$	SCZ_{EUR}	-0.076 (0.035)	0.032	SCZ_{EAS}	-0.051 (0.193)	0.793
SI_{TAG}	$SI_{SCZ,EUR}$	0.624 (0.202)	0.002	·	·	·
CPD_{TAG}	$CPD_{SCZ,EUR}$	0.689 (0.443)	0.120	·	·	·

For each pair of traits, r_g is the estimated genetic correlation; *P* is the significance of $r_g \neq 0$; *P'* is a 1-sided test of whether $r_g>0$ or $r_g<0$ in the replication sample. For comparisons of TAG phenotypes to SCZ risk, *EUR* and *EAS* denote European and East-Asian cohorts.

Table 4. Association results for top SNP associations.

Trait	Chr	SNP	A1/ A2	*Discovery*			*Replication Phase*		Combined P	Gene (+/-Kb)
				Frq Info	Z	P *n*	*Z*	P *n*		
SI	1	rs58215884	T/G	0.162 0.975	4.53	5.9×10^{-6} 4991	2.09	0.037 1776	6.8×10^{-7}	*FCRL2* (+7.2)
	5	rs1592907	A/G	0.454 0.983	-4.44	9.2×10^{-6} 4991	-2.19	0.029 1760	8.5×10^{-7}	*FBXL17* (+91.2)
	9	rs117381175	T/C	0.031 0.792	-4.55	5.3×10^{-6} 4991	-2.29	0.022 1746	6.9×10^{-7}	intergenic
	13	rs754168	A/C	0.352 0.767	-4.85	1.2×10^{-6} 4991	-1.57	0.116 1277	4.6×10^{-7}	*LINC01044* (0)
CPD	1	rs3896119	A/G	0.018 0.832	4.77	1.9×10^{-6} 3321	1.45	0.148 1078	5.0×10^{-7}	intergenic
	1	rs1210	T/C	0.028 0.745	5.06	4.2×10^{-7} 3321	2.11	0.034 1052	5.2×10^{-8}	*RGS8* (+4.7)
	2	rs1900325	T/C	0.479 0.924	5.32	1.1×10^{-7} 3344	0.18	0.854 1011	2.0×10^{-6}	*CBWD2* (-39.4)
	3	rs833663	A/G	0.038 0.982	4.58	4.7×10^{-6} 3344	2.07	0.038 1097	4.7×10^{-7}	*CADPS* (0)
	7	rs148253479	A/C	0.988 0.694	-4.89	1.0×10^{-6} 2442	-2.54	0.011 1078	3.2×10^{-8}	*TMEM106B* (-22.6)

SI is smoking initiation, CPD is cigarettes-per day, SNP and Chr information for build hg19; INFO is the statistical imputation information; Freq is the frequency of the reference (first listed) allele, and *Z* is its estimated standardized effect; *P* is the *P*-value for association; *n* is the sample size. The nearest gene within 100Kb is shown; its position relative to a gene is given parenthetically and with respect to direction of transcription (negative and positive kb values indicate up- and downstream positions).

Table 5. Association of smoking variables with clinical features in SCZ.

	Smoking initiation			Cigarettes per day		
	N	*β* (SE)	*P*	*N*	*β* (SE)	*P*
Sex	4991	-0.507 (0.069)	1.38×10^{-13}	3344	-0.210 (0.073)	0.004
Age	4991	-0.005 (0.003)	0.061	3344	0.018 (0.003)	5.53×10^{-10}
Age-of-onset	4658	-0.098 (0.038)	0.009	3168	-0.022 (0.021)	0.289
Positive	3846	0.157 (0.038)	3.23×10^{-5}	2796	0.071 (0.029)	0.015
Negative	3845	0.046 (0.038)	0.225	2794	-0.003 (0.029)	0.929
Mania	3740	0.034 (0.038)	0.367	2736	0.019 (0.019)	0.305
Depression	3740	-0.013 (0.038)	0.728	2735	0.047 (0.019)	0.014

For SCZ Age-of-onset and symptom factor scores, *N* is the number of subjects with non-missing data for both traits; *β* and SE are the beta regression coefficient and standard error from logistic or linear regression; *P* is the significance of the association between a given pair of traits.