Assessing the potential effects of unmeasured confounders in a single and a meta-analysis of opioid use disorder studies

by

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Sensitivity Analysis on Unmeasured Confounders for Studies of Opioid Use Disorder

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Incidence of opioid abuse disorder (OUD) and overdose death have reached epidemic proportions. In the intervention of OUD, it is necessary for healthcare providers to understand the relationship between subjects' characteristics and usage of medication for OUD. As the largest financing source in the US for OUD treatments, Medicaid provides a wealth of data for researchers to examine the exposure-outcome relationship, yet a major concern is that unmeasured confounders could explain away the observed relationship.

The goal of this thesis is to apply a sensitivity analysis measure to examine the unmeasured confounding effect that could influence the association between the effect of a Medicaid enrollee's characteristics and the OUD outcomes, where the effects included individual characteristics of interest include race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, others) and eligibility group (pregnant women, youth, adults with disability, nondisabled adults), and the outcomes included receiving medication for OUD and OUD medication continuity for 180 days. The associations have been previously studied among Medicaid enrollees form a US individual state and from meta-analysis with multiple US states. Based on the published estimated associations, the study investigated about how strong the unmeasured confounding must be in order to completely explain away the effect of an enrollee's characteristics on the OUD outcomes. Results showed that the reported 95% confidence intervals of the estimated effects changes so much as to include the null hypothesis of no effects when the effects of unmeasured confounders, in a risk ratio scale, are ranging from 1.03 to 1.51. For meta-analysis, the minimum confounding

strength required to explain away the confounded effects in one out of ten states with true effects exceeding the scientific importance threshold is ranging from 2.24 to 2.80. These results showed that the associations between enrollees' characteristics and the OUD outcomes are weak and not robust to unmeasured confounders.

Public health significance: E-value is a useful tool used to perform sensitivity analysis of the impact of unmeasured confounding for observational study. Results of sensitivity analysis should be included for researchers to correctly assess the robustness of exposure-outcome relationships leading to a design strategy or a medical decision.

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1.0 Introduction

Started from the 1990s, the increasing incidence of opioid abuse disorder and overdose death from making opioid reached epidemic proportions (Rudd, et al., 2016). About 21 to 29 percent of patients were prescribed opioid medication for chronic pain, and 8-12 percent of them developed an opioid abuse disorder (Vowles et al., 2015; Webster, 2017). Based on the data published by CDC in 2020, the number of drug overdose deaths increased by about 30% over the past year, with nearly three-quarters of all drug overdose death related to inappropriate usage of opioids (CDC, 2020).

Because of the high prevalence and death rate of opioid use disorder (OUD), it is necessary to find a better treatment to control the prevalence of opioid use disorder. Possible treatments for OUD include initiative opioid agonist treatment (with buprenorphine-naloxone or methadone), slow-release oral morphine and adjunct psychosocial treatment interventions (Bruneau et al., 2016). In order to understand the effectiveness of each treatment strategy, it is important to estimate the causal treatment effects of each strategy on OUD and the relationship between patients' characteristics and outcomes related to OUD interventions.

Causal treatment effect is a concept in causal inference. Cause is different from risk factor because it must satisfy three conditions: 1) risk factor precedes the situation; 2) changes in the independent variable accompanies by changes in the dependent variable, and 3) there is still causal effect between risk factor and situation after removing all extraneous variables (LaMorte, 2019). Causal exposure effect is defined as the comparison of potential outcomes for the same subjects under different exposure conditions (Imbens et al. 2015; John et al., 2019). Exposure is defined as

a situation or intervention that a person can be exposed or unexposed (Imbens et al. 2015). When exposure is a treatment, causal exposure effect is the causal treatment effect.

To estimate causal treatment effect from observational data, the data needs to satisfy the SUTVA condition and the assumptions of consistency, positivity, and ignorability. Stable Unite Treatment Value assumption (SUTVA) requires that the potential outcome observed on one subject should not be affected by the treatment for other subjects (Imbens et al., 2015; Rubin, 1977; Rubin, 1978). This assumption implies no interference between subjects. The consistency assumption requires that there are no two versions of treatment; in other words, among the treated people, the treatment they received should be absolutely the same (Rehkopf et al., 2016; Cole et al., 2009). This assumption requires a clearly defined treatment procedure in the study design. The second assumption is positivity which means that any individual has a potential (i.e., positive probability) of receiving or not receiving a certain treatment (Hernán et al., 2006; Cole et al., 2009). The third assumption is ignorability, also known as the no unmeasured confounder assumption. This assumption considers other variables, the pre-treatment covariates, that could potentially influence the relationship between treatment and outcomes. It assumes that subjects among different treatment group should have the same value on other variables that could potentially influence the outcomes and there are no other unmeasured covariates that could affect the relationship between treatment and outcomes (Taback, 2016).

Researchers usually found that the ignorability assumption could be difficult to satisfy in the real-world setting (Sibbald et al., 1998). Randomized controlled trial (RCT) is considered as the most powerful tool to examine the causal relationship between treatments and outcomes, because it can randomly assign subjects into treatment groups, which will make multiple treatment groups comparable for known and unknown baseline factors. As an RCT provides an estimate of

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treatment effectiveness that is unlikely to be explained by other factors, the treatment effect estimates can be considered as causal treatment effects (Sibbald et al., 1998). However, the treatment effect estimates obtained from an observational analysis are associational and may, or may not, have a causal interpretation, since there is no randomization and there may be some other unknown factors influencing the relationship between the treatment and outcomes (John et al., 2019).

Medicaid enrollees were not randomized according to their underlying characteristics and therefore might be subject to some unmeasured confounders that could influence their effects on the OUD outcomes, for example, social or family environments are factors that are difficult to assess among Medicaid enrollees. However, these factors could be associated with an enrollee's exposure status and the outcome. Therefore, to report the effect of an enrollee's characteristic on the outcomes, we will need to examine the impact of unmeasured confounding effect on this relationship.

The goal of this thesis is to apply a sensitivity analysis measure, i.e., the E-value (Ding and VanderWeele, 2016; VanderWeele and Ding, 2017) to examine the unmeasured confounding effect that could influence the association between the effect of a subject's characteristic and the OUD outcomes, including receiving medication for OUD (yes/no) and OUD medication continuity for 180 days (yes/no). Individual characteristics of our interest include race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, others) and eligibility group (pregnant women, youth, adults with disability, adults newly eligible under the ACA Medicaid expansion, adults without disability). The associations have been studied among Medicaid enrollees from 11 US states (Brown et al, 2021). Based on the published estimated associations, we investigate how

strong would unmeasured confounding have to be in order to completely explain away the effect of an enrollee's characteristic on the OUD outcomes.

In Chapter 2, we introduce some causal terminology, definition of average causal treatment effect, and four causal assumptions for estimating the effect using data collected from observational studies. In Chapter 3, we describe the formula used to calculate the E-value and its interpretations. We also describe the sensitivity analysis for meta-analysis and its formulas for calculating the minimum unmeasured confounding that could explain away the association between the treatment-outcome relationships in meta-analysis of observational studies. In Chapter 4, we apply the E-value and sensitivity analysis techniques to a single study and to meta-analysis using Medicaid data to examine the robustness of the covariate effects. Finally, conclusions and discussions are presented in Chapter 5.

2.0 Causal Inference

Suppose that in an observational study with a binary outcome Y, the estimated relative risk (RR) is assumed to be obtained after controlling for several covariates believed to be confounders in the relationship between exposure and outcome. Let X denote a binary exposure variable (X=0: unexposed, X=1: exposed), Y a binary outcome (Y=0 or Y=1), A a set of measured confounders, and U one or more unmeasured confounders.

A **counterfactual outcome** is a potential outcome, or an outcome that would have been observed in a situation but did not actually happen. For a subject who is not exposed to the condition X, his/her counterfactual outcome is defined as $Y^{X=0}$. For a subject who is exposed to the condition X, his/her counterfactual outcome is defined as $Y^{X=1}$. Causal effect at the individual level a comparison between the potential outcomes for a given individual , $Y^{X=1} - Y^{X=0}$. However, for a subject, only one of the two potential outcomes can be observed. This is called the Fundamental Problem of Causal Inference (Holland, 1986). Therefore, we usually estimate the causal effect at the population level. Let the expected potential outcomes $\mathbb{P}(Y^{X=0} = 1)$ and $\mathbb{P}(Y^{X=1} = 1)$ be the proportion of subjects who would have developed the outcome $Y = 1$ among all subjects in the population of interest who did not expose to condition X and among all subjects in the population of interest who were exposed to condition X, respectively. Then the causal effect at the population level, the **average causal effect**, is defined as the difference of these two expected potential outcomes $\mathbb{P}(Y^{X=1} = 1) - \mathbb{P}(Y^{X=0} = 1)$. We say that X has a causal effect on Y if $\mathbb{P}(Y^{X=1} = 1) \neq \mathbb{P}(Y^{X=0} = 1)$.

In order to estimate the causal effect of X on Y using data collected from an observational study, the Stable Unit Treatment Value Assumption (SUTVA) and the assumptions of consistency, positivity, and ignobility must hold. That is that, under these assumptions, we can estimate the expected potential outcomes $\mathbb{P}(Y^{X=0} = 1)$ and $\mathbb{P}(Y^{X=1} = 1)$ by the observed outcomes $\mathbb{P}(Y = 1|X = 0)$ and $\mathbb{P}(Y = 1|X = 1)$.

The **SUTVA** assumes that the value of Y for subject i when exposed to treatment X will be the same no matter what mechanism is used to assign treatment X to subject i and no matter what the treatment other subjects received. Therefore, SUTVA implies that potential outcomes for a given subject respond only to his/her own treatment status.

The **consistency** assumption indicates that an individual's observed outcome Y under treatment condition $X = x$ is equal to his potential outcome $Y^{X=x}$, where $x = 0$ if unexposed and $x = 1$ if exposed. This assumption transforms expression of the counterfactual quantities $Y^{X=x}$ into expression of observed quantities $Y|X = x$. Consistency is simply a natural consequence that automatically holds for structural causal model if researchers properly define the structural causal mode (Galles et al., 1998). However, consistency is still an assumption, not something that is true by definition. Consistency can hold if the intervention or exposure is well-defined in the study proposal. In contrary, there might be multiple different types of initiative opioid agonist treatments for OUD. When measure $Y^{X=1}$ in people who were assigned to initiative opioid agonist treatment group and the treatments was not clearly defined in study, there would be multiple counterfactual variables: one for people who used buprenorphine-naloxone and another for people who used methadone. Since there is no clear definition of the intervention, the construct $Y^{X=1}$ would be a composite quantity, which could not be used to predict the consequences of the intervention.

The **positivity** assumption indicates that any individual has a positive probability to be assigned into any of the treatment exposure group $X = x$, implying that people who were treated and people who were not treated can be found in each subgroup. If positivity does not hold, we will not have information about the distribution of $Y^{X=x}$ for that value of x, and therefore it will be impossible to estimate the average causal effect between exposure and outcome in that subgroup. Positivity can be checked by examining if there are individuals with exposure and individuals without exposure in all strata; if so, this can be considered as the satisfaction of positivity.

The **ignorability** assumption indicates that for a given set of pre-treatment covariates A, exposure X is independent of the potential outcomes. This implies that among individuals with the same value of A, exposure X is randomly assigned. Ignorability assumption can also be interpreted as no unmeasured confounders influencing the relationship between the exposure and the outcome. The assumption can be depicted by a directed acyclic graph (DAG). In the left panel of **Figure 1**, the DAG shows that ignorability assumption is violated since A is a common cause of exposure X and outcome Y. Under this scenario, there is a non-causal association between X and Y. The right panel of Figure 1 shows the treatment assignment mechanism is ignorable. Ignorability assumes that all unobserved variables that affect the outcome Y have no effect on exposure X.
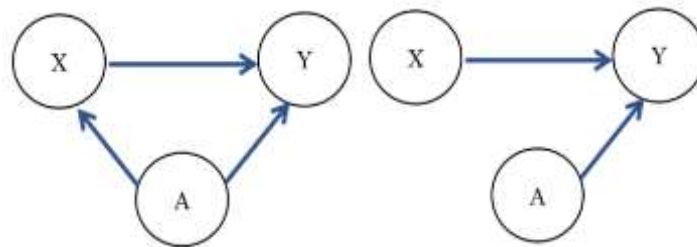

Figure 1 Relationship between Confounders, Exposures and Outcomes

In randomized experiments, the exposure or treatment can be considered as ignorable, because there will be equal probability for subjects with different level of covariates assigned into the exposure group or the control group, which means confounders are controlled during the randomization. However, in an observational study, the probabilities of having individuals with different level of covariates in two exposure groups might be different, so there might be confounders that could influence the relationship between the exposure and the outcome. Although confounding effect can be controlled by adding more potential confounders into a regression model, it is still possible that some important confounders, which could cause unmeasured confounding effect and decrease the reliability of the estimates.

In data collected from an observational study, ignorability assumption is almost always violated; therefore, additional measures may be needed for the study, for example, if patients' intention to quit the use of medication for opioid use disorder (MOUD) can influence the effectiveness of MOUD, it would be advisable to have a pre-treatment measure of patients' intention and include this as an input in the regression model to increase the plausibility of the ignorability assumption. However, in fact, patients' intention to quit the use of MOUD is difficult to measure, and there may be factors influencing the relationship between MOUD and OUD unaware of by the researchers. In general, one can never prove that the exposure or an intervention assignment in an observational study is ignorable—it is always possible that the choice of treatment or exposure is dependent on relevant information that has not been recorded. In the study of MOUD, this information could be family support that are related both to MOUD assignment and to the OUD outcomes such as the continuation of the use of MOUD. Thus, for observational study, results could be unreliable for not being able to control all confounders, therefore, it is

necessary to find a way to measure the unmeasured confounding effect and also check the strength and reliability of the study results. (Gelman and Hill, 2007)

3.0 E-value

3.1 E-value for Individual Study

As mentioned in the previous section, in an observational study, it is difficult to control the effects of all confounders on the relationship between a predictor and the outcome. Therefore, it is impossible to satisfy the ignorability assumptions for data obtained from an observational study, and the estimated effects are subject to bias. To improve the reliability of study results, it is necessary to conduct a sensitivity analysis, which is a procedure to access how strong the unmeasured confounding must be in order to explain away the association (Greenland, 2005; Rosenbaum, 2005). In this thesis, I will use a sensitivity analysis technique, called the E-value proposed by VanderWeele and Ding (2016, 2017) to assess the robustness of the reported relationship between Medicaid enrollees' characteristics and the usage of medication for OUD.

E-value represents the minimum magnitude of association between unmeasured confounders with exposure (RR_{UE}) and outcome (RR_{UO}) that is needed to explain away the association between an exposure and the outcome. It is an assessment of the robustness of an association to potential uncontrolled confounders, with higher number indicating a stronger confounder association needed to change the observed association. Since RR_{UE} and RR_{UO} have a negative relationship to determine the minimum confounder relationship, the E-value essentially sets these two parameters RR_{UE} and RR_{UO} equal. The equation used to calculate the E-value for an observed (or confounded) risk ratio is:

$$\text{E-value} = RR + \sqrt{RR \times (RR - 1)},$$

where RR is the observed (confounded) risk ratio.

This equation applies to a risk ratio greater than 1. For a risk ratio less than 1, the observed risk ratio should be inversed first and then applies the equation. E-value equation can also apply to odds ratio and hazard ratio. Many other statistics including risk difference, standardized mean difference, and linear regression coefficient can be first converted to risk ratio and then apply the equation to calculate the E-value (VanderWeele, et al. 2017).

3.2 E-value for Meta-analysis Study

Based on the definition and calculation method of the E-value for a single study, an extension of the E-value for meta-analysis has been developed and was used to check the strength of the causal relationship between exposures and outcomes reported in multiple studies. These values were used to measure the strength of the associations in meta-analysis include 3 parts: 1) proportion of studies with true causal effects more extreme than scientific meaningful threshold $P(q)$; 2) the minimum bias factor needed to explain away the results $T(r, q)$; and 3) the minimum unmeasured confounding strength needed to explain away the results $G(r, q)$.

We use $P(q)$ to denote the proportion of studies with effect size above a chosen threshold of scientific importance. Let q represent the minimum threshold of scientific importance; Φ is the standard normal cumulative distribution function; B^* represents the bias factor on log scale $B^* = \log B$ and $B^* \sim N\left(\mu_{B^*}, \sigma_{B^*}^2\right)$, in which B represents the ratio of the confounded risk ratio to the true risk ratio. The y_R^C denotes the pooled point estimate of risk ratio. To calculate the proportion of studies $P(q)$ for confounded pooled risk ratio greater than 1, the equation is below:

$$P(q) = 1 - \Phi\left(\frac{q + \mu_{B^*} - y_R^C}{\sqrt{\tau_C^2 - \sigma_{B^*}^2}}\right).$$

In a meta-analysis, the greater the $P(q)$ is, the stronger the proportion of the true effect size is as compared with the threshold of scientific importance, which means that effects measured by most studies are strong enough to satisfy scientific interest.

We use $T(r, q)$ to denote the minimum bias factor needed to explain away the results and r denotes the minimum proportion of true effect above the minimum threshold of scientific importance. $T(r, q)$ can be calculated by this equation when the risk ratio is greater than 1:

$$T(r, q) = \exp\left\{\Phi^{-1}(1 - r)\sqrt{\tau_C^2} - q + y_R^C\right\}.$$

A large $T(r, q)$ indicates that it would take substantial unmeasured confounding to explain away the results of the meta-analysis, which means that the meta-analysis results is robust to unmeasured confounding.

Let $G(r, q)$ denote the minimum unmeasured confounding strength needed to explain away the results, which is calculated by this equation no matter the risk ratio is lower or higher than 1:

$$G(r, q) = T(r, q) + \sqrt{\{T(r, q)\}^2 - T(r, q)}.$$

A large $G(r, q)$ value indicates a large strength of confounding needed to explain away the results of the meta-analysis, which means that the results is robust to unmeasured confounding.

When we compute $P(q)$, $T(r, q)$ and $G(r, q)$, it is critical to choose an appropriate value for q and r. A general guideline for q could be $q = \log 1.1$ or $q = \log 0.9$ as the minimum threshold for an apparently causative risk ratio (risk ratio > 1) or preventive risk ratio (risk ratio < 1) (Mathur, 2019). The r represents the percentage of studies which have effective sizes above our threshold q, and this number can be set as 0.20, which is a general number used in sensitivity

analysis when the total number of studies is between 10 and 15 (VanderWeele, et al. 2017). The σ_{B*}^2 can be from 0 to a value less than τ_c^2, based on similarity on confounders controlled by the studies and the similarity of studies' population. Since all studies in meta-analysis were adjusted to the same group of confounders and populations were very similar, to get the most conservative results, it is reasonable to set σ_{B*}^2 as 0. If the value of μ_{B*} is log1.15, then 95% of the studies will have B at 1.15, which means that studies rarely get point estimates that are inflated by more than 1.15 folds due to unmeasured confounding, and we believe that this number should be reasonable for our study since the risk ratio reported in our studies are small and many confounders were controlled by studies. Therefore, μ_{B*} can be decided as log1.15 in this study.

4.0 Application to Studies of Opioid Use Disorder

In this thesis, we apply E-value to investigate the robustness of the estimated effects due to unmeasured confounding in results reported by the Medicaid Outcomes Distributed Research Network (MODRN) (Donohue et al., 2021). MODRN is a collaborative effort analyzing Medicaid data across multiple states to facilitate learning among Medicaid agencies. The objective of the paper published in JAMA 2021 is to examine the use of medications for opioid use disorder (OUD) and potential indicators of quality of care in 11 states. These 11 states included Delaware, Kentucky, Maine, Mayland, Michigan, North Carolina, Ohio, Pennsylvania, Virginia, West Virginia, and Wisconsin, which covered more than 20% Medicaid enrollees and 6 of 10 states reported the highest overdose deaths in United States (CDC, 2018).

Participating universities in these 11 states received the claims and enrollment data for a census of enrollees directly from their states' Medicaid agency and transformed the raw Medicaid data into a common data model with the same structure and data elements using a previously validated process. With the data from these 11 states, MODRN analytic group conducted a meta-analysis to examine the effects of enrollees' demographic and clinical factors on the outcomes. The demographic and clinical factors include age (12-20, 21-34, 35-44, 45-54, and 55-64 years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and others), rural or urban residence, 5 eligibility groups (pregnant women, youth, adults with disability-related Medicaid eligibility, adults newly eligible under the ACA Medicaid expansion and traditionally eligible non-disabled adults). The outcomes of interest include enrollees' receiving any medications for OUD and the continuity of Medication for OUD.

We apply E-value formula to examine the robustness of their findings to unmeasured confounding (1) for individual study using Medicaid data in Pennsylvania and (2) for meta-analysis aggregating the results from the 11 states. We will report the minimum bias factor that can explain away their estimated significant associations between exposures and outcomes. The exposures we used in the calculations include race/ethnicity (non-Hispanic White is the reference group) and the 5 eligibility groups on a person-year basis (nondisabled adults and expansion adult is reference group), because these two exposures were reported as having significant relationship with enrollees' receiving any medications for OUD and the continuity of Medication for OUD in MODRN study.

4.1 Software

The R-package EValue developed by Mathur can be used to calculate the E-values and produce various plots. An R-Shiny dashboard created based on this EValue package is also available to implement the main functions in the EValue package. We performed data analysis using functions in this R-Shiny dashboard. This dashboard can be found in the website: https://mmathur.shinyapps.io/meta_gui_2/.

4.2 Results

In this chapter, we demonstrate the sensitivity analysis results for (1) individual study for the exposure effects estimated from one state, and (2) meta-analysis for the exposure effects

estimated from pooled results from 11 states. The exposure effects of interest include race/ethnicity and eligibility group for eligible Medicaid enrollees. The outcomes of interest are receiving medications for OUD and at least 1 period of 180 days of continuous OUD medications.

4.2.1 Results for Individual Study

The E-values of confounded odds ratio (OR) and confidence interval for enrollees' receiving any medications for OUD in Pennsylvania are shown in Table 1 and for enrollees' continuity of OUD medications are shown in Table 2.

In Table 1, compared to non-Hispanic White, an estimated confounded OR was 1.05 (95% CI: 1.04-1.07) and 0.77 (95% CI: 0.76-0.78) for Hispanic and Non-Hispanic Black, respectively. With these observed odds ratios, unmeasured confounders that were associated with both receiving any medications for OUD (outcome) and race/ethnicity (exposure), odds ratio 1.19 to 1.53-fold each, above and beyond the measured confounders, could explain away the estimates, but jointly weaker unmeasured confounding associations could not. Unmeasured confounders that were associated with both the outcome and the exposures by an odds ratio of 1.16 to 1.51-fold each, above and beyond the measured confounders, could shift the CI to include the null, but weaker confounding could not.

Compared to nondisabled adults, an estimated confounded OR was 0.79 (95% CI: 0.73-0.85), 1.03 (95% CI: 1.00-1.06), and 1.14 (95% CI: 1.11-1.17) for children, disabled adults, and pregnant women, respectively. With these observed odds ratios, unmeasured confounders that were associated with both receiving any medications for OUD (outcome) and eligibility group (exposure), odds ratio 1.14 to 1.51-fold each, above and beyond the measured confounders, could explain away the estimates, but jointly weaker unmeasured confounding associations could not.

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Unmeasured confounders that were associated with both the outcome and the exposures by an odds ratio of 1.03 to 1.39-fold each, above and beyond the measured confounders, could shift the CI to include the null, but weaker confounding could not.

Table 1. E-value for Individual Study for Patients' Receiving Medication for OUD

Variable	Odds Ratio (95% CI)	E-value for Point Estimate	E-value for the Confidence Interval
Race/ethnicity			
Hispanic	1.054 (1.039, 1.070)	1.19	1.16
Non-Hispanic Black	0.772 (0.761, 0.783)	1.53	1.51
Non-Hispanic Other	1.000 (0.980, 1.021)	--	--
Eligible group			
Children	0.785 (0.726, 0.849)	1.51	1.39
Disabled Adults	1.029 (1.001, 1.058)	1.14	1.03
Pregnant Women	1.141 (1.110, 1.172)	1.34	1.29

In Table 2, compared to non-Hispanic White, an estimated confounded OR was 1.09 (95% CI: 1.06-1.11) and 0.85 (95% CI: 0.83-087) for Hispanic and Non-Hispanic Black, respectively. With these observed odds ratios, unmeasured confounders that were associated with both continuity of receiving OUD medications (outcome) and race/ethnicity (exposure), odds ratio 1.25 to 1.38-fold each, above and beyond the measured confounders, could explain away the estimates, but jointly weaker unmeasured confounding associations could not. Unmeasured confounders that were associated with both the outcome and the exposures by an odds ratio of 1.21 to 1.35-fold

each, above and beyond the measured confounders, could shift the CI to include the null, but weaker confounding could not.

Table 2 E-value for Individual Study for Continuity of Medication for OUD

Variable	Odds Ratio (95% CI)	E-value for Point Estimate	E-value for the Confidence Interval
Race/ethnicity			
Hispanic	1.086 (1.061, 1.112)	1.25	1.21
Non-Hispanic Black	0.852 (0.833, 0.872)	1.38	1.35
Non-Hispanic Other	1.024 (0.989, 1.060)	--	--
Eligible group			
Children	0.826 (0.769, 0.887)	1.43	1.32
Disabled Adults	1.086 (1.058, 1.114)	1.25	1.20
Pregnant Women	1.148 (1.118, 1.179)	1.35	1.30

Compared to nondisabled adults, an estimated confounded OR was 0.83 (95% CI: 0.77-0.89), 1.09 (95% CI: 1.06-1.11), and 1.15 (95% CI: 1.12-1.18) for children, disabled adults, and pregnant women, respectively. With these observed odds ratios, unmeasured confounders that were associated with both continuity of receiving OUD medications (outcome) and eligibility group (exposure), odds ratio 1.25 to 1.43-fold each, above and beyond the measured confounders, could explain away the estimates, but jointly weaker unmeasured confounding associations could not. Unmeasured confounders that were associated with both the outcome and the exposures by an

odds ratio of 1.20 to 1.32-fold each, above and beyond the measured confounders, could shift the CI to include the null, but weaker confounding could not.

From both Tables 1 and 2, weak unmeasured confounding could potentially explain away the confounded effects, therefore, the estimated confounded effects are not robust to unmeasured confounding. These unmeasured confounders include social or family environments that are difficult to be assessed and measured among Medicaid enrollees.

4.2.2 Results for Meta-analysis

MODRN (Donohue et al., 2021) reported the meta-analysis results from 11 states that race/ethnicity and eligibility group were associated with two outcomes of interest: receiving of any OUD medications and continuity of receiving OUD medications. In this section, we describe the results of characterizing these pooled risk ratios sensitivity to unmeasured confounding. For all calculations, we assumed $q = \log(0.9)$ for confounded risk ratio < 1, $q = \log(1.1)$ for confounded risk ratio > 1, $r = 0.1$, $\mu_{B^*} = 1.15$, and $\sigma_{B^*}^2 = 0$.

For the outcome of receiving any medications for OUD, $\hat{p}(q) = 0$ to 0.68 indicate that 0-68% of the states whose true log risk ratio of race/ethnicity on receiving any medications for OUD are stronger than the threshold $q = \log(0.9)$ or $q = \log(1.1)$. Estimates of $\hat{T}(r, q)$ indicate that the minimum common bias factor (on the risk ratio scale) capable of reducing to less than 10% the states with effects surpassing $q = \log(0.9)$ or $q = \log(1.1)$ ranges from 1.31 to 2.11. Estimates of $\hat{G}(r, q)$ indicate that the minimum confounding strength required explain away the effects in less than 10% of the states with true effects exceeding $q = \log(0.9)$ or $q = \log(1.1)$ ranges from 1.95 to 3.65 (Table 3). For eligibility group, $\hat{p}(q) = 0.04$ to 0.44 indicate that 4-41% of the states

whose true log risk ratio on receiving any medications for OUD are stronger than the threshold $q = \log(0.9)$ or $q = \log(1.1)$. Estimates of $\hat{T}(r, q)$ indicate that the minimum common bias factor (on the risk ratio scale) capable of reducing to less than 10% the states with effects surpassing $q = \log(0.9)$ or $q = \log(1.1)$ ranges from 1.44 to 1.71. Estimates of $\hat{G}(r, q)$ indicate that the minimum confounding strength required explain away the effects in less than 10% of the states with true effects exceeding $q = \log(0.9)$ or $q = \log(1.1)$ ranges from 2.24 to 2.80 (Table 3).

For the outcome of continuity of receiving OUD medications, $\hat{p}(q) = 0.07$ indicates that 7% of the states whose true log risk ratio of race/ethnicity on receiving any medications for OUD are stronger than the threshold $q = \log(0.9)$ or $q = \log(1.1)$. Estimates of $\hat{T}(r, q)$ indicate that the minimum common bias factor (on the risk ratio scale) capable of reducing to less than 10% the states with effects surpassing $q = \log(0.9)$ or $q = \log(1.1)$ is 1.47. Estimates of $\hat{G}(r, q)$ indicate that the minimum confounding strength required explain away the effects in less than 10% of the states with true effects exceeding $q = \log(0.9)$ or $q = \log(1.1)$ is 2.30 (Table 4). For eligibility group, $\hat{p}(q) = 0.18$ indicates that 18% of the states whose true log risk ratio on receiving any medications for OUD are stronger than the threshold $q = \log(0.9)$ or $q = \log(1.1)$. Estimates of $\hat{T}(r, q)$ indicate that the minimum common bias factor (on the risk ratio scale) capable of reducing to less than 10% the states with effects surpassing $q = \log(0.9)$ or $q = \log(1.1)$ ranges from 1.33 to 1.55. Estimates of $\hat{G}(r, q)$ indicate that the minimum confounding strength required explain away the effects in less than 10% of the states with true effects exceeding $q = \log(0.9)$ or $q = \log(1.1)$ ranges from 1.98 to 2.47 (Table 4).

Table 3 Sensitivity Analysis for Meta-Analysis for Patient's' Receiving Medication for OUD

Variable	Confounded Log Risk Ratio (95% CI)	Confounded Risk Ratio (95% CI)	τ	$T(q,r)$	$G(q,r)$
Race/Ethnicity					
Hispanic	0.022 (-0.043, 0.087)	1.02 (0.96, 1.09)	0.089	--	--
Non-Hispanic Black	-0.325 (-0.441, -0.208)	0.72 (0.64, 0.81)	0.170	2.11	3.65
Non-Hispanic Other	0.080 (0.043, 0.116)	1.08 (1.04, 1.12)	0.050	1.31	1.95
Eligibility Group					
Children	-0.229 (-0.310, -0.148)	0.80 (0.73, 0.86)	0.103	1.71	2.80
Disabled Adults	-0.092 (-0.153, -0.031)	0.91 (0.86, 0.97)	0.087	1.44	2.24
Pregnant Women	0.166 (0.109, 0.223)	1.18 (1.11, 1.25)	0.081	1.55	2.47

Table 4 Sensitivity Analysis for Meta-Analysis for Continuity of Medication for OUD

Variable	Confounded Log Risk Ratio (95% CI)	Confounded Risk Ratio (95% CI)	τ	$T(q,r)$	$G(q,r)$
Race/Ethnicity					
Hispanic	0.019 (-0.012, 0.049)	1.02 (0.99, 1.05)	0.040	--	--
Non-Hispanic Black	-0.117 (-0.179, -0.055)	0.89 (0.84, 0.95)	0.085	1.47	2.30
Non-Hispanic Other	0.031 (-0.010, 0.072)	1.03 (0.99, 1.07)	0.056	--	--
Eligibility Group					
Children	-0.167 (-0.236, -0.097)	0.85 (0.79, 0.91)	0.087	1.55	2.47
Disabled Adults	0.016 (-0.027, 0.060)	1.02 (0.97, 1.06)	0.060	--	--
Pregnant Women	0.129 (0.099, 0.159)	1.14 (1.10, 1.17)	0.038	1.33	1.98

5.0 Discussion

This study applied E-value and sensitivity analysis techniques to assess the robustness of the confounded treatment (or exposure) effect to unmeasured confounding. We examined the effects of race/ethnicity and eligible group on Medicaid enrollees' receiving any medication for OUD and on enrollees' continuity of OUD medication.

In individual study, the association between exposures (race/ethnicity, eligibility group) and outcomes (receiving any OUD medications, continuity of receiving OUD medications) observed in Medicaid data are significant, but the E-values are small, which indicates that these associations are weak and not robust to unmeasured confounders. Without randomization and controlling of all confounders that could influence the relationship between exposure and outcomes, unmeasured confounding is often the biggest challenge in assessing evidence for causality in observational study. E-value can be used to measure the robustness to such unmeasured confounding and play a role as a sensitivity analysis to show the strength of the association between factors. Therefore, it is necessary that all observational studies that assess causality should report the E-value for the confounded point estimate along with its confidence interval, which is the minimum unmeasured confounder effect needed to explain away the observed significant results.

For sensitivity analysis of confounded estimates in meta-analysis from 11 states, the values of (r,q) for the two exposures and the two outcomes are small and close to 1, which indicate that even a weak unmeasured confounding effect can reduce the significant relationship to scientifically unimportant level. Therefore, all significant associations reported in the meta-analysis were weak and easily to be changed to non-significant. Even though they were significant

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reported in meta-analysis, the meta-analysis cannot be used as evidence for a causal relationship between exposures and outcomes. Assessing sensitivity to unmeasured confounding is also important in meta-analysis of observational studies. This is because that we will not be able to judge whether the effect size of the aggregated data is robust to unmeasured confounding by checking individual study's effect size and the width of its confidence interval.

There are several methods can be used to handle the unmeasured confounding caused by lack of randomization in the causal inference for observational study, such as external adjustment, instrumental variable, and negative control outcome methods (Mathur & VanderWeele, 2021; Rosenbaum, 2010). It is worth noting that these techniques may require confounders to satisfy strict conditions such as binary unmeasured confounders; only one unmeasured confounder; no interaction between the confounders (Schlesselman, 1978; Rosenbaum & Rubin, 1983). Moreover, some of techniques are subjective, which means that investigators can choose the sensitivity parameters to make the result seem robust to confounding (Lin, Psaty & Kronmal, 1998; VanderWeele & Arah, 2011). These assumptions are difficult to measure and to satisfy, so these approaches are not very useful in real clinical practice, and it is necessary to use a technique with no assumption to examine the unmeasured confounding effect in the relationship between exposure and outcome.

The sensitivity method based on E-value does not require specifying sensitivity parameters. E-value can be applied to other measures (e.g., risk difference, standardized mean difference) by first approximating these measures to a risk ratio and then applying E-value formula. Mathur et al. (2021) also extended the E-value method for interaction terms. Although E-value has also been applied to examine the robustness of a reported hazard ratio (HR) when outcome is time-to-event

type, we will need to use it with caution because HR does not have causal interpretation. This is also true for odds ratio with binary outcome with non-rare-event case.

An important note is that E-value is not the final indicator of robustness. Robustness of an association between exposure and outcome also depend on the correlation between the measured and unmeasured confounders. Researchers may need to further assess robustness by considering possible level of correlation between measured and unmeasured confounders after obtaining the E-value.

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