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Do Sex Differences Among Adults With Opioid Use Disorder Reflect Sex-specific Vulnerabilities? A Study of Behavioral Health Comorbidities, Pain, and Quality of Life

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Abstract

Objectives: Studies suggest that men and women have different vulnerabilities to a number of substance use disorders (SUDs). We examined whether differences between women and men with opioid use disorder (OUD) are significantly different from those without OUD for selected sociodemographic and health outcomes.

Methods: We used a cross-sectional survey design using data from 2012 to 2013 National Epidemiological Survey on Alcohol and Related Conditions Wave III, which surveyed nationally representative samples of non-institutionalized adults (n = 36,309 unweighted). Past-year OUD and other behavioral co-morbidities were defined using DSM-5 criteria. In bivariate analyses, we investigated sex differences in socio-demographic factors, behavioral co-morbidities, pain, and health-related quality of life (HRQOL) between women and men with past-year OUD, and then

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those without past-year OUD. We further used logistic regression analyses to evaluate interactions between effect of sex and past-year OUD status on behavioral co-morbidities, pain, and HRQOL.

Results: When extrapolated, about 2.1 million US adults met diagnostic criteria for past-year OUD. Women with OUD had a higher likelihood of having several past-year psychiatric disorders, and a lower likelihood of having any past-year SUDs compared to male counterparts. However, similar relationships were observed among those without OUD and significant interaction effects were not found on behavioral co-morbidities, pain, and HRQOL, indicating that general sex differences are not specific to OUD.

Conclusions: Although sex differences are not specific to OUD, concurrent disorders are not uncommon among women, as well as men, with OUD. There is a need to treat concurrent behavioral health conditions from a multimorbidity perspective in the treatment of OUD in both sexes.

Keywords

co-morbidities; opioid use disorder; pain; quality of life; sex disparities

Opioid use disorder (OUD) and overdose deaths represent a significant public health crisis in the US, with recent data showing that over 2 million individuals have an OUD and approximately 130 individuals die daily from opioid-related drug overdoses.[1,2] Although opioid use is more prevalent among men than women, women use heroin at increasing rates with concurrent increases in rates of opioid-related overdose deaths.[3] Given this evidence, there is a need to examine sex differences across the progression of OUD, including its initiation, maintenance, and treatment as well as prevention efforts.[4-6]

Among the hypothesized sex-sensitive factors for OUD are the role of psychiatric and substance use comorbidities, as well as pain experience among women,[4] and the subsequent impact of such experiences on quality of life. It has been previously observed that women with substance use disorders (SUDs), including OUD, have higher prevalence of psychiatric co-morbidities, specifically mood and anxiety disorders than men, while men with any SUDs have greater odds of co-occurring SUDs.[7-9] Additionally, women are reported to experience greater sensitivity to pain and higher prevalence of chronic pain than men, and studies have suggested that women are more likely than men to use opioids to manage both pain and increased psychological distress from concurrent psychiatric disorders.[4,8,10,11]

Furthermore, research suggests that women with any SUDs frequently report greater overall functional impairment than men across employment, social/family, and medical/psychiatric domains.[8,9,12] For instance, 1 study reported that in a sample of patients in methadone treatment, women reported more unmet needs and lower quality of life in several functional domains than men.[13] In another study of patients dependent on prescription opioids, while both sexes demonstrated overall diminished physical and mental quality of life, women had poorer mental quality of life than men.[14] The relationship between opioid use and both poor functioning and lower quality of life has been hypothesized to reflect their higher pain sensitivity and depressive symptoms,[7-10] both suggested to be more prevalent in women than men with any SUDs, and both associated with poorer health-related quality of life.[15]

However, while such differences between men and women with OUD have been previously examined, it is not clear whether the identified sex differences are specific to adults with OUD or represent more generally prevalent differences between men and women that occur regardless of the presence of OUD (ie, observed throughout the population). Further, studies have not yet examined whether differences between women and men with OUD are significantly different from differences between women and men without OUD.

Accordingly, the present study hypothesized that, as in previous studies, women with OUD would have increased likelihood of mood and anxiety disorders, self-reported pain and poorer quality of life than men with OUD, while men, would have increased likelihood of concurrent SUDs. In addition to confirming these previously observed sex differences among adults with OUD, we further hypothesized that these differences between women and men with past-year OUD would be magnified among those with OUD and would therefore be less pronounced, although still present, among adults without OUD. Accordingly, we, first compared women and men with OUD to each other, and then compared women and men without OUD in order to evaluate the significance and magnitude of sex differences between those with and without OUD. Finally, we conducted a series of analyses testing the significance of the interaction of OUD and sex to determine whether the magnitude of male-female differences differed in the hypothesized directions among those with and without OUD.

METHODS

Data Source and Study Sample

The present study used data from the National Epidemiological Survey on Alcohol and Related Conditions Wave III (NESARC-III).[16,17] Sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), NESARC-III was a nationally representative survey, conducted from April 2012 through June 2013, that collected comprehensive information regarding physical and mental health diagnoses, well-being and disabilities among non-institutionalized civilian adults aged 18 or older with a focus on alcohol and other substance use disorders among non-institutionalized civilians aged 18 or older in the US.[17,18] In this study, we grouped our sample in 4 groups by sex and by past-year OUD status, based on the criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (DSM-5)[19]: (1) male adults with OUD (n = 154 unweighted); (2) female adults with OUD (n = 176 unweighted); (3) male adults without OUD (n = 15,708 unweighted); and (4) female adults without OUD (n = 20,271 unweighted). We did not include past-year heroin use disorder (n = 41), which is distinct from OUD in NESARC, because 36.6% (n = 15) of those with heroin use disorder also met criteria for past-year OUD and the sample size for heroin use disorder alone would have been too small (n = 26) for analyses. The overall survey response rate of NESARC-III was 60.1%.[16,17] Further details of the survey, including descriptions, questionnaires, sampling methodology and datasets, are available on the NESARC-III website.[16] The study procedures for this secondary analysis of restricted data were approved by the Institutional Review Board (#2000022543) at Yale School of Medicine.

Measures

Socio-demographic Characteristics—Socio-demographic variables surveyed by NESARC-III included the following categorical variables[20-23]: age (18–44, 45–64, or 65+), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), marital status (married, never married or other), family income (<$20,000, $20,000–39,999, or ≥$40,000), education (<high school, high school or equivalent, some college, or ≥bachelor's degree), insurance coverage (private, Medicare, Medicaid, or other), and urbanity (rural or urban residence).[21-23] Additionally, we included self-reported pain (never, a little bit, moderately, quite a bit, or extremely) given its established link with opioid use/misuse across sexes.

Behavioral Health Diagnoses—NESARC-III utilized the Alcohol Use Disorder and Associated Disability Interview Schedule (AUDADIS) to evaluate DSM-5 diagnostic criteria of lifetime, past-year and prior to past-year diagnosis of the following psychiatric disorders: major depressive disorder, persistent depressive disorder (PDD, previously known as dysthymia in earlier DSM versions), bipolar I disorder, generalized anxiety disorder, post-traumatic stress disorder, and pain disorder.[20-23] The present study utilized past-year diagnoses of these disorders. Of note, major depressive disorder, PDD, and bipolar I disorder were treated as hierarchical variables such that the presence of one precludes a diagnosis of the others.[21] Additionally, we constructed a dichotomous variable to represent a diagnosis of any of these past-year psychiatric disorders.[22] We also included the following past-year SUDs based on DSM-5 criteria: alcohol use disorder, tobacco use disorder, and other illicit substance use disorders (ie, sedative, cannabis, cocaine, stimulant, hallucinogen, inhalant/solvent, or club drug).[20-23] Lifetime personality disorders (antisocial, borderline, and schizotypal) were also included. In view of the recent interest in behavioral multimorbidity which suggests that having multiple psychiatric disorders or SUDs is associated with especially serious dysfunction,[24-26] we included measures reflecting the presence of more than one psychiatric disorder or SUD.

Health-Related Quality of Life (HRQOL)—The Standard Short Form-12 (SF-12v2), was collected in NESARC-III and utilized in the present study as a multi-dimensional measure of physical and mental well-being.[27-29] The SF-12v2 includes 12 items that form the basis for 2 continuous component summary scores: Physical component summary and mental component summary scores. Standard scoring algorithms were applied, where each 10 points represents a 1 standard deviation difference, with 50 representing the US national average physical and mental HRQOL.[28] A lower score indicates worse HRQOL, and a higher score means better HRQOL.

Quality-Adjusted Life Years (QALYs)—Quality-adjusted life years (QALYs), on the other hand, represent a patient-reported, preference-based indicator of health state desirability on a cardinal scale where 0 indicates a state worse than or equal to death, and 1 indicates perfect health.[30] Using published algorithms,[31] we constructed a continuous QALYs variable, that is also in line with the widely used EuroQOL-5D approach using data included in the SF-12.

Data Analysis

First, bivariate logistic regression analyses were used to investigate sex differences in socio-demographic factors between women and men *with* past-year OUD, and then separately between women and men *without* past-year OUD. In view of the much smaller sample size of those with OUD as compared to those without OUD, we attended not only to statistical significance (ie, the likelihood that differences were due to chance) but also to the magnitude of these differences as represented by odds ratios. We repeated the same analyses for psychiatric and substance use disorders.

In order to investigate sex differences in the association of past-year OUD with socio-demographic factors and behavioral co-morbidities, further logistic regression analyses were conducted to determine the significance of the interaction of sex and past-year OUD status. These analyses included main effects for sex and past-year OUD in addition to the interaction term. These analyses thus addressed the significance of differences between men and women in each characteristic or diagnosis, as well as the significance of differences between people with and without past-year OUD in the total population. The interaction of sex and OUD on each characteristic tested whether the association of sex and the salient other factors was significantly different between those with OUD and those without OUD.

Finally, the magnitudes of HRQOL and QALYs between women and men with and without OUD were also estimated. Since HRQOL and QALYs are continuous measures, Cohen *d* (ie, the difference in means divided by the pooled standard deviation)[32,33] was calculated to evaluate the effect size of differences in HRQOL and QALYs between sexes with and without OUD, respectively. Interaction analyses were then conducted to determine the significance of differences between sexes in the association of OUD with reduced HRQOL and QALYs.

All statistical analyses were conducted in STATA MP/6-Core 15.1 and were weighted/accounted for NESARC-III survey design (eg, unequal probability of selection, clustering and stratification) using the “svy” commands.[17,34] We used $P < 0.05$ as the test of statistical significance.

RESULTS

Study Sample and Characteristics

Altogether, 330 respondents, representing about 2.1 million adults nationally, met diagnostic criteria for past-year OUD (Table 1). Of these, 49.5% were male and 50.5% were female. Among adults with OUD, no significant difference by sex was found in demographic factors, except that women with OUD were less likely to live in urban areas than men (odds ratio [OR] = 0.47; 95% confidence intervals [CI] = 0.24, 0.90). Among adults without OUD, all demographic factors were statistically significantly different by sex, except living in urban areas. Of those without OUD, women were *more* likely to be aged 65 or older and non-Hispanic black, covered by Medicare or Medicaid, and have pain than men ($P <$ 0.001 for all). On the other hand, women without OUD were *less* likely to be never married, employed, and have household income of $40,000 or greater ($P < 0.001$ for all).

Behavioral Co-morbidities

Among adults with OUD, women were more likely to have past-year generalized anxiety disorder (OR = 2.64; 95% CI = 1.25, 5.58) and post-traumatic stress disorder (OR = 2.69; 95% CI = 1.21, 5.96) than men (Table 2). Women with OUD were also *more* likely to have 2 or more psychiatric disorders than men with OUD in the past year (OR = 2.25; 95% CI = 1.16, 4.39), but were less likely to have alcohol use disorder, cannabis use disorder, and cocaine use disorder than men with OUD *(*$P < 0.05$ for all). Of personality disorders, women with OUD were less likely to have antisocial personality disorder than men with OUD (OR = 0.42; 95% CI = 0.20, 0.90).

In contrast to those with OUD, among adults without OUD, women were significantly more likely to have *all* past-year psychiatric disorders than men, except bipolar disorder ($P < 0.001$ for all) albeit with odds ratios in the same direction on most comparisons and of generally comparable magnitudes. Women were also more likely to have two or more psychiatric disorders than men in the past year (OR = 2.16; 95% CI = 1.89, 2.46). As among those with OUD, women without OUD were *less* likely to have alcohol use disorder, tobacco use disorder, and any substance use disorder ($P < 0.001$ for all). Of individual drug use disorders, women without OUD were less likely to have cannabis use disorder ($P < 0.001$), cocaine use disorder ($P < 0.05$), and club drug use disorder ($P < 0.01$) than men without OUD, respectively. Of personality disorders, women without OUD were less likely to have antisocial personality disorder than men without OUD (OR = 0.38; 95% CI = 0.33, 0.45).

When bivariate interaction analyses were conducted to determine the significance of differences sex and OUD status on self-reported pain and behavioral co-morbidities (Table 3), the only significant interaction involved PDD (OR = 0.49; 95% CI = 0.25, 0.95), and suggested that women with past-year OUD demonstrated a *lower* likelihood of having past-year PDD than men as compared to adults without OUD. Thus, such sex differences reflect a stronger association of sex and PDD among those without OUD.

Health-related Quality of Life (HRQOL)

Regardless of OUD status, men demonstrated slightly better physical and mental health-related quality of life than women (Table 4). As determined by the Cohen *d*, however, the effect sizes for differences between sexes, which ranged from 0.04 to 0.29 were small, or not significant. In addition, we found no significant interaction effect of OUD and sex on HRQOL, indicating that the adverse OUD effects were not differed by sex on HRQOL.

DISCUSSION

The present study sought to explore whether the previously established sex differences observed in adults with OUD[7-12] are specific to OUD or are indicative of general differences between men and women. Based on previous findings, we hypothesized that women with OUD would have an increased likelihood of mood and anxiety disorders, pain and a lower quality of life than males with OUD and that these differences would be significantly greater among those without OUD. However, our findings showed that there was only one significant sex difference among men and women with OUD as compared to those without

OUD, and that interaction suggested the association of psychiatric co-morbidity and female sex was weaker among those with OUD for PDD than among those without OUD and that there was no significant interaction on other concurrent behavioral co-morbidities.

A previous study suggested that women with OUD have higher rates of psychiatric comorbidities than men with OUD,[7] our findings are in line with such evidence for those with OUD. In particular, Grella and colleagues[7] demonstrated an association between lifetime diagnoses of OUD and presence of a lifetime Axis I disorder. Women with lifetime OUD were observed to be approximately twice as likely to have a lifetime diagnosis of a mood or anxiety disorder, whereas men were more likely to have a co-occurring SUD. Our findings are fully consistent with these findings among adults with OUD even when we focused on past-year, rather than lifetime, behavioral co-morbidities. In addition, our findings are also consistent with another previous study that highlighted sex-specific co-morbid burden among those with OUD.[35]

Using odds ratios as measures of effect size, our study also found that sex differences in the odds ratio of psychiatric comorbidities observed in OUD were similar in magnitude to sex differences in the general population (ie, among those without OUD) even when differences were not statistically significant in the OUD group. For instance, on 2 psychiatric diagnoses, women both with and without OUD had odds ratios greater than 2.0 as compared to men, and on 2 others, they had odds ratios greater than 1.5 even though the OUD group odds ratios were not statistically significant. In addition, women were 2.25 times more likely than men to have 2 or more psychiatric disorders within the OUD population, and 2.16 times more likely than men to have 2 or more psychiatric disorders among those without OUD, both of which were statistically significant.

Women without OUD also had a higher likelihood of psychiatric co-morbidities than men without OUD, while men without OUD also had a higher likelihood for SUDs than women without OUD. However, given the elevated rates of psychiatric comorbidies in both men and women with OUD, their clinical significance becomes more pressing. For example, almost one third of women with OUD have PTSD, compared to about 14% for men. These rates are much higher than those without OUD, 5.9% and 3.1% for women and men, respectively. Although many of these behavioral co-morbidities were more often significant among those without OUD than among those with OUD; such differences reflect the greater sample size of those without OUD, and the direction of the odds ratios was most often the same with similar effect sizes.

In addition, our findings are in line with research demonstrating that women, in general, are more likely to meet diagnostic criteria for internalizing disorders, especially mood/anxiety disorders, compared to males.[36] Thus, previous research detailing sex differences in co-morbidities among individuals with OUD may be illustrating generally observed sex differences in psychiatric symptoms, among males and females. These results highlight the need to screen for and target psychiatric symptomatology among both women and men with OUD, with the expectation that women with OUD will have higher comorbidity rates than men with OUD. However, the epidemiological data do not support distinct sex-related risk factors for OUD among women, at least as reflected by diagnostic co-morbidities.

It is especially important to note that these findings do not rule out sex differences in psychological distress specific to OUD measured in ways not addressed in this study.

While previous research has also postulated that sex differences in pain sensitivity may impact the etiology of OUD,[36] in that women experience greater sensitivity to pain and more chronic pain than men, the present study did not find significant sex differences between men and women with past-year OUD on measures of self-reported pain in the past 4 weeks, but unexpectedly did find substantial differences in pain experience among those without OUD. A recent review noted that while the underlying mechanisms of the sex different in pain have yet to be elucidated, females are more sensitive to experimental pain, as modelled and assessed in the laboratory.[11] The failure to find the expected sex differences in pain response may reflect the analgesic effect of opioids among both men and women who regularly use these drugs. Thus, future studies are warranted to explore the role of sex in pain sensitivity among individuals with OUD, utilizing experimental pain paradigms with more sensitive measures.

We observed sex differences in quality of life of small to moderate magnitude with lower scores of similar magnitudes among women than men—*both* with and without OUD. Both males and females with past-year OUD had lower QALYs and HRQOL when compared to non-OUD counterparts, consistent with recent evidence that adults with OUD have significant reduction in mental and physical health.[22] Furthermore, such reductions in HRQOL among adults with current OUD have been associated with concurrent psychiatric and SUDs,[24] thus illustrating the impact of multiple concurrent behavioral health diagnoses on quality of life among individuals with OUD, regardless of sex. Again, sex differences were no greater among those with OUD than those without OUD.

While the present data are cross-sectional in nature and thus limits the ability to examine the role of sex differences in the etiology of OUD, this study does importantly demonstrate that females with OUD exhibit similar difficulties relative to men as their counterparts without OUD in rates of behavioral health morbidities.

The lack of sex-specific differences associated with OUD should not be taken as minimizing the importance of these concurrent disorders. Recent data advocate for the treatment of disorders, such as OUD, from a multimorbidity perspective, as these disorders often clinically present with multiple concurrent behavioral health and medical conditions that likely impact the screening and treatment of OUD.[24,25] Given the extensive multi-morbidities associated with OUD in both sexes and their subsequent negative impact on quality of life and functioning, this study suggests the need to treat OUD from a multimorbidity perspective regardless of sex; thus, importantly incorporating psychiatric and medical care into OUD management interventions to improve treatment outcomes.[1,37-40] Our data merely suggest that the greater presence of these concurrent disorders among women does not appear to be specific to those with OUD. Treatment of these concurrent disorders may be critical in effectively treating OUD.

Several limitations of the present study warrant mention. First, the small sample size limited statistical power for comparison between men and women with OUD on some

co-morbidities. However, effect size trends were similar among those with and without OUD diagnoses. Second, the NESARC-III survey excludes active duty military, as well as homeless and incarcerated individuals, or institutionalized elsewhere. These factors may limit the generalizability of the present results to these demographic groups. Finally, temporal sequences of behavioral co-morbidities and quality of life in relation to OUD were not able to be explored and thus warrant subsequent investigation using longitudinal data and methods. Finally, the survey was conducted in 2012 to 2013 and the opioid epidemic has accelerated rapidly since then. While circumstances may have changed, we believe that it is likely that the epidemiological sex relationships observed here have probably persisted.

Despite these limitations, the present study has several strengths, including the use of data from a nationally representative dataset which included psychiatric and SUD diagnoses that were based upon DSM-5 diagnostic criteria, and measures of other validated, standardized variables (eg, pain and health-related quality of life). Overall, the present results highlight the fact that sex differences observed among men and women with OUD are not dissimilar from those observed among men and women without OUD suggesting that such differences, at least those measured here, may not be distinct sex-related risk factors for OUD. Nevertheless, concurrent disorders do exist among the OUD population in both men and women and there is a clear need to treat concurrent behavior health conditions from a multimorbidity perspective in the treatment of OUD in both sexes.

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TABLE 1.

Socio-demographic Characteristics of US Adults by Past-year Opioid Use Disorder (OUD) Status and Sex

	With OUD				Without OUD			
	Total	**Male**	**Female**	**Bivariate Odds Ratio**	**Total**	**Male**	**Female**	**Bivariate Odds Ratio**
Sample size								
Unweighted sample	330	154	176		35,979	15,708	20,271	
Weighted population (Row %)	2,092,822 (100.0%)	1,036,696 (49.5%)	1,056,126 (50.5%)		233,319,135 (100.0%)	112,175,123 (48.1%)	121,144,012 (51.9%)	
Age								
18–44	1,159,112	56.9	53.9	Reference	110,439,302	48.6	46.2	Reference
45–64	771,317	38.6	35.1	0.96	81,689,655	35.2	34.9	1.04
65+	162,393	4.5	11.0	2.60	41,190,179	16.2	19.0	1.23†
Race/ethnicity								
Non-Hispanic white	1,489,043	73.8	68.5	Reference	154,324,773	66.6	65.7	Reference
Non-Hispanic black	288,042	10.7	16.8	1.69	27,463,740	11.0	12.5	1.15†
Hispanic	242,317	10.5	12.7	1.31	34,449,514	15.3	14.3	0.95
Other‡	73,420	5.1	2.0	0.43	17,081,108	7.1	7.5	1.08
Marital status								
Married	678,649	30.7	34.1	Reference	119,840,001	53.5	49.4	Reference
Never married	556,573	28.1	25.1	0.81	52,454,065	25.1	20.1	0.87†
Other§	857,600	41.2	40.8	0.89	61,025,069	21.5	30.5	1.54†
Family income								
<$20,000	986,168	52.9	41.5	Reference	52,691,275	19.9	25.1	Reference
$20,000–$39,999	490,614	20.0	26.8	1.71	56,270,149	23.4	24.8	0.84†
≥$40,000	616,040	27.1	31.7	1.49	124,357,712	56.8	50.1	0.70†
Employment								
No	904,828	41.3	45.1	Reference	69,644,719	24.4	34.9	Reference
Yes	1,187,994	58.7	54.9	0.86	163,674,416	75.6	65.1	0.60†
Education								

	With OUD				Without OUD			
	Total	Male	Female	Bivariate Odds Ratio	Total	Male	Female	Bivariate Odds Ratio
<High school	455,229	23.6	19.9	Reference	30,174,070	13.3	12.6	Reference
High school or equivalent	733,136	39.0	31.2	0.95	59,947,543	26.8	24.7	0.97
Some college	714,840	28.9	39.3	1.62	77,130,322	31.3	34.7	1.17†
≥Bachelor's degree	189,616	8.5	9.7	1.36	66,067,200	28.7	28.0	1.03
Insurance coverage‖								
Private (%)	798,190	32.9	43.3	1.55	135,283,214	57.8	58.2	1.02
Medicare (%)	600,790	26.3	31.1	1.26	49,704,734	20.2	22.4	1.14†
Medicaid (%)	525,835	25.7	24.6	0.94	23,698,278	7.3	12.8	1.87†
Other¶ (%)	788,982	33.4	42.0	1.45	104,700,513	44.9	44.9	1.00
Self-reported pain								
Never	398,176	18.5	19.6	Reference	135,770,032	60.9	55.8	Reference
A little bit or moderately	753,534	36.1	36.0	0.94	73,125,412	29.8	32.8	1.20†
Quite a bit or extremely	941,112	45.5	44.5	0.92	24,303,116	9.4	11.4	1.33†
Urbanity								
Rural	441,944	14.9	27.3	Reference	49,585,999	21.1	21.4	Reference
Urban	1,650,878	85.1	72.7	0.47*	183,733,136	78.9	78.6	0.98

*<0.05.

†<0.001.

‡Indicates Native American or Asian.

§Indicates living with partner/being widowed, divorced or separated.

‖Indicates that each insurance type has a response of yes or no.

¶Indicates public health insurance programs other than Medicare and Medicaid.

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TABLE 2.

Psychiatric and Substance Use Co-morbidities of US Adults by Past-year Opioid Use Disorder (OUD) Status and Sex

	With OUD				Without OUD			
	Total	**Male**	**Female**	**Bivariate Odds Ratio**	**Total**	**Male**	**Female**	**Bivariate Odds Ratio**
Sample size								
Unweighted sample	330	154	176		35,979	15,708	20,271	
Weighted population (row %)	2,092,822 (100.0%)	1,036,696 (49.5%)	1,056,126 (50.5%)		233,319,135 (100.0%)	112,175,123 (48.1%)	121,144,012 (51.9%)	
Lifetime personality disorder								
Any personality disorder (%)	1,018,357	50.9	46.4	0.84	27,753,395	12.5	11.4	0.90 *
Antisocial personality disorder (%)	300,998	19.6	9.3	0.42 *	5,752,622	3.6	1.4	0.38 ≠
Borderline personality disorder (%)	942,055	44.8	45.2	1.02	22,836,586	9.6	10.0	1.04
Schizotypal personality disorder (%)	458,285	23.5	20.3	0.83	9,849,443	4.2	4.2	1.00
Past-year psychiatric disorder								
Any psychiatric disorder (%)	1,275,195	54.1	67.7	1.78	42,249,248	13.4	22.5	1.88 ≠
Major depressive disorder (%)	637,954	24.4	36.5	1.78	23,825,610	7.0	13.2	2.02 ≠
Persistent depressive disorder (%)	394,034	20.5	17.2	0.81	8,322,745	2.7	4.4	1.66 ≠
Bipolar 1 disorder (%)	242,730	13.0	10.2	0.76	3,385,904	1.5	1.4	0.90
Generalized anxiety disorder (%)	353,739	10.3	23.4	2.64 *	12,146,610	3.8	6.6	1.80 ≠
Post-traumatic stress disorder (%)	467,788	14.0	30.5	2.69 *	10,505,198	3.1	5.9	1.97 ≠
Panic disorder (%)	326,324	13.3	17.9	1.43	6,895,771	1.8	4.1	2.34 ≠
Total number of past-year psychiatric disorders								
None	817,626	45.9	32.3	Reference	191,069,887	86.6	77.5	Reference
1	598,110	29.1	28.1	1.37	27,559,224	9.1	14.3	1.75 ≠
≥2	677,086	25.0	39.6	2.25 *	14,690,024	4.3	8.2	2.16 ≠
Past-year substance use disorder								

	With OUD				Without OUD			
	Total	Male	Female	Bivariate Odds Ratio	Total	Male	Female	Bivariate Odds Ratio
Alcohol use disorder (%)	886,305	49.7	35.2	0.55*	31,761,385	17.3	10.2	0.54‡
Any substance use disorder (%)	771,643	40.7	33.1	0.72	6,856,433	3.9	2.1	0.52‡
Sedative use disorder (%)	381,015	18.5	17.9	0.96	498,041	0.2	0.3	1.73
Cannabis use disorder (%)	490,919	29.1	18.0	0.53*	5,490,937	3.3	1.5	0.46‡
Cocaine use disorder (%)	149,077	10.8	3.6	0.30*	671,764	0.4	0.2	0.57*
Stimulant use disorder (%)	193,309	11.2	7.3	0.63	560,973	0.2	0.3	1.07
Hallucinogen use disorder (%)	51,203	3.0	1.9	0.65	62,878	0.0	0.0	0.56
Inhalant/solvent use disorder (%)	39,011	3.8	0.0	-§	58,653	0.0	0.0	0.21
Club drug use disorder (%)	52,886	3.6	1.5	0.40	226,668	0.2	0.1	0.33†
Tobacco use disorder (%)	1,326,481	67.7	59.2	0.69	45,821,118	22.9	16.7	0.67‡
Total number of past-year substance use disorders								
None	1,321,178	59.3	66.9	Reference	226,462,702	96.1	98.0	Reference
1	478,946	22.6	23.1	0.91	6,368,118	3.7	1.9	0.50‡
≥2	292,697	18.1	10.0	0.49	488,316	0.2	0.2	0.85

*<0.05.

†<0.01.

‡<0.001

§Cannot be calculated due to no observation in female adults with OUD.

TABLE 3.

Association of Sex and Past-year OUD Status on Psychiatric and Substance Use Comorbidities Among US Adults

	Independent Variable		
Dependent Variable	**Being Female**	**Having an OUD**	**Interaction of Sex and OUD**
Self-reported pain			
Moderately, quite a bit, or extremely	1.28‡	7.75‡	0.84
Lifetime personality disorder			
Any personality disorder	0.90*	7.28‡	0.93
Antisocial personality disorder	0.38‡	6.52‡	1.09
Borderline personality disorder	1.04	7.63‡	0.98
Schizotypal personality disorder	1.00	6.98‡	0.83
Past-year psychiatric disorder			
Any psychiatric disorder	1.88‡	7.62‡	0.95
Major depressive disorder	2.02‡	4.29‡	0.88
Persistent depressive disorder	1.66‡	9.33‡	0.49*
Bipolar I disorder	0.90	9.62‡	0.85
Generalized anxiety disorder	1.80‡	2.96‡	1.47
Post-traumatic stress disorder	1.97	5.20	1.36
Panic disorder	2.34‡	8.47‡	0.61
Number of past-year psychiatric disorder §	1.79‡	4.83‡	0.79
Past-year substance use disorder			
Alcohol use disorder	0.54‡	4.70‡	1.02
Tobacco use disorder	0.67‡	7.07‡	1.03
Any substance use disorder	0.52‡	16.93‡	1.39
Sedative use disorder	1.73	146.73‡	0.55
Cannabis use disorder	0.46‡	12.17‡	1.17

Dependent Variable	Independent Variable		
	Being Female	Having an OUD	Interaction of Sex and OUD
Cocaine use disorder	0.57*	32.36‡	0.54
Stimulant use disorder	1.06	53.98‡	0.59
Hallucinogen use disorder	0.56	87.59‡	1.15
Inhalant/solvent use disorder	0.21	91.61‡	-//
Club drug use disorder	0.33†	25.13‡	1.20
Number of past-year substance use disorder §	0.55‡	18.83‡	1.15

For coding, being female=1 versus being male = 0 and having an OUD = 1 and not having an OUD = 0.

*<0.05.

†<0.01.

‡<0.001.

§Indicates that the incidence rate ratio was reported using Poisson regression modeling.

//Cannot be calculated due to no observation in female adults with OUD.

TABLE 4.

Quality of Life (QOL) and Interaction Effects of Sex and Past-year Opioid Use Disorder (OUD) on QOL Among US Adults

	With OUD			Without OUD			Interaction	
	Male	**Female**	**Cohen *d***	**Male**	**Female**	**Cohen *d***	**Coefficient**	***P***
Health-related Quality of Life								
Physical component summary (PCS)	40.4 ± 13.5	38.3 ± 12.0	0.16	50.0 ± 10.2	49.6 ± 10.6	0.04	1.74	0.322
Mental component summary (MCS)	41.9 ± 11.0	39.9 ± 12.5	0.17	51.6 ± 9.4	49.7 ± 10.5	0.19	−1.38	0.328
Quality-adjusted Life Year								
EuroQOL-5D (EQ-5D)	0.75 ± 0.15	0.71 ± 0.14	0.29	0.90 ± 0.11	0.88 ± 0.12	0.17	0.00	0.897

For coding, being female = 1 versus being male = 0 and having an OUD = 1 and not having an OUD = 0.