

## Young Adult Healthcare Exposure and Future Opioid Misuse: A Prospective Cohort Study



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**Introduction:** Outpatient opioid prescribing is associated with opioid misuse in young adults, but the longitudinal association between general healthcare exposure and opioid misuse has not been explored. The objective of this study is to examine the association between healthcare exposure in young adulthood and future opioid misuse.

**Methods:** Data were drawn from the National Longitudinal Study of Adolescent to Adult Health (2001–2018) and analyzed in 2021. Healthcare exposure (i.e., inpatient hospitalization and visits to the clinic, emergency department, mental-health facility, or dentist) between individuals aged 18 and 26 years was the primary independent variable; only patients who did not report opioid misuse at baseline were included. *Opioid misuse* was defined as using prescription painkillers without a doctor's permission and was measured 17 years after exposure. Multivariable logistic regression was used to examine any associations with opioid misuse (ages 33–43 years).

**Results:** A total of 8,225 young adults with a mean baseline age of 21.8 (SE=0.12) years met inclusion criteria. Approximately 13.7% reported new opioid misuse at follow-up. Those reporting opioid misuse at follow-up were more likely to be White, lack a college education, or report depression. Those exposed to inpatient hospitalization, emergency departments, or mental-health facilities had an increased risk of future opioid misuse.

**Conclusions:** In young adults reporting no opioid misuse at baseline, healthcare exposure was associated with an increased risk of opioid misuse later in adulthood in this large, national cohort. Physicians encounter this at-risk population daily, reinforcing the importance of responsible prescribing practices and the need for targeted screening, patient education, and intervention efforts in the healthcare setting.

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### INTRODUCTION

The opioid epidemic looms large as a public health crisis and is fueled by *opioid misuse*, defined as using opioids in a manner or dose other than that prescribed, using someone else's prescription, or using opioids to feel euphoria.<sup>1</sup> Opioid misuse in the U.S. dramatically increased from 1999 to 2017,<sup>2</sup> and although having declined slightly in the past few years, it is a major cause of morbidity and mortality across all ages. The dramatic rise in highly potent synthetic opioids, such as fentanyl and related analogs, has emerged in recent years as a driver of the ongoing opioid

epidemic.<sup>2</sup> Prescription opioid misuse rises across adolescence and peaks in young adulthood,<sup>3</sup> marking early adulthood as a particularly high-risk period for initial exposure to opioids, which often occurs during

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interactions with the healthcare setting. The National Survey on Drug Use and Health for 2017 reported opioid misuse in 7.1% of young adults aged 18–25 years and 6.9% of those aged 26–34 years.<sup>4</sup> Opioid misuse in young adults has been associated with increased risk of secondary substance abuse,<sup>5</sup> long-term opioid use disorder,<sup>6</sup> and opioid overdose.<sup>7</sup> Among U.S. adults in 2015, approximately 1 in 3 reported using prescription opioids, and about 4.7% of adults were estimated to be misusing opioids.<sup>8</sup>

According to the National Survey on Drug Use and Health, more than half of those misusing opioids obtained them from friends or relatives, whereas 25% obtained opioids from the healthcare system.<sup>5</sup> In a national study of high school seniors who misused opioids from a previous personal prescription, 45% received the prescription from an emergency department physician, and 27% received the prescription from a dentist.<sup>9</sup> Although several studies have established outpatient opioid prescribing to be a risk factor for opioid misuse in adolescents and young adults,<sup>9,10</sup> few studies have assessed whether healthcare exposure alone in young patients is a risk factor. This study aims to examine the impacts of exposure to a healthcare setting in young adulthood (ages 18–26 years) on future opioid misuse (ages 33–43 years) using a nationally representative, prospective longitudinal cohort design over a 17-year period. It is hypothesized that patients exposed to a healthcare setting would have a higher risk of opioid misuse than those not exposed to a healthcare setting.

## METHODS

### Study Population

The National Longitudinal Study of Adolescent to Adult Health (Add Health) is a longitudinal cohort study that took place from 1994 to 2018 in 5 data collection waves (Waves I–V), following adolescents in grades 7–12 (ages 11–18 years) through adulthood (ages 34–43 years). It is a nationally representative sample with respect to region, urbanicity, size and type of school, and ethnicity of students from 80 U.S. high schools with paired middle schools. The Add Health study design has been described previously.<sup>11</sup> This study used data from Waves III (2001–2002) and V (2016–2018) of Add Health.<sup>11</sup> Of the 12,300 participants remaining in the cohort at the data collection of Wave V, the final follow-up visit, a total of 1,936 participants were excluded for reporting previous opioid misuse at baseline, and 2,139 were missing opioid misuse data at follow-up. This resulted in a total study population of 8,225 participants. The University of North Carolina IRB approved this original study, and informed consent was obtained from participants at the outset of study participation.

### Measures

The primary exposure of interest, healthcare exposure, was measured during 2001–2002 (Wave III) when the participants were young adults (ages 18–26 years). This study used 5 healthcare exposures as

predictors of opioid misuse: (1) doctor's visit in the past 2 years, (2) inpatient hospitalization in the past 5 years, (3) emergency department visit in the past 5 years, (4) mental-health facility visit in the past 5 years, and (5) dentist's visit in the past year. Unexposed individuals did not report these activities within these timeframes.

*Previous opioid misuse* was reported at baseline and defined as taking pain killers such as Darvon, Demerol, Percodan, or Tylenol with codeine without a doctor's permission. All participants reporting opioid misuse from 2001 to 2002 (Wave III) were excluded from the study to exclude patients with opioid misuse at baseline and assess whether healthcare exposure was associated with new opioid misuse. The outcome, new opioid misuse, was measured from 2016 to 2018 (Wave V, ages 33–43 years), 17 years after the exposure was reported. *New opioid misuse* was defined as taking prescription pain killers that “were not prescribed for you, taken in larger amounts than prescribed, more often than prescribed, for longer periods than prescribed, or that you took only for the feeling or experience they caused.”

Age, sex, and race/ethnicity were self-reported, and participants could select multiple race categories. Age at baseline (2001–2002) was used as a covariate. Education was dichotomized into high school or less versus more than high school (college and vocational training), similar to that used in other large population-based studies in young adults, and was measured at the end of follow-up.<sup>12</sup> Health insurance consisted of individuals reporting coverage for  $\geq 1$  month in the past year (2001–2002, Wave III), at the time of exposure to the healthcare setting. Depressive symptoms measured at the Add Health baseline report were based on the modified 20-item Center for Epidemiologic Studies Depression Scale measured in Wave I, which uses a 4-response Likert scale.<sup>13</sup> The variable for previous substance use, also measured in Wave I, used combined dichotomous responses into 6 substance use questions and then into a single ordinal categorical variable, adding 1 point for each *yes* response. Substance use questions included (1) ever smoking  $\geq 1$  daily cigarette for 30 days; (2) drinking  $\geq 5$  alcoholic drinks in a row at least once in the past year; ever used (3) marijuana, (4) cocaine, or (5) inhalants in lifetime; and (6) ever used illicit drugs such as lysergic acid diethylamide, phenyl cyclohexyl piperidine, ecstasy, mushrooms, speed, ice, heroin, or pills. This previous substance use categorization is similar to that used in previous studies.<sup>14</sup>

### Statistical Analysis

Statistical significance was set at a 2-sided alpha,  $\alpha=0.05$ , and all analyses were conducted in Stata, version 15. For all analyses, Add Health's preconstructed sample weights were used to yield nationally representative estimates. Multiple imputations using chained equations methods were employed for all missing covariates and healthcare exposure (predictor) data. Missing data ranged from 0% (age, depression, previous drug use variables) to a maximum of 5% (emergency department visit). Missing data were determined to be most likely missing at random, and the investigators elected for multiple imputations over list-wise deletion.<sup>15</sup> After sample weighting, multiple imputation was conducted using the *mi impute chained (logit)* command, including each variable in the prediction model, and chained, iterative equations were thus used to generate the imputed data. Descriptive statistics are reported for demographic and health characteristics, using chi-square tests and *t*-tests to compare young adults with and without opioid misuse. The difference in the proportion reporting opioid misuse according to healthcare exposure is measured by the

proportion using opioids among participants exposed to health-care settings minus the proportion using opioids among participants unexposed to health-care settings. A test of proportions was conducted to construct 95% CIs. A total of 5 separate multivariable logistic regression models were constructed to predict opioid misuse on the basis of each health-care exposure. The 2 models presented adjust for previous covariates: Model 1 adjusts for age and sex only, whereas Model 2 adjusts for age, sex, race/ethnicity, college education, health insurance, depression, and previous drug use. There was no evidence of multicollinearity.

## RESULTS

A total of 8,225 young adults met the inclusion criteria with a mean age of 21.8 (SE=0.12) years at baseline. Approximately 13.7% of the participants reported new opioid misuse over the 17-year study period. Demographic and health characteristics according to their

new opioid misuse are shown in Table 1. Among those reporting opioid misuse, a higher proportion was male, was White, reported lower educational attainment at follow-up, reported previous substance use, and reported symptoms of depression. The adjusted models also showed a nonstatistically significant association between depression and opioid misuse, with an OR ranging from 1.10 to 1.13 across the 5 models, as illustrated in the Appendix Tables (available online). A higher proportion of patients visited the hospital, visited the emergency room, or had been to a mental-health facility in the last 5 years in the opioid misuse group. A lower proportion of patients had visited the dentist in the past year. No statistically significant differences were observed for the proportion visiting the doctor in an outpatient setting in the past 2 years between these groups.

**Table 1.** Demographic and Health Characteristics by Opioid Misuse Status (N=8,225)

Characteristics	No opioid misuse, <sup>a</sup> %	Opioid misuse, <sup>a</sup> %	p-value
Demographic characteristics			
Age at baseline, mean (SE)	21.8 (0.12)	21.6 (0.15)	<b>0.022</b>
Sex, %			<b>0.003</b>
Male	47.0	54.3	
Female	53.0	45.7	
Race, <sup>b</sup> %			
White	76.2	80.9	<b>0.022</b>
Black/African American	17.5	13.9	<b>0.036</b>
Asian/Pacific Islander	5.0	4.6	0.688
Hispanic, %			0.076
No	87.4	90.1	
Yes	12.6	9.9	
Education status, %			<b>0.011</b>
High school or less	43.6	50.2	
College or vocational training	56.4	49.8	
Health characteristics			
Previous substance use, %	36.7	52.2	<b>&lt;0.001</b>
Depression, %	20.5	23.9	<b>0.038</b>
Health insurance, %	83.0	79.6	0.083
Healthcare exposure			
Doctor's visit, <sup>c</sup> %	91.3	92.8	0.318
Hospitalization, <sup>d</sup> %	24.8	30.7	<b>0.004</b>
Emergency department visit, <sup>d</sup> %	56.4	64.7	<b>0.001</b>
Mental-health facility visit, <sup>d</sup> %	1.2	2.5	<b>0.027</b>
Dentist visit, <sup>e</sup> %	59.0	52.8	<b>0.004</b>

Note: Boldface indicates statistical significance ( $p < 0.05$ ).

All means and percentages are calculated with weighted data to reflect the representative proportion of the target U.S. population.

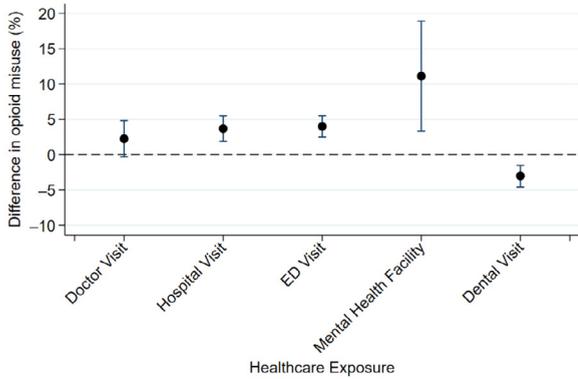
<sup>a</sup>Opioid misuse measured ages 18–26 years and defined as taking pain killers such as Darvon, Demerol, Percodan, or Tylenol with codeine without a doctor's permission.

<sup>b</sup>Participants can select >1 race; percentages may not add to 100%.

<sup>c</sup>Doctor's visit in the past 2 years, measured at baseline (2001–2002).

<sup>d</sup>Emergency department visit, hospitalization, or mental-health facility visit within the past 5 years, measured at baseline (2001–2002).

<sup>e</sup>Dentist's visit in the past year, measured at baseline (2001–2002).



**Figure 1.** Difference in proportion of opioid misuse according to each healthcare exposure.

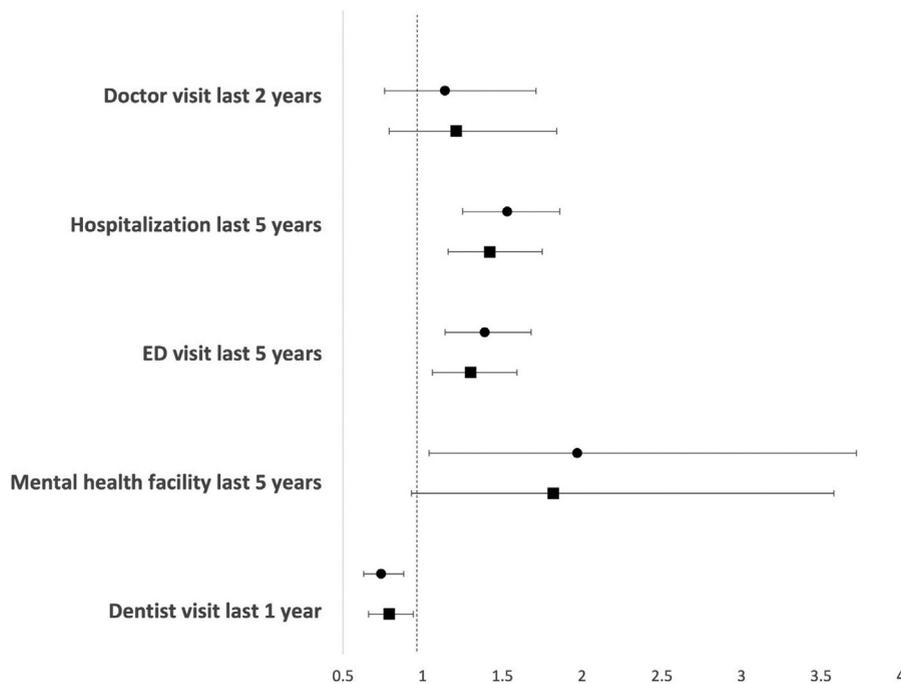
Note: Difference is measured by the proportion exposed minus the proportion unexposed to healthcare settings. Differences above the dotted line represent a higher proportion of opioid misuse among those exposed to a given healthcare setting. ED, emergency department.

The difference in the proportion reporting opioid misuse according to healthcare exposure is shown in Figure 1. In absolute differences, those exposed to the inpatient hospital setting in adolescence, for example, had a 3.7% higher proportion of opioid misuse than those unexposed. Those visiting the emergency department or mental-health facility had a 4.0% and 11.1% higher proportion of opioid misuse, respectively.

The risk of opioid misuse according to healthcare exposure is presented in Appendix Table 1 (available online). Model 1 adjusted for age and sex only, and Model 2 adjusted for age, sex, race/ethnicity, education status, health insurance, depression, and previous drug use. In Model 2, young adults with healthcare exposure had an increased odds of future opioid misuse, including those hospitalized (OR=1.42, 95% CI=1.16, 1.75) and those who visited the emergency department (OR=1.30, 95% CI=1.06, 1.59) in multivariate models adjusting for age, sex, race/ethnicity, education status, health insurance, depression, and previous drug use. By contrast, those who visited the dentist in the past year had a decreased odds (OR=0.79, 95% CI=0.66, 0.94) of opioid misuse. Results of the multivariable analysis of the association between healthcare exposure and opioid misuse are illustrated in Figure 2.

### DISCUSSION

This study sought to determine whether a prospective long-term association exists between healthcare exposure (both inpatient and outpatient) and future opioid misuse in adulthood in a nationally representative longitudinal cohort study. The notable findings were three-fold. First, almost 1 in 7 adults with no opioid misuse at baseline reported new misuse over the 17-year follow-up period. Exposure data from this time period (ages



**Figure 2.** Multivariable analysis of the association between healthcare exposure (2001–2002) and opioid misuse (2016–2018). Note: ORs and 95% CIs for unadjusted (circle) and adjusted (square) multivariate analyses. ED, emergency department.

18–26 years) was chosen because adolescence/young adulthood is a critical period in the development of substance misuse,<sup>16</sup> and this study sought to evaluate the potential impact of healthcare exposure over a significant time period. Second, populations with a higher incidence of adult-onset opioid misuse included those who were White, were male, were depressed, reported previous substance use, and did not report more than a high school education at follow-up. Non-Hispanic White adolescents have been found to be a high-risk group in other similar studies.<sup>10,17</sup> However, researchers seeking to describe the recent sociodemographic shifts in the adolescent opioid epidemic found that non-Hispanic Black adolescents were more likely to use and misuse opioids, which is concerning for a shift in misuse toward minority patients.<sup>17</sup> This study confirms other researchers' findings that in the young adult population, noncollege graduates are also at the highest risk for misuse.<sup>18</sup>

Third, 2 healthcare exposures were associated with increased odds of future opioid misuse: emergency department admission and inpatient hospitalization. Whereas emergency department admission and inpatient hospitalization had 1.33 and 1.46 times the odds of opioid misuse, respectively, mental-health facility admission was not associated with new opioid misuse in unadjusted models. The rarity of exposure in this sample may have decreased the power to detect a difference in the full model. In addition, engaging in routine, preventive healthcare behaviors (i.e., routine physical examinations) at a doctor's visit in the past 2 years was not associated with opioid misuse. Attending a dental visit was protective against opioid misuse; however, it is important to note that preventive and procedural dental visits were pooled together as a single predictor. One possible explanation, which stands in contrast to that in previous studies,<sup>9,19</sup> is that those engaged in routine health care are more health conscious and risk averse. Targeted opioid prevention interventions and quality improvement projects may be best for emergency department and inpatient healthcare settings.

The study results were consistent with the authors' hypothesis and suggest that early exposure to the healthcare system is a risk factor for opioid misuse later in life. There may be several reasons. First, a visit with a healthcare provider for something such as a sports injury in the emergency department can lead to an initial opioid prescription and the patient's first experience using opioids.<sup>16</sup> Second, young adults with chronic illnesses or chronic pain, which are known to be associated with a higher likelihood of chronic opioid use, may be more likely to seek medical care.<sup>20</sup>

The clinical settings in which opioid misuse was the highest were somewhat surprising given that the emergency department has one of the lowest rates of prescribing opioids. Although other groups have shown a short-term association between opioid prescriptions for interventions such as wisdom tooth surgery<sup>19</sup> and opioid misuse, this study focused on being exposed to a healthcare setting, either as inpatient or outpatient, and evaluated the long-term risk of misuse over a lengthy period. The fact that encounters with the healthcare system outside of routine care seem to be associated with an increased risk of opioid misuse suggests that it is healthcare providers' responsibility, in a myriad of settings, to minimize opioid prescribing and consider nonopioid alternatives. Although mid-adolescence is the highest-risk period for the initiation of prescription pain pill misuse,<sup>21</sup> this study suggests that young adulthood is also a high-risk period. In 2019, the U.S. Preventive Services Task Force added a recommendation for providers to screen for illicit drug use, including the non-medical use of prescription pills. The Tobacco, Alcohol, Prescription Medication, and Other Substance Use Tool is a brief screening instrument to assess unhealthy use of multiple substances<sup>22</sup>; this and similar tools could be seamlessly integrated into clinics and hospitals. Frequent screening to identify opioid misuse and offer regular counseling and education is critical across all healthcare settings. In addition, novel interventions have been developed in recent years, such as a web-based program (POP4Teens) aimed at preventing prescription opioid use among adolescents and young adults.<sup>23</sup>

## LIMITATIONS

This study is limited by incomplete baseline opioid prescription data, residual confounding, and possible reporting bias. First, the exclusion of those who reported opioid misuse at baseline means that this study is not representative of all young adults. The independent, temporal association found in this study lends support to the hypothesis that some opioid misuse is iatrogenic in origin. Still, the investigators did not assess how frequently patients were exposed to the healthcare system within the defined timeframes nor the presence or extent of opioid prescriptions in these encounters. Similarly, it is not known when opioid misuse occurred within the 17-year follow-up period. In addition, the authors recognize that early exposure does not equate to continuous exposure, which can have an impact on opioid use patterns, as seen from studies focused on patients with chronic pain. However, the goal was to look at the exposure to health care rather than the frequency of exposure. The quality of the data relies on the honesty of

those completing the self-report survey, and there may be some reporting bias. Because people tend to under-report their use, the correlation may in reality be more positive.<sup>24</sup> Finally, comparing the results with others is challenging given the varying definitions of misuse or abuse. Some studies use the criteria in the Diagnostic and Statistical Manual of Mental Disorders, which were updated in 2013 to eliminate the abuse category in the 5th Edition, whereas others define it by meeting certain criteria on the basis of answers to screening questions. This study defined *misuse* as taking any prescription painkillers that were not prescribed to the individual; taken in larger amounts, frequencies, or lengths of time than prescribed; or if taken for the experience of getting high.

Despite these limitations, this study has several strengths. Data were gathered longitudinally from a large, national, prospectively collected database allowing for evaluation of young people exposed to the healthcare system in general and the effect of this exposure over the ensuing 2 decades. Whereas other studies focused on the adult population or adolescents/young adults known to have exposure to opioids, such as those with chronic pain,<sup>14</sup> this study focused on the mere exposure to healthcare settings. None of the studies mentioned earlier looked at the impacts of healthcare settings alone, and this study is one of the largest nationally representative prospective cohort studies to investigate this issue. Many studies only followed patients for short periods after exposure<sup>25</sup>; arguably, this may not be enough time to glean any true impacts. This study followed patients for 17 years after exposure.

## CONCLUSIONS

With the growing opioid epidemic, it is imperative that healthcare providers and policymakers identify the clear risk factors and associations with opioid misuse to develop effective interventions for prevention. These results support the notion that adolescents and young adults who engage with the healthcare setting outside of routine care are an at-risk population for future opioid misuse.

Future research should investigate the role of opioid prescription sources—such as in an emergency department, postoperative care unit, or primary care setting—and long-term opioid misuse. Physicians and hospital systems encounter this population every day, reinforcing the need for screening and intervention efforts throughout adolescence and adulthood. Providers should consider avoiding the distribution of controlled substances and incorporating more non-opioid adjuncts in this population. There is room for targeted screening and education in both the school setting, ideally in high

school to capture those who are not college bound, and the healthcare setting. Parents and providers should be aware that young adults who visit the doctor outside of routine care early in adolescence may need to be more heavily monitored or counseled regarding opioid misuse.

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## SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at <https://doi.org/10.1016/j.amepre.2021.12.026>.

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