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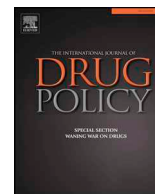
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Research Paper

Impact of health reform on health insurance status among persons who use opioids in eastern Kentucky: A prospective cohort analysis

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ABSTRACT

Background: Health insurance improves health and reduces mortality. Expanding insurance is a central feature of the Affordable Care Act (ACA). Persons who use drugs (PWUDs) have historically been at high risk of being uninsured. It is unknown if Appalachian PWUDs, who live in an extremely economically distressed region, are more likely to be insured since implementation of the ACA.

Methods: Data from a cohort of 503 PWUDs from eastern Appalachian Kentucky, who were interviewed at seven time-points between 2008 and 2017, were analysed using mixed effects regression models.

Results: At baseline, only 33.8% of participants were insured, which increased to 87.3% of the cohort at the last follow-up interview. The final multivariate model, which included baseline characteristics and interactions by time, indicated there were significant baseline differences in insurance status by gender, age, education, income, and history of injection. Differences in the predictive margin probabilities of being insured across these groups had dissipated by the final follow-up interview.

Conclusions: After Kentucky's implementation of the ACA, this cohort of Appalachian PWUDs made substantial gains in obtaining insurance that far exceeded the increases reported in national studies.

Introduction

People who use drugs (PWUDs) have historically been at greater risk for being uninsured in the United States (Cummings, Wen, Ritvo, & Druss, 2014). In 2011–2013, before full implementation of the federal Patient Protection and Affordable Care Act of 2010 (ACA), about 26% of people with substance use disorder (SUD) in the US were uninsured (Saloner, Bandara, Bachhuber, & Barry, 2017), compared to about 20% of the general adult population (Garfield, Licata, & Young, 2014). For PWUDs and those with SUD, having insurance, particularly via Medicaid (Bouchery, Harwood, Dilonardo, & Vandivort-Warren, 2012), is a critical enabling factor for SUD treatment utilization (Ilgen et al., 2011). Having insurance is associated with improvements in physical and mental health (Courtemanche & Zapata, 2014) and reductions in mortality (Sommers, Long, & Baicker, 2014). Individuals without health insurance are more likely to report unmet needs for mental health treatment (Roll, Kennedy, Tran, & Howell, 2013), less likely to receive preventive care (Holden, Chen, & Dagher, 2015), and more likely to

have chronic conditions that are not appropriately controlled (Hogan et al., 2015).

Although having health insurance is beneficial to the health of PWUDs, structural obstacles to health insurance have been longstanding because, unlike other industrialized nations, the US does not have a system of universal health insurance. Instead, individuals must navigate a fragmented insurance system that involves both private and public entities. For working age adults, private health insurance may be provided by employers as an employee benefit, but employees still incur costs (e.g., monthly insurance premiums, co-payments for services). Self-employed and part-time workers typically have lacked access to employment-based insurance in the US. For individuals above age 65, the federal Medicare program is a major source of public insurance. Some low-income individuals who lack private health insurance have had access to public insurance through Medicaid, which is a program where the federal government and states jointly bear its costs. Because individual states contribute funding to support residents on Medicaid, states have historically had discretion over its

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implementation, so long as states met minimum federal requirements for covering specific groups. The federal requirements, before the ACA, only required Medicaid coverage for children, pregnant women, parents of dependent children, and individuals with disabilities (Garfield et al., 2014). As a result, only about half of low-income individuals in the US were covered by Medicaid before the ACA (Rosenbaum, 2003).

Reduction in the uninsured population is a central goal of the ACA. The primary policy mechanisms within the legislation for expanding insurance coverage are the individual and employer mandates, health insurance marketplaces that sell subsidized health insurance, and Medicaid expansion. The individual mandate requires all individuals without employer-sponsored insurance to purchase health insurance, and the employer mandate requires all employers with 50 or more full-time employees to offer affordable insurance to their employees (French, Homer, Gumus, & Hickling, 2016). To help consumers and small businesses to purchase insurance, the ACA established health insurance marketplaces (also called exchanges) where insurance plans can be compared in terms of costs and benefits and then purchased (Henry J. Kaiser Family Foundation, 2019a). States have varied in their implementation of the health insurance marketplaces, with some states operating their own state-based marketplaces, while other states have relied upon the federal marketplace at Healthcare.gov. States that have elected to operate their own marketplaces must meet several requirements, such as developing and implementing outreach plans for marketing the exchanges to consumers (Krinn, Karaca-Mandic, & Blewett, 2015). The ACA also mandated the expansion of Medicaid to cover all individuals with incomes below 138% of the federal poverty level, but the Supreme Court, in *National Federation of Independent Business v. Sebelius*, gave states the option to decline expanding Medicaid. As of April 2019, 36 states and the District of Columbia have adopted the Medicaid expansion (Henry J. Kaiser Family Foundation, 2019b). National data have shown that the ACA has reduced the percentage of uninsured individuals while also making meaningful reductions in the percentages of individuals who lack access to a personal physician, cannot afford care, and report being in poor health (Sommers, Gunja, Finegold, & Musco, 2015). States that have expanded Medicaid have experienced greater reductions in the uninsured rate than non-expansion states (Courtemanche, Marton, Ukert, Yelowitz, & Zapata, 2017).

The Commonwealth of Kentucky has been identified as an example of successful implementation of the ACA. Through an executive order issued by then-governor Steven Beshear, Kentucky established Kynect, a state-based insurance exchange, and also expanded Medicaid. These policy changes, coupled with strategic outreach efforts, have yielded impressive changes in the rate of uninsured residents, dropping from 25% of state residents in 2013 to 13% in 2015 (Foundation for a Healthy Kentucky, 2016). The change for low-income Kentuckians has been even more dramatic, from an uninsured rate of 35% in 2013 to 11% in late 2014 (Benitez, Creel, & Jennings, 2016). Furthermore, Kentucky has been more successful in reducing its uninsured rate than other states that did not implement both the Medicaid expansion and a state-based exchange (Sommers, Maylone, Nguyen, Blendon, & Epstein, 2015).

Given the greater risk of being uninsured among PWUDs, it is important to consider the impact of the ACA for this particular population, especially in the context of the ongoing epidemic of opioid use disorder for which effective medical treatments are available. A prospective longitudinal cohort study of PWUDs in eastern Kentucky offers a unique opportunity to measure changes in insurance status over time, with data collected before and after the implementation of the ACA. Eastern Kentucky, which is located in the Appalachian region, represents an important context for studying the impact of the ACA given its elevated rates of poverty and premature mortality (Moody, Satterwhite, & Bickel, 2017). The Appalachian part of Kentucky is largely rural, with 54 counties characterized by small populations and high economic distress (Starcher, Gueurin, Shannon, & Whitley, 2017). Appalachian Kentucky counties have mortality rates from “diseases of despair” (i.e.,

overdose, suicide, and liver disease/cirrhosis from alcohol) that are 33% higher than non-Appalachian counties in Kentucky (Meit, Heffernan, Tanenbaum, & Hoffman, 2017). The current study was conducted in Perry County, which has a population of 26,500 individuals living in a land area of approximately 880 km². In Perry County, the median household income is US\$31,800 (about 45% lower than the US median household income), fewer than 13% of the population has a bachelor's degree, and about one-quarter of the population under the age of 65 has a disability (United States Census Bureau, 2019a, 2019b).

The aims of this study are two-fold. First, we examine whether the rate of insurance has increased over time among Appalachian PWUDs during the implementation of the ACA. Second, we consider whether growth in rates of insurance varies by gender, age, education, income, and history of injection drug use at baseline. Testing for differences in growth may identify sub-groups of PWUDs who remain at elevated risk of being uninsured and may have implications for future outreach efforts to expand insurance within this population.

Methods

Sample and data collection

Data were drawn from the Social Networks Among Appalachian People (SNAP) study, a longitudinal cohort study of people who use drugs in rural Appalachian Kentucky. As has been described elsewhere (Havens et al., 2013), 503 Appalachian PWUDs were recruited between November 2008 and September 2010. Participants were recruited using respondent-driven sampling, in which 107 individuals with a lifetime history of injection drug use were identified as seeds, who then invited peers who also used drugs to participate. To be eligible, individuals were required to be at least 18 years of age and to report past-month use of prescription opioids, heroin, cocaine, or methamphetamine. All individuals reported a lifetime history of illicit opioid use. Informed consent was obtained from all participants, and a Certificate of Confidentiality was obtained. Trained interviewers administered a detailed questionnaire, and participants' responses were directly entered into a laptop computer. Participants received \$50 for completing the baseline interview. Follow-up interviews were conducted approximately every 6 months through 2012, and annually thereafter with the most recent wave of follow-up interview completed in February 2017. Participants received \$50 for each follow-up interview. Retention rates at the 6 follow-ups were 93.6% (n = 471), 92.2% (n = 464), 93.0% (n = 468), 86.5% (n = 435), 82.5% (n = 415), and 81.3% (n = 409), respectively. This study was approved by the University of Kentucky's medical institutional review board, and all procedures adhered to the Declaration of Helsinki.

Measures

The present analysis draws upon seven waves of data regarding participants' insurance status and covariates measured at baseline. The outcome variable of interest was self-reported insurance status at each time point. Specifically, participants were asked, “What is your health insurance status?” during each interview, and responses were coded into three mutually exclusive categories: (1) uninsured, (2) private insurance, and (3) Medicaid or Medicare. Because few participants were privately insured, the private insurance and public insurance groups were combined, resulting in a dichotomous variable where 1 = insured and 0 = uninsured.

Time was measured as a set of categorical indicators that compared each follow-up period to baseline. We initially considered measuring time as a continuous variable, but our hypothesis was that periods after the implementation of ACA (i.e., the 5th and 6th follow-ups) were most likely to indicate change relative to baseline; we did not hypothesize that there would be changes during the pre-ACA periods. Participants'

demographic and socioeconomic characteristics were measured at baseline. Demographic variables included self-reported sex (1 = female, 0 = male), age in years, and a dichotomous measure of race (1 = non-white, 0 = white). Socioeconomic status at baseline was measured by education in years, legal income in the prior 30 days, and history of injection. The measure of legal income summed responses to items about the money received in the past-month from employment, unemployment compensation, social welfare programs, retirement benefits, and family/friends, and then a median split divided respondents into two groups (1 = past month income \geq US\$500; 0 = past month income $<$ US\$500). Finally, because injection drug use represented unique health risks as well as drug use severity, those who reported injection behaviours (= 1) were compared to those who reported no history of injection at baseline (= 0).

Statistical analysis

All analyses were performed in Stata 15.1 (StataCorp, College Station, TX). Descriptive statistics were calculated for all variables. A series of multilevel mixed effects logistic regression models were estimated to examine change in insurance status over time while accounting for the correlation of observations within individuals. Significance was set at $p < .05$ (two-sided test). In the first model, the categorical indicators for time and the baseline characteristics were entered, which allowed for an examination of change over time in insurance status and whether participant characteristics were associated with the intercept (i.e., insurance status at baseline). A final model was then estimated with baseline characteristics and time-by-characteristic interactions. Both models used maximum likelihood which has the advantage of using all observations, not just cases with complete data (Rabe-Hesketh & Skrondal, 2012). Predictive margins of the probabilities of being insured for specific groups, while adjusting for other variables in the final model, were calculated and graphed (Mitchell, 2012).

Results

Of the 503 PWUDs living in eastern Kentucky, 43.1% were female ($n = 217$), and nearly all participants were white (94.2%, $n = 474$). At baseline, the average participant was 32.5 years of age ($SD = 8.5$). Participants averaged 11.1 years of education ($SD = 2.0$), and the median monthly legal income at baseline was US\$500 (inter-quartile range = 200–900). The majority of participants reported a lifetime history of injection drug use (78.3%, $n = 394$). At baseline, only about one-third of participants were insured, and rates of being insured for the first four follow-ups were similar (see Fig. 1). At the 5th follow-up, 50.6% were insured. By the 6th follow-up, the vast majority of participants were insured (87.3%).

In the first stage of model building, only the indicators for time and baseline covariates were entered. As seen in Table 1, participants were significantly more likely to be insured at the 5th and 6th follow-up interviews, when compared to the likelihood of being insured at baseline. In addition, several of the baseline characteristics were associated with the intercept (i.e., baseline likelihood of being insured). Women were more likely at baseline to be insured than men. The likelihood of being insured at baseline was positively correlated with age. Those with greater legal income were more likely than those with less legal income to be insured at baseline. There was a negative association between years of education and the likelihood of being insured at baseline.

In the final model, associations for time, the covariates, and time-by-covariate interactions were estimated (see Supplemental File). Predictive margin probabilities, which allow for additional consideration of group differences over time while adjusting for all other variables in the model, further elucidated these findings (Fig. 2). Regarding demographics, the association between gender and the intercept (i.e., baseline likelihood of being insured) continued to be statistically

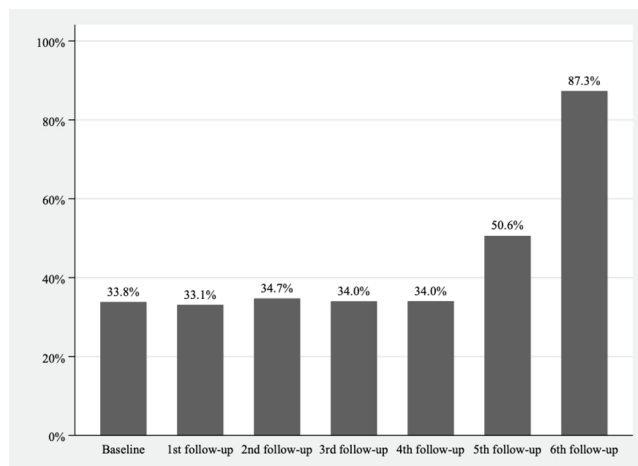


Fig. 1. Percent of participants with health insurance in a cohort of persons who use drugs in eastern Appalachian Kentucky, 2008–2016.

Table 1

Insurance status over time in a cohort of persons who use drugs in eastern Appalachian Kentucky, 2008–2016.

	Model 1 Unstandardized Coefficient b (95% CI)
Time	
Baseline	Reference
1 st follow-up interview	−0.06 (−0.44, 0.32)
2 nd follow-up interview	0.03 (−0.35, 0.41)
3 rd follow-up interview	0.03 (−0.35, 0.42)
4 th follow-up interview	0.03 (−0.36, 0.42)
5 th follow-up interview	1.46 ^{***} (1.06, 1.85)
6 th follow-up interview	4.73 ^{***} (4.19, 5.26)
Sex	
Female	1.87 ^{***} (1.38, 2.35)
Male	Reference
Age in years	0.07 ^{***} (0.04, 0.10)
Race	
Non-white	0.70 (−0.28, 1.68)
White	Reference
Past-month legal income	
< \$500	Reference
\geq \$500	1.39 ^{***} (0.91, 1.86)
Education in years	−0.19 ^{**} (−0.30, −0.07)
Lifetime injection drug use	
Ever injected	−0.36 (−0.91, 0.19)
Never injected	Reference
Constant	−2.79 ^{**} (−4.52, −1.05)

Note: CI = confidence interval.

* $p < .05$.

** $p < .01$.

*** $p < .001$ (two-tailed tests).

significant ($b = 2.15$, 95 CI = 1.43, 2.87, $p < .001$), but there were no interactions between gender and time. As seen in the predictive margin probabilities in Fig. 2, there were consistent differences between men and women through the 4th follow-up, and the increases in the probabilities of being insured at the 5th and 6th follow-ups, relative to the likelihood of being insured at baseline were of similar magnitudes for women and men.

Age was positively associated with insurance status at baseline ($b = 0.07$, 95% CI = 0.03, 0.11, $p = .002$), but there were no age-by-time interactions. As seen in Fig. 2 where predictive margin probabilities were calculated for individuals at the mean age as well as mean ± 1 SD, the differences between these three groups were consistent across the first five time points. At the last follow-up, the predictive margin probabilities were similar.

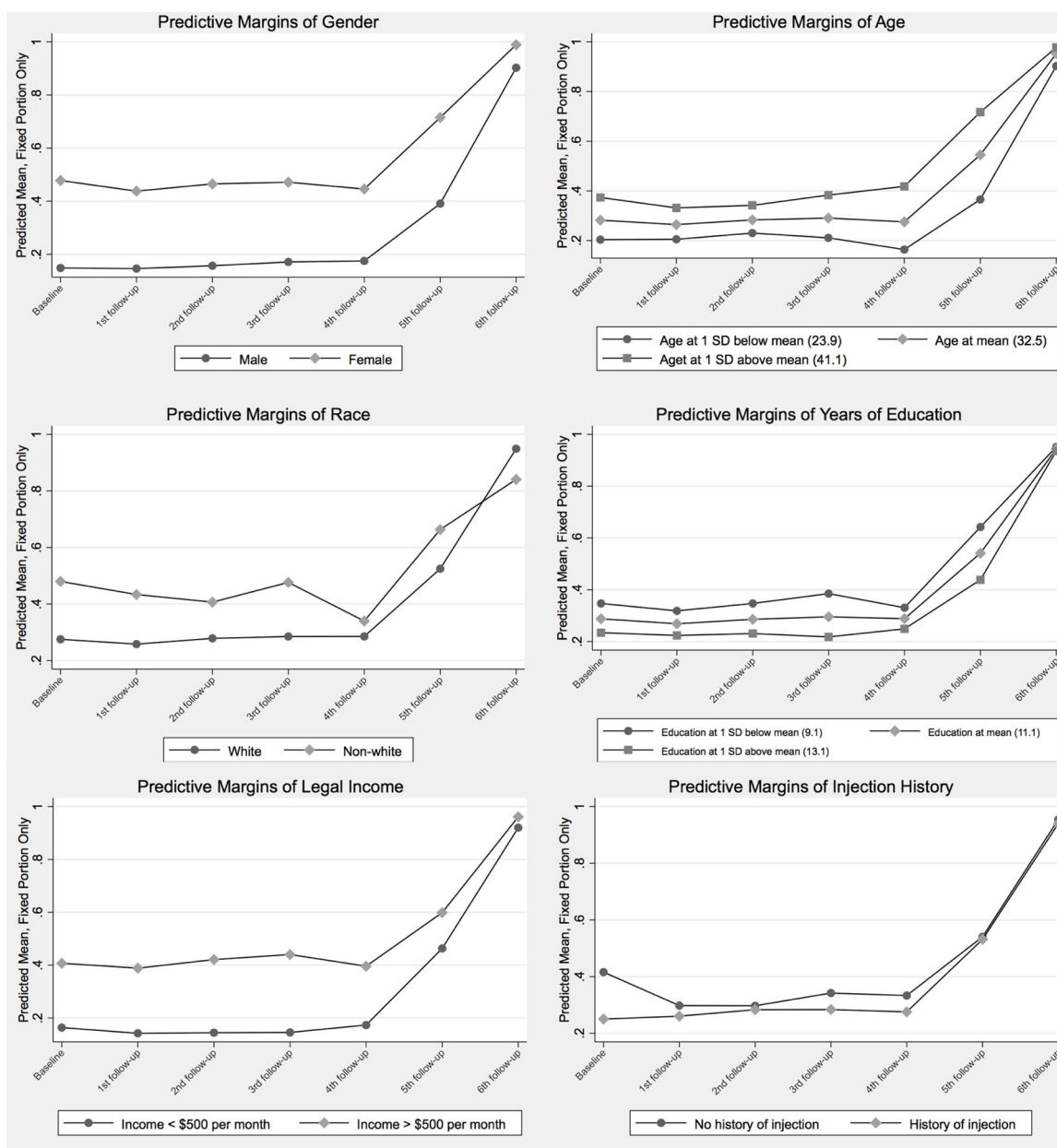


Fig. 2. Predictive margin probabilities of insurance status by demographic and socio-economic variables in a cohort of persons who use drugs in eastern Appalachian Kentucky, 2008–2016.

For race, there was no difference in the likelihood of being insured at baseline ($p = .07$), but one interaction was statistically significant. Specifically, the change in the probability of being insured at the 6th follow-up, relative to baseline, was significantly smaller for non-white participants than for white participants ($b = -2.73$, 95% CI = $-4.49, -0.98$, $p = .002$). As seen in Fig. 2, white participants had a particularly large increase in the likelihood of being insured, relative to their baseline likelihood, at the 6th follow-up interview.

Years of education was negatively correlated with the likelihood of being insured at baseline ($b = -0.20$, 95% CI = $-0.37, -0.03$, $p = .02$), and there were no significant time-by-education interactions. As seen in Fig. 2, where predictive margin probabilities were calculated for individuals with the mean years of education as well as those with mean ± 1 SD of education, there were fairly consistent differences across the first five time-points, but then the probabilities converge at the last follow-up interview.

Income was positively associated with the intercept ($b = 1.68$, 95% CI = $0.96, 2.40$, $p < .001$), and there was one statistically significant interaction. Relative to baseline, the change in likelihood of being insured at the 5th follow-up was significantly smaller for higher income participants than for lower income participants ($b = -0.94$, 95% CI = $-1.74, -0.13$, $p = .02$). In the predictive margin probabilities presented in Fig. 2, there was a considerable difference between these two groups for the first 5 interviews where the probability of being insured was about double for individuals who were in the higher income group. At the 5th follow-up, lower income participants had a larger increase in their probability of being insured, and the probabilities generally converged at the 6th follow-up.

Finally, injection status was associated with the intercept and two time-by-injection status interactions were significant. At baseline, individuals with a history of injection were significantly less likely to be insured ($b = -1.08$, 95% CI = $-1.90, -0.27$, $p = .009$) than

individuals with no history of injection. At the 2nd follow-up, the interaction of time and injection history was positive ($b = 0.99$, 95% CI = 0.08, 1.90, $p = .03$). As seen in Fig. 2, those with no history of injection experienced a decrease in the likelihood of being insured from baseline (margin = 0.42) to 2nd follow-up (margin = 0.30), while those with a history of injection had a very small increase (baseline margin = 0.25; 2nd follow-up margin = 0.28). The time interaction was also significant at the 5th follow-up, with those having a history of injection having a larger increase in the likelihood of having insurance, relative to their baseline likelihood, when compared to those who had never injected ($b = 1.03$, 95% CI = 0.11, 1.95, $p = .03$). Notably, the probability of being insured at the last follow-up was essentially identical for the two groups.

Discussion

This longitudinal cohort study of PWUD who lived in eastern Kentucky found large-scale growth in the percentage of participants who were insured, with this growth aligning with Kentucky's implementation of ACA. For the first five interviews, which preceded ACA implementation, the insured rate was virtually unchanged. However, the percentage of individuals who were insured more than doubled by the final follow-up interview. Within this cohort, there were considerable differences in the likelihood of being insured at baseline by demographic and socioeconomic characteristics. Groups varied somewhat in their timing of when they experienced significant increases in the likelihood of becoming insured, but differences in the probability of being insured by these characteristics had largely dissipated by the most recent follow-up interview after the full implementation of the ACA.

This growth is particularly notable given the disparities in insurance status experienced by this cohort relative to the Commonwealth and the nation. About one-quarter of all Kentuckians were uninsured in 2013, before ACA implementation, a rate that was nearly halved by 2015 (Foundation for a Healthy Kentucky, 2016). At the last time point of the current study, only 13% of participants remained uninsured, which is congruent with the statewide rate, despite this population of PWUDs being far more likely to be uninsured at baseline. Nationally, data have shown that the ACA has increased the rate of insurance for people with SUD or serious psychological distress, but the gains were more on the order of about 5–10 percentage points rather than the dramatic 50 percentage point increase found in this cohort (Creedon & Cook, 2016; Saloner et al., 2017). However, the finding that some individuals remained uninsured despite the implementation of the ACA is consistent with the literature. Massachusetts adopted universal health coverage policies well before the ACA, and their state-level data indicated that a substantial proportion of individuals with opioid use disorder remained uninsured despite this policy change (Stein, Bailey, Thurmond, & Paull, 2014). Similarly, data from the 2014 National Survey on Drug Use and Health (NSDUH), conducted post-ACA implementation, indicated that 20.8% of individuals with SUD remained uninsured (Saloner et al., 2017).

Although these gains in health insurance were substantial, it is important to note that having insurance may not be sufficient to ensure receipt of SUD treatment. Recent studies point to the importance of being insured, being aware that one's insurance covers SUD treatment (Cummings et al., 2014), and perceiving a need for treatment (Ali, Teich, & Mutter, 2015). To date, most analyses of national data on the impact of the ACA have found that treatment utilization has not increased despite the increasing proportion of individuals with SUD who have insurance (Feder et al., 2017; Saloner et al., 2017). A recent analysis comparing treatment utilization in Medicaid expansion vs. non-expansion states found no difference (Olfson, Wall, Barry, Mauro, & Mojtabai, 2018). However, there have been some promising signs in the wake of the ACA. Fewer people with OUD reported financial reasons as the barrier to treatment post-ACA (McKenna, 2017). At the

state-level, there has been greater growth in utilization of buprenorphine within the Medicaid program (Wen, Hockenberry, Borders, & Druss, 2017) and outpatient medications for addiction treatment in expansion states (Meinhofer & Witman, 2018).

A number of other challenges in accessing treatment remain, including policy and organizational barriers. For example, an analysis of health insurance plans in the post-ACA health insurance exchanges found variation in state requirements regarding which SUD treatment services, such as specific medications, outpatient treatment, and residential treatment, must be covered (Tran Smith et al., 2018). In addition to variation in coverage, it is notable that about 45% of specialty SUD programs do not accept Medicaid and a similar percentage does not accept private insurance (Aletraris, Edmond, & Roman, 2017)—another barrier to treatment access.

In rural areas, there are additional barriers to care. There is a lack of qualified treatment providers in Appalachia (Moody et al., 2017), and Appalachian Kentucky experiences substantial disparities regarding primary care and specialty physicians. More than half of rural counties in the US still do not have any practitioners who hold the waiver to prescribe buprenorphine to treat OUD (Andrilla, Moore, Patterson, & Larson, 2019). Furthermore, only about half of rural physicians holding the buprenorphine waiver are accepting new patients (Andrilla, Coulthard, & Patterson, 2018). Such disparities in service availability helps to explain, for example, why individuals living in rural areas are significantly less likely to receive specialty OUD treatment (Romo, Ulbricht, Clark, & Lapane, 2018).

Several limitations should be noted. First, this study was conducted in a region within a single state that has largely embraced key provisions in the ACA; it is unknown whether there are other states where the observed increase in insurance among PWUDs has occurred to the same degree. The findings also do not generalize to other countries with different methods of structuring health insurance. A strength of this study is the longitudinal cohort design, as most other analyses of the ACA have relied upon repeated cross-sectional surveys (i.e., NSDUH data) rather than measuring change within a cohort. However, the study design is observational, so causality cannot be firmly established. While Kentucky's implementation of the ACA represents one of the most significant changes within the state during the study period, it is possible that other factors may have prompted some individuals to obtain insurance. Furthermore, the impact of the separate components of Kentucky's implementation of ACA cannot be determined. For example, Kentucky's implementation of ACA has included the Medicaid expansion, the establishment of a state-based health insurance exchange, a well-publicized website for insurance enrolment, and the widespread use of community-based navigators and other outreach efforts to encourage enrolment. Our data cannot address the specific impact of each of these mechanisms on the likelihood of insurance enrolment.

This longitudinal study of PWUDs in Eastern Kentucky found significant increases in the proportion of cohort members who became insured after the implementation of the ACA. Given the substantial literature on the positive benefits of being insured on health outcomes, these gains may have meaningful benefits for a population who have historically experienced substantial barriers to SUD treatment and other health care as well as very high morbidity and mortality rates. Future research is needed about the health-related impacts of gaining insurance within this cohort, particularly given the structural obstacles to care in the region such as limited availability of SUD treatment. Such analyses will be possible because we continue to collect data from this cohort. It should be noted that in 2016, the Commonwealth of Kentucky (2016) submitted a Section 1115 waiver to the Centers for Medicare and Medicaid Services (CMS), seeking to impose co-payments, monthly premiums, and work/volunteering requirements for its Medicaid program. These changes were challenged, with a federal judge blocking the Section 1115 waiver's implementation (Henry J. Kaiser Family Foundation, 2018a). CMS re-approved Kentucky's Section 1115 waiver in late November 2018 with implementation of these changes planned

for April 2019 (Henry J. Kaiser Family Foundation, 2018b), but a federal judge recently blocked their implementation. If implemented, these changes would likely impact this cohort who largely are insured by Medicaid. Our ongoing research will seek to capture the impact of such changes.

Conflict of interest

Hannah Knudsen and Jennifer Havens have no conflicts of interest to declare. In recent years, Michelle Lofwall has received contract funding to support research from Braeburn Pharmaceuticals (which has developed a buprenorphine product), has provided consultation to Braeburn, CVS Caremark, and Indivior (which manufacture buprenorphine products), and has received honoraria from PCM Scientific, which received unrestricted educational grant funds from Reckitt Benckiser (now Indivior), for work in developing and presenting educational talks on opioid use disorder. Sharon Walsh has received consulting fees and research support from Braeburn Pharmaceuticals, consulting fees from Camurus, honoraria and travel support from Indivior, and honoraria from PCM Scientific, through an unrestricted educational grant from Reckitt Benckiser, for serving as a speaker and conference organizer.

CRediT authorship contribution statement

Hannah K. Knudsen: Conceptualization, Formal analysis, Visualization, Writing - original draft. **Michelle R. Lofwall:** Writing - original draft, Writing - review & editing. **Sharon L. Walsh:** Writing - original draft, Writing - review & editing. **Jennifer R. Havens:** Methodology, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugpo.2019.04.008>.

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