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Abstract

Importance—Although early mortality in severe psychiatric illness is linked to smoking and alcohol, no studies have comprehensively characterized substance use behavior in severe psychotic illness. In particular, recent assessments of substance use in individuals with mental illness are based on population surveys that do not include individuals with severe psychotic illness.

Objective—To compare substance use in individuals with severe psychotic illness to substance use in the general population.

Design—We assessed comorbidity between substance use and severe psychotic disorders in the Genomic Psychiatry Cohort (GPC). The GPC is a clinically assessed, multi-ethnic sample consisting of 9,142 individuals with the diagnosis of schizophrenia, bipolar disorder with psychotic features, or schizoaffective disorder, and 10,195 population controls.

Primary Outcome Measures—Smoking (smoked > 100 cigarettes lifetime), heavy alcohol use (> 4 drinks/day), heavy marijuana use (>21 times of marijuana use in a single year), and recreational drug use.

Results—Relative to the general population, individuals with severe psychotic disorders have increased risk of smoking (OR 4.6, 95% CI 4.3-4.9), heavy alcohol use (OR 4.0, 95% CI 3.6-4.4), heavy marijuana use (OR 3.5, 95% CI 3.2-3.7), and recreational drug use (OR 4.6, 95% CI 4.3-5.0). All ethnicities (African American, Asian, European American, and Hispanics) and both sexes have greatly elevated risks of smoking, alcohol, marijuana, and drug use. Of specific concern, recent public health efforts that have successfully decreased smoking among individuals under age 30 appear to have been ineffective among individuals with severe psychotic illness (p-value for interaction effect between age and severe mental illness on smoking initiation $P=4.5 \times 10^{-5}$).

Conclusions and Relevance—In the largest assessment of substance use among individuals with severe psychotic illness to date, we found odds of smoking, alcohol, and other substance use to be dramatically higher than recent estimates of substance use in mild mental illness.

Individuals with severe mental illness die approximately 25 years earlier than the general population and the cause of this early death is largely due to medical illness that can be attributed to substance use disorders [1-3]. For example, although suicide and injury are more common among individuals with chronic mental illness, 60% of premature deaths in persons with schizophrenia are due to medical conditions including heart and lung disease and infectious illness caused by modifiable risk factors such as smoking, alcohol consumption, and IV drug use[1]. In addition to early mortality, the severity and prognosis of the primary mental illness is worsened in the context of substance dependence [4,5].

The 2009-2011 National Survey on Drug Use and Health (NSDUH) identified adults with mental illness (based on 14-items related to psychological distress and disability) and found that 36% of adults with mental illness are current smokers, relative to 21% of adults without mental illness [6]. In addition, they found that adult smokers with mental illness are less likely to quit than adult smokers without mental illness. This discrepancy highlights the public health disparity in the mentally ill, a uniquely vulnerable population.

In addition to increased smoking among individuals with mental illness, alcohol and other substance use disorders have increased prevalence in individuals with mental illness [7-17]. Several large epidemiological surveys have assessed comorbidity of affective and psychotic illness with tobacco, alcohol and drug use disorders in the general population [8,9,12,16,18-20]. In these studies, alcohol and drug dependence were found to be more than twice as common among individuals with anxiety disorders, affective disorders, and psychotic disorders[9,10,13,16,21]. There is also evidence that associations between substance use/dependence and other psychiatric illness are true for both men and women [18], and extend to African Americans [22] and Hispanics [7].

Despite strong epidemiological studies of the general population showing increased comorbidity of smoking, alcohol, and drug use in mental illness, these studies do not address comorbidity of smoking, alcohol and drug use in severe psychotic illness. Not only is severe psychotic illness rare in the general population, but individuals with severe psychotic illness are difficult to contact in general population surveys, and so there is no large-scale survey of substance use among clinically ascertained individuals with severe psychotic illness. Specifically, it is unknown whether the rates of substance use among individuals with mild mental illness, as ascertained in population surveys, apply to individuals with severe psychosis. To address this issue, we assessed substance use in a large, multi-ethnic sample of individuals with schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features, and corresponding population controls. Using this powerful sample, we are able to not only gain insight into substance use among individuals with severe psychosis, but also determine the differences in substance use between genders, and racial/ethnic subgroups.

Methods

The Genomic Psychiatry Cohort (GPC) program is a multi-institutional collaboration [23]. This resource includes a NIMH managed repository of genomic samples and detailed clinical and demographic data for investigations of schizophrenia and bipolar disorder. The current sample consists of 9,142 individuals with either the diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features, and 10,195 population controls. Individuals with bipolar disorder without psychotic features represented a relatively small subgroup (n=621) and are therefore not included in these analyses.

Psychiatric diagnoses

Individuals were collected through 12 clinical collaborating sites across the United States. All individuals ascertained to the GPC completed a screening questionnaire eliciting demographic (e.g., race, ethnicity, gender) data as well as a brief personal and family

psychiatric and medical history. Individuals with psychotic illness were ascertained as in-patients in acute care or chronic care facilities, and out-patient settings. Control subjects were drawn from the same geographic area as cases, either within health care facilities or as community volunteers recruited from internet advertising or community groups (e.g. church congregations, health fair attendees) and screened to ensure absence of schizophrenia or bipolar disorder within themselves and their first degree relatives.

To confirm the psychiatric diagnoses, case subjects were interviewed by trained clinicians using a structured psychiatric interview instrument, the Diagnostic Interview for Psychosis and Affective Disorder (DI-PAD). The DI-PAD is based on the Diagnostic Interview for Genetic Studies (DIGS[24]) and includes 90 phenomenological symptom items that are used with the Operational Criteria Checklist (OPCRIT) computer algorithm [25] to arrive at diagnoses using Diagnostic and Statistical Manual of Mental Disorders (DSM)[26]). Clinicians confirmed diagnoses for schizophrenia, schizoaffective disorder, or bipolar disorder with psychosis based on DSM-IV criteria.

Substance use measurements

As part of the screening questionnaire, a set of questions were asked of all participants regarding the individual's substance use. The questions were adapted from the DIGS [24], and other validated instruments [27,28].

1. Do you often have more than 4 drinks in one day?

2. Over your lifetime, have you smoked more than 100 cigarettes?

3. Have you ever had a period of one month or more when you smoked cigarettes every day?

4. Have you ever smoked marijuana more than 21 times in a single year?

5. Have you ever used recreational (street) drugs [other than marijuana] or prescription drugs more than 10 times to feel good or get high?

Epidemiological Sample

To benchmark our sample with epidemiological studies, we looked at items in the National Survey on Drug Use and Health (NSDUH), a population-based epidemiological survey on substance use [29]. Because the controls used for this dataset were drawn almost exclusively from the Los Angeles area, we restricted the surveyed data to subjects age 20-55 from California. We used the following items, directly corresponding to the substance use measurements in the GPC:

1. During the past 30 days ... on how many days did you have 5 or more drinks on the same occasion (DR5DAY)? [an answer of > 3 (weekly or more) was used to correspond to GPC item 1]

2. Have you smoked 100 cigarettes in your entire life (CIG100LF)?

3. Has there ever been a period in your life when you smoked cigarettes every day for at least 30 days (CIGDLYMO)?

4. Total # of days used marijuana in the past 12 months (MJYRTOT). [an answer of > 0 was used to correspond to GPC item 4]

5. Illicit drug use (except marijuana), past year (IEMYR).

Statistical analysis

The goal of this study is to evaluate substance use in individuals with chronic psychotic disorders (cases) as compared to population controls. With the 5 measures listed above as independent variables, we used logistic regression to model the probability of substance use based on case/control status, adjusted for race & ethnicity, gender, age (< age 30, age 30-49, or age 50), and recruitment site. We also evaluated whether there are significant interactions on substance use between case control status and race & ethnicity, gender, or age. All analyses were performed using SAS 9.2 for Windows[30].

Results

Table 1 compares the demographics of the sample across controls and the four psychiatric diagnoses that constitute our sample of individuals with chronic psychotic disorder: schizophrenia, schizoaffective disorder depressed subtype, schizoaffective disorder bipolar subtype, and bipolar disorder with psychotic features. The sample used for this study is a multi-ethnic sample, including African Americans, Asians, European Americans and Hispanics. There are more female subjects with bipolar disorder than with schizophrenia (p<0.001). There is a wide age range among all individuals, although cases are older than the controls in this sample (p<0.001). Therefore, further analyses evaluate associations between the severe psychotic disorders and substance use only after adjusting for race/ethnicity, age, and gender.

The prevalence of various measures of substance use are much higher among individuals with schizophrenia, schizoaffective disorder (both depressed and bipolar subtype), and bipolar disorder with psychotic features (Table 2). For ease of interpretation, we classified individuals with schizophrenia, schizoaffective disorders, and bipolar disorder with psychotic features as "cases with severe psychotic disorder," and analyzed substance use with respect to case/control status. The prevalence of these measures is uniformly high in individuals with severe psychotic illness relative to the control populations. The odds ratio of cases versus controls for each measure of substance use is given in Table 3. Overall, the smoking measures were more strongly associated with case/control status than alcohol or other drugs, with estimated odds ratios of 4.61 for smoking >100 cigarettes (p < 1.0 E-325), and 5.11 for daily smoking >1 month (p<1.0 E-325). The estimated odds ratios for alcohol use (OR 3.96, p=1.2 E-188), marijuana use (OR 3.47, p=2.6 E-254), and recreational drug use (OR 4.62, p<1.0 E-325) were also highly clinically and statistically significant.

Although the prevalence of measures of substance use across gender, race/ethnic group, and age group varies, it is markedly higher among individuals with psychotic illness within each group. We tested whether the association between substance measures and case/control status is stronger within each group (i.e. whether there is a statistical interaction between case/control status and group). All the items measured showed similar patterns of

association. For illustrative purposes, Figure 1 illustrates select associations between substance use and severe psychosis. In groups where the controls had lower rates of substance use (Asians and Hispanics relative to European Americans, females relative to males, and individuals under age 30 relative to 30-50 year olds), the odds ratios were significantly higher than the reference odds ratios, leading to statistically significant interaction effects. This suggests that although belonging to certain groups may be protective for substance use in the control population, this protective effect is lost with the development of a severe mental illness. For example women are at lower risk for using recreational drugs in the general population (7% of women versus 18% of men in the general population have used recreational drugs at least 10 times), but the rates of recreational drug use are much more comparable between men and women among individuals with severe psychosis (37% of women versus 45% of men with severe psychosis have used recreational drugs at least 10 times).

Discussion

Individuals with severe mental illness bear an enormous burden due to smoking, alcohol and drug use. In a large, multi-ethnic sample we found substance use among individuals with severe psychotic disorder to be markedly higher than in population controls at a rate that far exceeds previous estimates based on assessments in individuals with mild mental illness [6]. This association extends across substances (alcohol, smoking, and other drugs), across psychiatric diagnosis (bipolar disorder, schizoaffective disorder, and schizophrenia), across race and ethnicity (African American, Hispanic, Asian, and European American), across genders, and across age groups. This is the first large-scale study to robustly demonstrate these associations across subgroups. Although substance use among individuals with psychotic disorders has been documented [12,13,20,31], this study shows that there is a continuing pressing need to target smoking, alcohol, marijuana, and drug use among individuals with severe mental illness.

The most striking finding of this study is the evidence that societal-level protective effects do not extend to individuals with severe mental illness. Specifically, we found that among groups with lower than average rates of substance use (Hispanics and Asians relative to European Americans, and females relative to males), the protective effects of belonging to these groups did not carry over to individuals with severe psychotic disorder: the odds of substance use increased to mitigate the protective effects. For example, relative to non-Hispanic whites, individuals of Hispanic ethnicity have lower rates of heavy alcohol use in controls (5.7% of n=3,424 in Hispanics, 8.1% of n=3,748 in non-Hispanic European Americans, p<0.0001). However, individuals of Hispanic descent with severe psychotic illness have *higher* rates of heavy alcohol use than non-Hispanic European Americans (28.8% of n=1,583 in Hispanics, 27.3% of n=4,343 in non-Hispanic whites, p=0.001). This highlights the need for targeting substance use specifically among individuals with severe psychotic illness, as protective influences may not carry over from the general population.

The strongest associations between severe psychotic illness and substance use were seen with cigarette use. This is notable because most of the mortality seen in severe psychiatric illness is due to smoking related disorders. Also, it appears that recent public health efforts

that have successfully decreased smoking in the general population have not been effective in individuals with severe psychotic disorder. Specifically, the decrease in smoking among individuals under age 30 that has been seen among the general population [32] and is present in the controls in this dataset does not extend to cases: the OR of smoking daily for a month or more is 8.2 among individuals younger than 30, which is significantly higher than the OR of 5.2 among individuals age 30-49, and the OR of 3.9 among individuals age 50 or older (interaction p=4.5×10^{-5}). Given that (1) early mortality in cases is largely due to cardiovascular and pulmonary disease, and (2) many psychotropic medications used to treat psychotic symptoms have severe metabolic side effects that increase the risk of diabetes and cardiovascular disease, it is imperative that we specifically target smoking in these individuals. This is consistent with relatively recent calls for the field of psychiatry to specifically target smoking in severe mental illness[15].

Although these data illuminate characteristics of substance use in psychotic disorders in a large, multi-ethnic population, further study is required to better understand the nature of the comorbidity between psychotic disorders and substance dependence. The first step is to specifically evaluate comorbid substance dependence in individuals with severe psychotic illness, rather than individual measures of use as assessed in this study. In addition, the validity and reliability of this series of questions has not been established in any population. However, this series of questions was extracted from the DIGS, a standardized instrument with high test/retest validity and reliability. A further limitation of this study is that it is not a population survey. Because the individuals were not randomly sampled, there may be biases in the dataset that limit extrapolation of the rates of substance use to the general populations of both cases with severe psychotic illness and controls without a personal or family history of bipolar disorder or schizophrenia. However, the sample was not selected for substance use, so therefore the odds ratios of substance use for cases versus controls should be accurate.

Nicotine, alcohol and other drugs of abuse target dopaminergic, glutamatergic, and GABAergic transmission, which are also involved in the pathophysiology of severe mental illness. Specifically, nicotine can increase the metabolism of anti-psychotics by activation of the cytochrome P450 enzymes [33], and is thus hypothesized to help reduce side effects of individuals taking antipsychotics. Conversely, exposure to substances increases risk of severe mental illness: marijuana use at age 16 is associated with psychosis at age 19 [34], and smoking precedes the onset of symptoms of mental illness [35,36]. Additionally, substance use leads to higher rates of psychiatric emergencies and hospitalizations [37]. This highlights the importance of understanding the biological connection between substance use and severe mental illness.

In summary, the prevalence of substance use in severe psychosis has been underestimated, and spans social and cultural strata. This is the largest study of substance use in individuals with severe psychotic illness to date. The study not only highlights the comorbid pathology of substance use among those with severe psychotic illness, it also suggests that public health efforts to reduce substance use have not been successful in one of our most vulnerable populations, individuals with severe psychotic illness. It is time to use our recent scientific

and public health advancements to improve scientific understanding of the comorbidity between substance use and psychotic disorders, and improved treatment of both.

Acknowledgments

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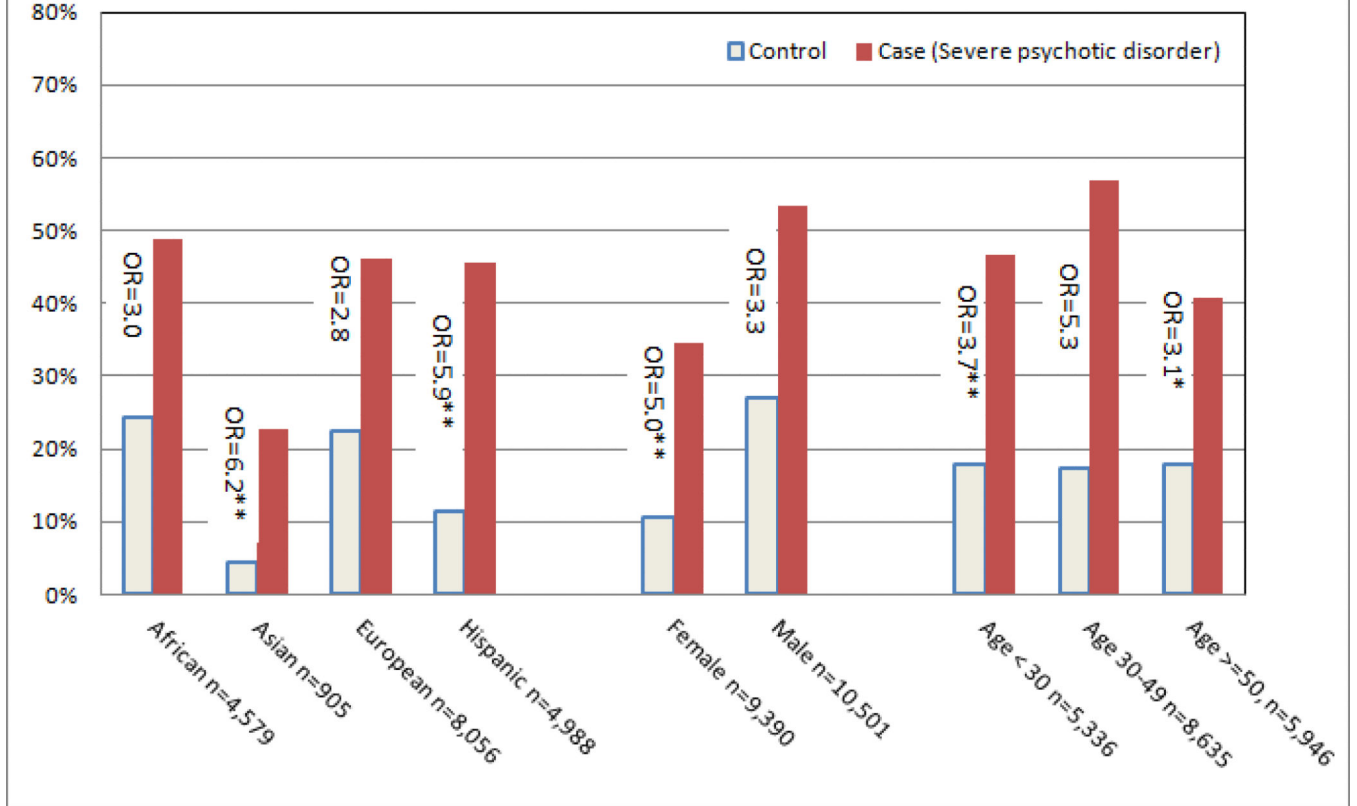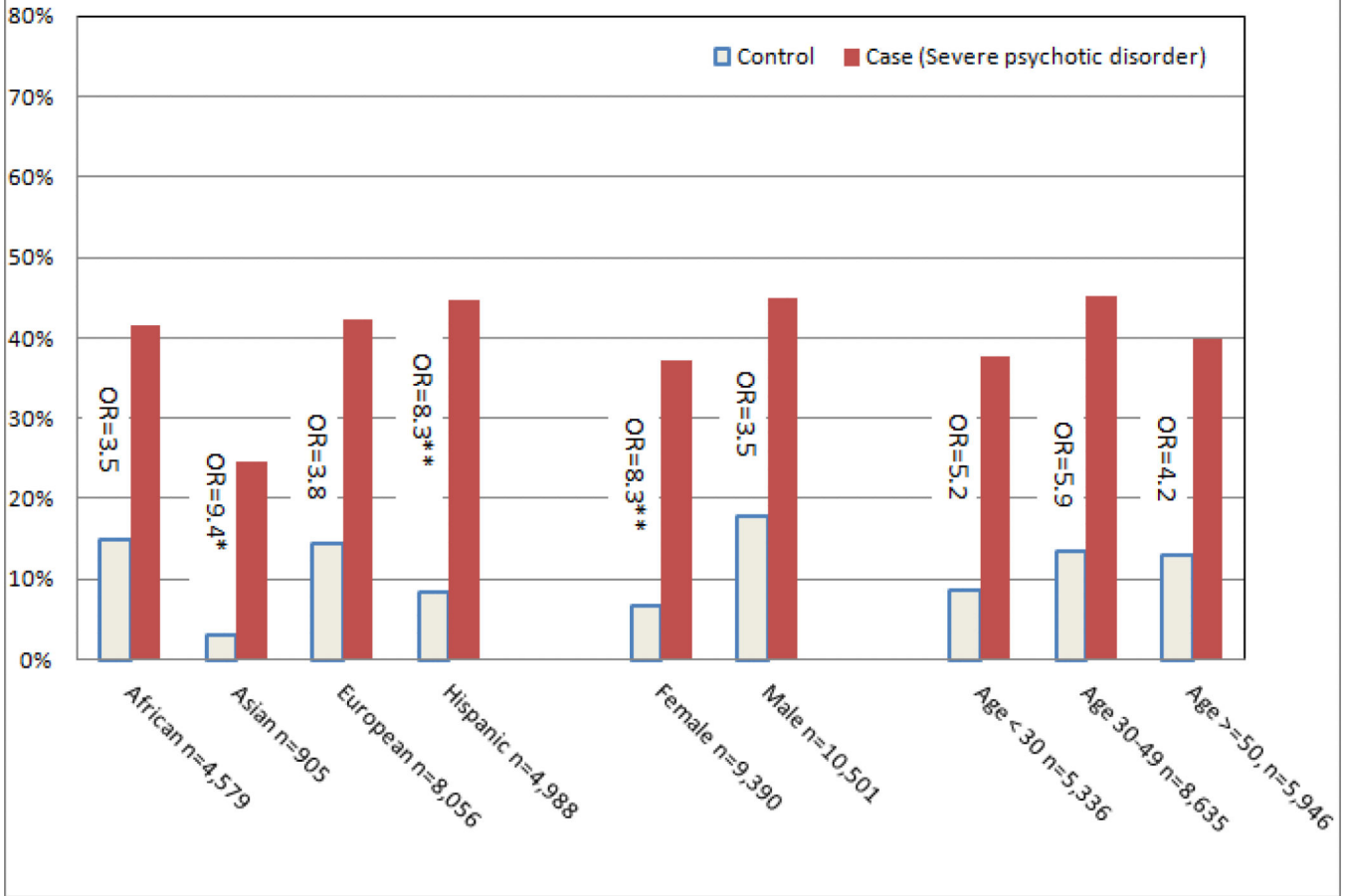
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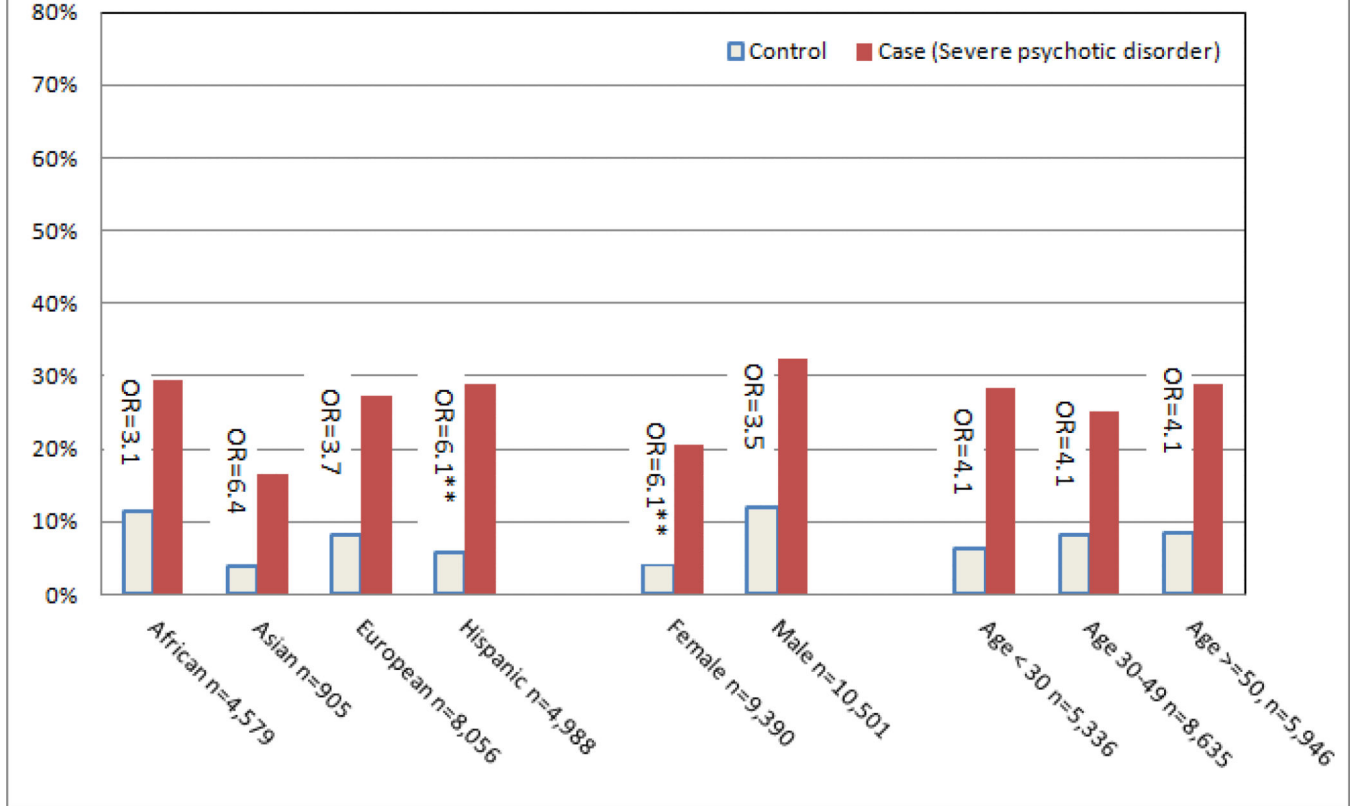
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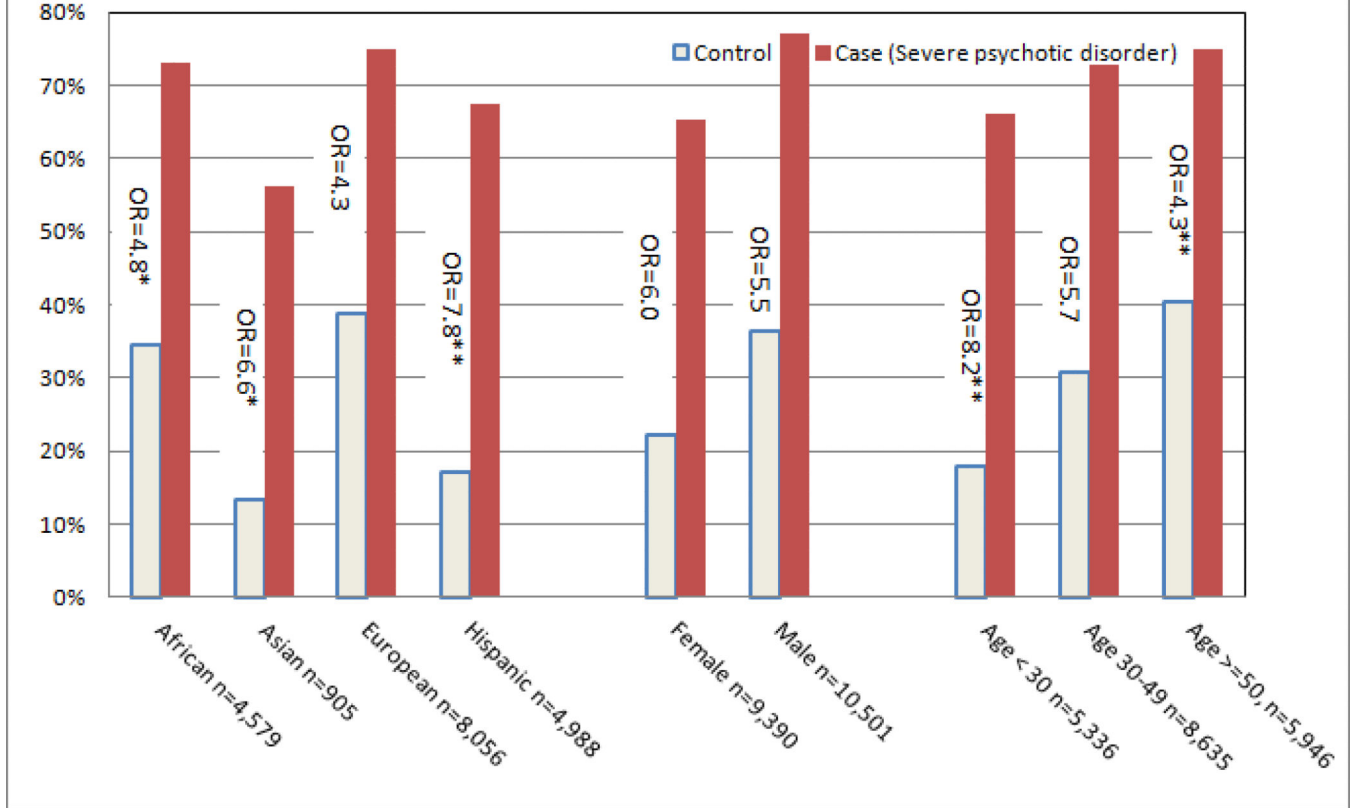
C. Marijuana use > 21 times in a single year

Figure 1.
Frequency of alcohol (Figure 1A), smoking (Figure 1B), marijuana (Figure 1C) and other drug (Figure 1D) use contrasted among subgroups. Odds ratios correspond to odds of the prevalence of the symptom among cases with chronic psychotic illness versus controls. The OR's are contrasted with one another. When an OR is statistically different from the reference (European descent for ethnicity, male for gender, and 30-49 for age group), this is indicated by * (p<0.05) or ** (p<0.001).

Table 1

Sample Characteristics

	Bipolar with psychosis	Schizoaffective bipolar subtype	Schizoaffective depressed subtype	Schizophrenia	Controls	NSDUH Population survey
N	1,507	1,486	552	5,586	10,311	18,612
Hispanic	18%	19%	14%	15%	34%	37.9%
African American	18%	24%	30%	35%	17%	6.2%
Asian	2%	2%	1%	2%	7%	--
European American	55%	46%	49%	39%	37%	40%
mixed race	4%	4%	2%	3%	2%	--
% female	51%	42%	45%	30%	56%	49%
% male	49%	58%	55°%	70%	44%	51%
Age						
Average	43	44	44	44	38	38
25th percentile	33	35	35	35	25	28
75th percentile	51	52	52	53	49	47

Table 2

Prevalence of substance use measures across psychiatric diagnoses.

	Bipolar w/Psychosis	Schizophrenia	Schizoaffective-Bipolar	Schizoaffective-Depressed	Controls	NSDUH Population survey
N	1,501	5,582	1,482	555	10,194	18,290
Alcohol > 4/day	26%	28%	29%	30%	8%	9.5%
100 cigarettes	74%	74%	80%	75%	33%	34%
daily smoking > 1 month	71%	72%	79%	73%	29%	29%
Marijuana > 21xs in a year	52%	43%	54%	49%	18°%	16%
Recreational drugs > 10xs	53%	35%	54%	45%	12%	10%

Table 3

Prevalence of substance use measures compared between cases with chronic psychotic illness and controls. ORs are calculated from logistic regression modeling probability of symptom as a function of diagnosis, adjusted for gender, race, age, and data collection site.

		OR			
	N	estimate	95% CI lower	95% CI upper	P
Alcohol > 4 /day	19,878	3.96	3.61	4.35	1.2×10^{-188}
100 cigarettes	19,931	4.61	4.31	4.94	$< 1.0 \times 10^{-325}$
daily smoking > 1 month	19,882	5.11	4.78	5.46	$< 1.0 \times 10^{-325}$
Marijuana > 21xs in a year	19,859	3.47	3.23	3.72	2.6×10^{-254}
Recreational drugs > 10xs	19,864	4.62	4.27	4.99	$< 1.0 \times 10^{-325}$