Measuring the Long-Term Effects of Neighborhood Alcohol Outlet Density and Alcoholics Anonymous on Alcohol Relapse Using Longitudinal Targeted Maximum Likelihood Estimation

by

Deysia L. Levin

A dissertation submitted in partial satisfaction

of the requirements for the degree of

Doctor of Philosophy

in

Epidemiology

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Jennifer E. Ahern, Chair
Professor Maya L. Petersen
Professor Denise Herd

Spring 2017

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Abstract

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Background

Alcohol continues to adversely affect the lives of Americans, particularly individuals suffering from addiction. The majority of treated alcoholics relapse to alcohol abuse or dependence. Between 66% and 80% of adults relapse in the six months after an episode of community- or hospital-based drug or alcohol treatment and 40% will re-enter treatment. Thus, the aftercare and follow-up plan have potential to affect long-term treatment success. Research that tracks treatment outcomes for alcohol addiction has shown that while a variety of treatment interventions are effective, the progress clients make in treatment is frequently undermined if they are surrounded by or reside in an environment that triggers relapse. Although individual-level risk factors for alcoholism have been well-established they do not fully explain variability in recovery suggesting that environmental and social factors need to be explored.

Neighborhood alcohol outlet density (AOD) and Alcoholics Anonymous (AA) affiliation are two environmental and social factors that show promise for intervention on a moderate time scale. Despite the contributions of research on how one's living and social environment can affect alcohol use, very little is known about the impact of AOD and AA on recovery over time. To date, there are no studies examining the effect of AOD on relapse among alcoholics in recovery. Similarly, in spite of a vast body of literature on AA, few studies have examined the effectiveness of long-term affiliation with AA on relapse. Moreover, no studies have utilized parameters based on a causal inference framework to examine the potential impacts of these factors on relapse and recovery.

Methods

Using a 7-year prospective cohort study of alcoholics in recovery, the purpose of this dissertation was to estimate the effects of AOD and AA on relapse (past 30-day abstinence), applying improved analysis techniques. The most widespread statistical method in studies of AOD and AA associations with drinking rely on conventional

regression. This approach does not appropriately adjust for time-dependent confounding, and the modeling assumptions may not always be met. An alternative approach is to estimate parameters motivated by the causal inference literature, which can be interpreted as estimates of the outcome under hypothetical interventions to the exposure of interest. In this framework, a key step is careful consideration of the assumptions necessary to interpret the parameter as a causal effect. The current work is stronger than past work with respect to some of the assumptions. In the first chapter, I estimate the longitudinal impact of AOD on abstinence using a parameter motivated by the causal inference literature. In the second chapter, I again examine the longitudinal impact of AOD on abstinence with a focus on specific types of alcohol outlets. In the third chapter, I examine the longitudinal impact of AA participation on abstinence. For all study questions, I use data-adaptive estimation (SuperLearning) combined with a recently released R package, Longitudinal Targeted Maximum Likelihood Estimation (*ltmle*), an estimation method that encourages an explicit process for specifying and estimating target parameters to address causal questions that specifically incorporate time-dependent confounders.

Significance

This work will contribute to epidemiologic research in several ways. First, we hope to begin to fill the gap in the literature on the association between neighborhood AOD and drinking among alcoholics in recovery. Second, we aim to determine whether specific alcohol outlet types confer distinct drinking risks among alcoholics in recovery. Third, we hope to contribute to the limited literature examining the long-term impact of AA on alcohol recovery. Moreover, this work represents the first application of *ltmle* to the field of alcohol epidemiology. We hope to demonstrate how it can provide a powerful way of estimating parameters with direct public health relevance using observational data. Extensions of this research can help to improve understanding of how environmental and social contexts contribute to alcohol recovery, and identify ways to optimize future interventions in this area. Conceptually, this work will contribute to efforts aimed at promoting recovery by examining to what extent AOD exposure and AA participation are associated with drinking among alcoholics over time, two areas that warrant further research. Understanding the interrelationships between neighborhood context, social network, and subsequent alcohol use is critical to better understand alcohol relapse and recovery.

Dedication

To Noah and Hugo, whose unbridled affection sustained me throughout this process.

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Acknowledgements

First, I would like to express my utmost gratitude to my advisor and dissertation chair, Jennifer E. Ahern, for her guidance and direction, her generosity, and her unending encouragement. Jen is a model of excellence in epidemiology, a wonderful person, and someone I admire very much. She was always responsive to my needs, from helping to secure funding to providing immediate feedback to any question or challenge. She was readily available despite juggling countless responsibilities, and never made me feel like I was a burden. Moreover, I could not anticipate the challenges involved in completing my doctoral studies while caring for twins, and Jen provided the steady foundation I desperately needed to make it to the end. I feel extremely lucky and proud to have been her advisee, and only wish that I could have had even more opportunities to engage with and learn from her.

I would also like to acknowledge my other committee members, Maya L. Petersen and Denise Herd, whose valuable input allowed me to significantly improve my scholarship. I am also very grateful to Katherine Karriker-Jaffe at The Alcohol Research Group (ARG) for dedicating time and resources, and providing insight, feedback and assistance relating to these chapters. Thanks to other collaborators at ARG who provided the data used in this dissertation. Thank you to Joshua Schwab for developing ltmle and fielding all my questions related to its use. Thank you to all my fellow epidemiology classmates, who have been supportive and encouraging. Thank you to Deb Karasek for checking in regularly, providing encouragement, and relating to the joys and challenges of motherhood. Thank you also to Emily Yette for her unwavering friendship and support.

Thank you to my mother for her unconditional love and support, and for cheering me on every step of the way. The numerous sacrifices she made throughout her life made it possible for me to achieve all that I have and I am forever grateful. Thanks to my entire family for always being present despite being three thousand miles away. And to my dear friends, both near and far, who buoyed me with visits, messages, calls, and lots of jokes.

Last, but not least, thank you to my husband for 15 years of love and support, and to the little lights of my life, Noah and Hugo.

Chapter 1

Introduction

1.1 Motivation

The burden of disease associated with excessive alcohol use is substantial. Alcohol is the fourth leading preventable cause of death in the nation (1) and is responsible for 2.5 million years of potential life lost (YPLL) (2). It contributes to over 200 diseases, most notably liver cirrhosis, cancers, and injuries (3), and can lead to a variety of social, psychological, and cognitive ailments (2). In 2010, the economic impact of excessive alcohol use in the United States approached an estimated $249 billion (2).
Moreover, the majority of alcohol consumption occurs in a relatively small portion of the population who drinks; an estimated 71% of Americans reported consuming alcohol in the past year (1) yet more than half of the alcohol in any given year is consumed by the top 10% of drinkers (4). Alcohol is also the most abused drug among people in recovery for substance abuse; in 2015, 15.1 million adults ages 18 and over had an alcohol use disorder and 1.3 million adults received treatment for alcohol (1).

The majority of individuals treated for alcohol abuse and dependence relapse (5). Between 66% and 80% of adults relapse in the six months after an episode of community- or hospital-based treatment (6-8) and 40% will re-enter treatment (9). Thus, the aftercare and follow-up plan have potential to affect long-term treatment success. Research that tracks treatment outcomes for alcohol addiction has shown that while a variety of treatment interventions are effective, the progress clients make in treatment is frequently undermined if they are surrounded by or reside in an environment that triggers relapse (10).

Perhaps the most basic manner in which the environment can be considered to affect relapse is by facilitating access to alcohol. For alcoholics, environments with high accessibility to alcohol can not only pose a situational risk but can also contain environmental cues that can activate craving for alcohol (11, 12). A potentially modifiable environmental factor that can affect this risk is alcohol outlet density (AOD). AOD refers to “the number of physical locations in which alcoholic beverages are available for purchase either per area or per population” (13). A substantial body of research indicates that high alcohol outlet density (AOD) is associated with increased alcohol consumption (13-17). A recent systematic review of the AOD literature concluded that reducing the number of alcohol outlets would be an effective method to reduce harm attributable to alcohol (18, 19).

Research has documented the important role of social environment features related to personal interactions on relapse. Continued association with peers who enable or promote alcohol use has been associated with higher rates of relapse out-of-treatment (20-22). In addition, social support for abstinence increases the likelihood that gains made during treatment are reinforced and sustained (23-25). The oldest peer social support network for alcohol recovery in the country, Alcoholics Anonymous (AA), remains the most widely

used single intervention for alcohol addiction in the United States (26). As of January 2016, there were 60,698 AA groups and 1,262,542 members in the United States (27). The chronic, relapse-prone aspect of alcohol addiction make it necessary for many alcoholics in recovery to have access to ongoing social support that formal treatment cannot provide, and AA often engages members more intensely and for longer periods than do professional treatment programs (28, 29).

Despite the contributions of research on how the residential and social environment can affect alcohol use, very little is known about the role of these factors in the processes of recovery over time. There are no studies to date examining the impact of AOD on relapse among alcoholics in recovery. Similarly, in spite of a vast body of literature on AA, little is known about the effectiveness of long-term affiliation with AA on relapse. The majority of studies on AA have focused on short-term remission rates among individuals who have been treated for alcohol use disorders, but fewer studies have focused prospectively on longer-term impacts among this group (22, 30).

Studies to date on the effect of AOD on alcohol consumption in the general population are largely confined to point-in-time measures. This cross-sectional approach requires that we assume that AOD exposure comes before drinking, but the reverse may also be true (31). Similarly, with few exceptions, the literature that indicates a relationship between AA participation and relapse (26, 29, 32-35) are cross-sectional, making it difficult to establish if AA determines relapse, or if the actual direction of the effect may be the reverse, or in both directions (36). While experimental studies on AA effectiveness exist, they have inconsistent findings, with the most recent meta-analysis concluding that there were "2 trials finding a positive effect for AA, 1 trial finding a negative effect for AA, and 1 trial finding a null effect." (37). In the rare longitudinal studies that address questions about AOD, AA and drinking, conventional regression methods are used. These approaches do not appropriately adjust for time-dependent confounding and the modeling assumptions may not always be met.

Building on previous work investigating the impacts of AOD and AA on drinking, this study (1) fills an important gap in the literature on the link between AOD and relapse and contributes to the limited literature on the long-term effect of AA on relapse among alcoholics in recovery, (2) takes advantage of a longitudinal design to improve the potential for causal interpretation, and (3) uses a novel method that adjusts for time-dependent confounding and thus avoids the shortcomings of conventional regression. We review the literature on and challenges of estimating effects of AOD and AA on alcohol use, focusing on limitations of study designs and statistical methods used. Following this discussion, we use a counterfactual framework to define parameters of interest for the longitudinal effects of AOD and AA on abstinence among alcoholics in recovery, and discuss assumptions necessary for valid estimation and interpretable causal parameters. Finally, using data from the Community Epidemiology Laboratory, a 7-year prospective cohort study of alcoholics in recovery, we estimate the longitudinal impact of neighborhood AOD and AA interventions on abstinence via a parameter motivated by the causal inference literature. In our case, we define the parameters of interest as the expected difference in the counterfactual probability of abstinence at fixed longitudinal

intervention profiles. Differences of those means inform us regarding how a potential pattern of intervention could affect relapse over time. The parameters of interest are estimated using Longitudinal Targeted Maximum Likelihood Estimation (*ltmle*), incorporating data-adaptive estimation (SuperLearning), an estimation method that encourages an explicit process for specifying and estimating target parameters to address clearly defined questions while avoiding unnecessary assumptions about model form and accounting for time-dependent confounding (38).

1.2 Specific Aims

Our fundamental questions are: 1) **How would consistent exposure to high compared to low AOD affect individual risk of alcohol abstinence; and 2) How would consistent exposure to high compared to low AA participation affect individual risk of alcohol abstinence?**

My specific aims are as follows:

1. To estimate the average causal effect of consistent high compared to low AOD exposure on past 30-day abstinence over time (Chapter 2);
2. To estimate the average causal effect of consistent high compared to low exposure to on- vs. off-premise alcohol outlets on past 30-day abstinence over time (Chapter 3); and
3. To estimate the average causal effect of high compared to low AA participation on past 30-day abstinence over time (Chapter 4).

This dissertation is organized into five chapters. Chapter 1 introduced the background, specific aims, and significance. Chapter 2 presents the results of the longitudinal effect of neighborhood AOD on abstinence using *ltmle*. Chapter 3 presents the results of the effect of types of alcohol outlets on abstinence using *ltmle*. Chapter 4 presents the analysis of AA effects on abstinence using *ltmle*. Chapter 5 concludes the dissertation by reviewing the findings from the three studies conducted and proposes suggestions for future research. All three aims will use a dataset from the Community Epidemiological Laboratory that followed over the course of 7 years a group of alcoholics who were recruited from public and private chemical dependency programs in Contra Costa County, California.

Chapter 2: Long-Term Effects of Alcohol Outlet Density on Relapse

2.1 Background

The majority of treated alcoholics relapse to alcohol abuse or dependence (5). Between 66% and 80% of adults relapse in the first six months after an episode of community- or hospital-based alcohol treatment (6-8) and 40% will re-enter treatment (9). Forty percent of patients who have been sober for 2 years will relapse, but at 5 years of sobriety the chance of relapse is less than 15%. Various studies have identified factors associated with relapse to alcohol abuse or dependence. Among treated individuals, these factors include greater social pressure, more severe alcohol related problems, lack of self-efficacy, poor coping skills, co-morbid mood disorder and anxiety disorder (22, 30, 39-41). Research has also shown that the progress made in treatment is frequently undermined if individuals are in an environment that triggers relapse (10, 42). Notwithstanding, only a few studies have examined the relationship between an alcoholic's environment and alcohol relapse (42-46).

Perhaps the most basic manner in which the environment can be considered to affect relapse is by facilitating access to alcohol. For alcoholics, environments with high accessibility to alcohol can not only pose a situational risk but can also contain environmental cues that can activate craving for alcohol (11, 12). A potentially modifiable environmental factor that can affect this risk is alcohol outlet density (AOD). AOD refers to "the number of physical locations in which alcoholic beverages are available for purchase either per area or per population" (13). Based on availability theory, reducing alcohol availability through reducing AOD will reduce drinking (47). In addition, applying an "out of sight, out of mind" theory, lower AOD means fewer visual stimuli to trigger cravings or actual use (11, 12). The association of AOD on alcohol consumption has been widely explored in the literature, and has largely reported a significant positive relationship between greater outlet density and increased alcohol consumption in the general population (17, 48-54). Furthermore, a recent systematic review of the AOD literature concluded that reducing the number of alcohol outlets would be an effective method to reduce harm attributable to alcohol (18, 19).

Despite the contributions of research on how the residential environment can affect alcohol use, very little is known about the role of these factors in the processes of recovery over time. There are no studies to date investigating how neighborhood AOD impacts relapse among alcoholics in recovery. In addition, studies on the effect of AOD on alcohol consumption in the general population are largely confined to point-in-time measures. This cross-sectional approach requires that we assume that AOD exposure comes before drinking, but the reverse may also be true (31). While a longitudinal design improves the potential for causal interpretation, most of the studies rely largely on conventional regression models that do not appropriately adjust for time-dependent confounding and in which the modeling assumptions may not always be met.

Building on previous work investigating the impacts of AOD and AA on drinking, this study represents the first to examine the impact of AOD on relapse, measured by past 30-

day abstinence, among alcoholics in recovery. We begin by using a counterfactual framework to define our parameters of interest for the longitudinal effects of neighborhood AOD on abstinence. Then, with data from the Community Epidemiology Laboratory, we follow a prospective cohort of alcoholics in recovery, measuring neighborhood AOD five times over seven years, and estimate the difference in the counterfactual probability of abstinence under high versus low AOD exposure, with the hypothesis that sustained high AOD would result in decreased abstinence. The parameters of interest are estimated using longitudinal targeted maximum likelihood estimation (*ltmle*) incorporating data-adaptive estimation (SuperLearning), an estimation method that encourages an explicit process for specifying and estimating target parameters to address clearly defined questions while avoiding unnecessary assumptions about model form and accounting for time-dependent confounding (38).

2.2 Methods

Motivating Framework

The practice of epidemiology requires causal questions to understand why patterns of disease and exposure exist and how we can best intervene to change them. Recent developments in formal frameworks for causal inference have the potential to improve our ability to specify clear scientific questions and design a statistical analysis that comes as close as possible to answering the motivating causal question, while making clear the assumptions required to give the resulting estimates a causal interpretation. In this section, we follow the targeted learning road map as presented by van der Laan and Rose (55) and Petersen and van der Laan (56). The framework involves the following steps:

1. Specify the Questions
2. Specify the Observed Data and Causal Model
3. Specify the Causal Parameter of Interest
4. Assess Identifiability
5. Commit to a Statistical Model and Target Parameter of the Observed Data Distribution
6. Estimate the Chosen Parameter of the Observed Data Distribution (section 2.3)
7. Interpret Results (section 2.5)

1. Causal Question

What is the effect of consistent high compared to low neighborhood AOD exposure on past 30-day abstinence?

2. Observed Data and Causal Model

Each observed subject history can be written as $O = (\bar{A}(K), \bar{L}(K+1))$, where the overbar represents the history of a random variable and where $k = 1$ indicates baseline, $k = 2$ indicates 1 year post-treatment, $k = 3$ indicates 3 years post-treatment, $k = 4$ indicates 5 years post-treament, and $k = 5$ indicates 7 years post-treatment. $K + 1$ denotes the maximum follow-up time (here equal to 5). $\bar{A}$ is defined as the full history of time-point specific exposure and censoring $A(k)$ up to time point K: $\bar{A} = A(0), \ldots, A(K)$. For a given time point, $k, A(k)$ contains neighborhood exposure status $A_1(k)$ (defined as

AOD above versus below the median) in the interval k and also includes a censoring indicator, $C(k)$, defined as an indicator that a subject has been lost to follow-up by the start of interval k. Similarly, $\bar{L}$ is defined as the history of covariates up to time point K: $\bar{L} = L(0), \ldots, L(K)$, where baseline covariates are denoted $L(0)$, time-varying covariates measured in the interval k are denoted $L(k)$, and the outcome of interest, $Y(k)$, an indicator that a subject abstained from alcohol in the interval k, is included in $L(k)$. We assume the observed data over all subjects consists of n independent and identically distributed (i.i.d.) copies of the random (vector) variable O with some underlying probability distribution P_O.

The causal model, $\mathcal{M}^F$, is explicitly linked to our observed data, and thus reflects our beliefs about the time-ordering and relationships between the exposure, covariates, and the outcome of interest:

$$LL(k) = f_{L(k)}\big(Pa\big(L(k)\big), U_{L(k)}\big) \text{ for } k = 0, \ldots K+1$$

$$A(k) = f_{A(k)}\big(Pa\big(A(k)\big), U_{A(k)}\big) \text{ for } k = 0, \ldots K.$$

The functions f_A, f_L are non-parametric and deterministic. The U components denote unmeasured, independent (exogenous) variables, so that the variables that make up our data set are deterministic (but unknown) functions of the measured history, and some unmeasured error term.

3. Causal Parameter of Interest

The formal language of counterfactuals forces explicit statement of a hypothetical experiment to answer the scientific question of interest. The counterfactual outcomes of interest are $Y_{\bar{a}}(k), k = 1, \ldots, K+1$ for $\bar{a}$ equal to $\bar{1}$ or $\bar{0}$, where $Y_{\bar{a}}(k)$ is interpreted as the counterfactual abstinence at time k under a hypothetical intervention to set AOD= $\bar{a}$. Our target parameter of interest, $E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)], k = 1, \ldots, K+1$, was the expected difference in the counterfactual probability of being abstinent in the interval $k = 1, \ldots, 5$ among individuals consistently exposed to high versus low AOD

4. Assess Identifiability

An aspect of a statistical model is identifiable when the target causal parameter, which is a function of a data distribution we did not measure (i.e. a function of the counterfactual distribution), can be rewritten as a function of the observed data distribution (i.e. the two quantities will be equal under every data generating distribution compatible with the causal model). In order to estimate the marginal distribution of different counterfactuals from observed data, identifiability assumptions must be considered carefully to determine if the link can be made. In longitudinal data, one such assumption, the sequential randomization assumption (55) states that at each time point k, all common causes of the L nodes and $A(k)$ are measured and included in the dataset. This is a "no unmeasured confounders" type assumption, also sometimes called the randomization assumption. There is also the positivity assumption, which states that for each regimen of interest there is a non-zero probability of continuing to follow it at each time point, given you have followed it up to now irrespective of your observed past. However, the ability to prove equivalence between our target counterfactual quantity and an estimand under

these assumptions does not make these assumptions true, nor does it ensure that they can be readily evaluated. Additionally, we assume that ≥ X% of alcohol outlets in a neighborhood is considered "high." It does not matter for this analysis, which X% of the neighborhood is considered, and can be interchangeable with a different X% of the neighborhood population. Finally, special attention should be paid to the fact that the exposure in this causal question is a neighborhood-level variable, whereas the other covariates, and the outcome are measured at the individual-level.

5. Statistical Model and Target Parameter of the Observed Data Distribution

Our statistical estimand was the longitudinal G-Computation formula (57). In longitudinal settings, G-computation is an identifiability result derived from the sequential randomization assumption (55, 57). An ideal experiment that would answer our study question would be to randomize a cohort of alcoholics in recovery at baseline to each longitudinal pattern of AOD exposure, then follow up with the individuals, ensuring perfect adherence and no attrition. Given the cost and ethical barriers of doing a randomized controlled trial (RCT) in this setting, we rely on estimation methods where the parameters of interest returned can be interpreted, if the identifiability assumptions are met, as the exposure effects one typically estimates in an RCT appropriately adjusted for time-dependent confounders.

Study Participants

From February 1995 to March 1996, respondents were recruited from ten public and private chemical dependency programs in Contra Costa county, excluding methadone maintenance programs and programs limited to aftercare, a stage that occurs after completion of a treatment program. Programs included two HMO's offering long-term outpatient treatment; two private hospital programs offering short-term detoxification, inpatient, day treatment and outpatient; and six public programs (2 detoxification, 2 inpatient, 2 outpatient). In-person interviews were conducted within the first three days of treatment or within the first three outpatient sessions. Contra Costa County, located east of San Francisco, was selected due to its diverse population and mix of rural and urban areas.

Respondents were interviewed with a structured questionnaire that included questions on demographic and socioeconomic characteristics, as well as substance use and treatment history. Trained research staff who were not employees of the treatment agencies administered the questionnaire to all consenting participants by the end of their third day of residential treatment or third out-patient visit. There were 926 respondents interviewed at baseline. Respondents were re-interviewed at 1, 3, 5 and 7 years post-baseline (58). An intensive effort to locate subjects led to the high response rate throughout the study of 80% at baseline, 80% at wave 2, 79% at wave 3, 78% at wave 4, and 75% at wave 5. No differences in income, psychiatric or alcohol problem severity were among those lost to follow-up; however, males and African Americans were under-represented at follow-up (29). Figure 1 provides a useful timeline.

For our analysis, we excluded those who moved out of the state (n=23), were in prison (n=3), were homeless (n=6), did not live independently (n=34), or lacked a valid address at baseline (n=19). We further limited the sample to exclude those with *intermittent*

censoring over the study period (n=77). Our final sample included 764 respondents, roughly 80% of the original cohort.

Exposure Assessment

The exposure, neighborhood AOD, was defined as the number of active alcohol outlets within a 0.5-mile radius of a respondent's residence. By defining the exposure within a very limited distance of 0.5 miles or what might be considered "walking distance", we expect that there would be considerable distance between respondents' neighborhoods to prevent the possibility of a change in one neighborhood from affecting respondents in any other neighborhood. We also used this measure since studies have found that AOD within a buffer of one's residence was more strongly associated with alcohol consumption than AOD in one's census tract (59, 60). For the purpose of this study we did not differentiate between an individual who experienced a changed in AOD exposure due to moving and an individual who experienced a change in AOD exposure due to openings or closings of alcohol outlets. We calculated the median density at each wave and averaged across all five waves, which resulted in 4 alcohol outlets within 0.5-miles. Above the median of 4 alcohol outlets was defined as "exposed" and equal to or below the median as "unexposed." A value A_k=1 means that a person can be considered "exposed" at time point k, while a value A_k=0 means that they were "unexposed" at that time point k.

Respondents provided information about their residential address or nearest cross-streets, which were geocoded and linked with Census geocodes for 1990, 2000, and 2010, which converts addresses to an approximate longitude and latitude coordinate and returns information about the address range that includes the address and the census geography the address is within. We used the best effective residential address for the majority of the time corresponding to the 12-month period referred to in the interview. All respondents' addresses in the U.S. were successfully geocoded (1 respondent had moved overseas), matching all to a valid tract geocode (4% were based on a ZIP code centroid associated with a PO Box) and 92% to a valid block group geocode (61). There was no clustering at the block group level, but 8% of respondents shared a tract with someone else (61).

Alcohol outlet data were compiled from the California Alcoholic Beverage Association (ABC) (62), and included license information by year, physical address, type of license (on- or off-premise, bar/pub/restaurant/liquor store) and status (active/not). All alcohol outlets were then geocoded and linked with longitude and latitude coordinates and a Census geocode to facilitate linkage with respondents' neighborhood addresses. All respondents' addresses and alcohol outlets were geocoded using the ArcGIS software (63).

Outcome

We focused on abstinence from alcohol use, defined as the treatment goal of not consuming any alcohol, since the majority of substance use treatment centers in the United States, including Alcoholics Anonymous (AA), follow an abstinence-based model. The outcome was defined as past 30-day abstinence and the question used was: 1) "Thinking of the past 30 days, on how many days did you drink any kind of alcoholic

beverage – including beer, wine and/or liquor?". Respondent's answers to the survey question were dichotomized as "yes" if they completely abstained from any alcohol and "no" if they consumed any alcohol. We chose the 30-day time frame since studies have shown greater reliability in recall when drinking is assessed over shorter intervals (64).

Covariates
Measured baseline covariates included gender, race/ethnicity, age at onset of problem drinking, parental and spousal history of alcohol use, education level, Addiction Severity Index measures for alcohol use, drug use, and psychiatric history. The ASI provides an overview of problems related to substance rather than focusing on any single area (65). A composite score, which ranges from 0.00 to 1.00 for each ASI problem area, is calculated from interviewer severity ratings on a scale of 0- to 9-point estimates of problem severity, defined as the "need for additional treatment", and an objective composite score developed from a subset of items that reflect current status in a given problem area (66). At baseline, the ASI can provide a description of the study sample on a standard set of potentially important background characteristics over and above demographics (65).

Time-dependent variables included social support for sobriety, marital status, AA participation (number of days attendance), total income measured as the sum of taxable income the subject earned over the past year (inflated/deflated) and neighborhood federal poverty level (percent below).

2.3 Statistical Analysis

Complete information was not available on all of the covariates of interest for all subjects. We used multiple imputation to account for missing data in 10 datasets. The procedure involves three phases: 1) the imputation phase in which missing values are imputed, forming 10 complete data sets; 2) the analysis phase in which each of the 10 complete data sets is analyzed using a statistical model; and 3) the pooling phase in which parameter estimates obtained from each analyzed data set are combined for inference (67). Multiple imputation was performed using the Amelia package in R, and included all variables used in our analysis in the prediction model (68). We used the Zelig package in R to combine estimates from the imputed datasets using Rubin's rules to calculate adjusted point estimates and variances (69).

We then used longitudinal targeted maximum likelihood estimation (*ltmle*) to estimate our parameter of interest, $E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)], k = 1, \ldots, K+1$. *Ltmle* is an estimation approach that encourages an explicit process for specifying and estimating target parameters to address questions that specifically incorporate time-dependent confounders and avoids bias caused by incorrect parametric assumptions (38). The *ltmle* method also incorporates the possibility of including missing data and fixed (or dynamic) treatments of interest (70). Thus, *ltmle* allows for tremendous feasibility in the estimation of targeted statistical parameters based on potentially complex interventions. Specifically, for each time point, it requires estimates of the probability of being in the treatment group (e.g. high AOD) given the past (that is, all past covariates, treatments, and outcomes) (71). We incorporated data-adaptive methods using SuperLearner to reduce dependence on

correct parametric model specification when estimating outcome and treatment regressions. SuperLearner was used to build a library of candidate algorithms to provide a flexible, reasonable, and interpretable approach to fitting both the exposure and the outcome (72). Our pre-specified candidate SuperLearner library included main terms logistic regression, the mean estimate, multivariate adaptive regression spline models, generalized linear models, and generalized additive modeling. Given our modest sample size, we selected algorithms that allowed for flexible relationships and were not data-adaptive in a way that would invalidate reliable inference.

We tested the association between neighborhood AOD (above or below the median) and past 30-day abstinence separately for each intervention regimen and interval $k = 1, \ldots, 5$. We were specifically interested in differences in abstinence between the groups with consistent exposure to high compared to low neighborhood AOD. All analyses were conducted with the '*ltmle*' package in R v3.2.0 (www.r-project.org) (73). We created 95% confidence intervals (CIs) and conducted two-sided hypothesis tests controlling the type I error rate at 5% (α=0.05). We conducted sensitivity analyses using a dataset excluding participants who were never exposed to neighborhood AOD.

2.4 Results

We compare the baseline demographic characteristics of subjects by exposure categories defined by our median cut-off of 4 alcohol outlets within a 0.5 mile radius in Table 1. There were many similarities in the distribution of certain variables between both groups Namely, nearly 60% of study participants were male, the average age was approximately 39, ASI scores were similar, about 75% reported having a history of family alcohol abuse, and both groups reported an average of 4 social contacts that supported abstinence. Appreciable differences include the distribution by race/ethnicity with 35% of participants in high AOD neighborhoods identifying as black compared to 16% of participants in low AOD neighborhoods. In addition, among those in high AOD neighborhoods 37% reported incomes under 25K compared to 61% in low AOD neighborhoods, and 15% in high AOD neighborhoods reported living below the federal poverty level compared to 8% among those in low AOD neighborhoods. Lastly, participants in high AOD neighborhoods reported slightly higher frequencies of alcohol use in the past 30 days than participants in low AOD neighborhoods, 78.2% vs. 76.1%, respectively.

Table 2 presents subjects and past 30-day abstinence counts by wave, with and without restriction to those following the treatment regimen of staying in the same exposure category. By the end of the study, 7 years post-treatment, 58.6 % of subjects consistently exposed to high AOD neighborhoods (n=68) reported that they abstained from alcohol in the past 30 days compared to 56.9% of subjects exposed to consistently low AOD neighborhoods (n=82).

Table 3 shows the estimated differences in the probability of past 30-day abstinence for participants with sustained high neighborhood AOD exposure compared to sustained low neighborhood AOD exposure after controlling for gender, race/ethnicity, age at onset of

problem drinking, parental and spousal history of alcohol use, education level, Addiction Severity Index measures for alcohol use, drug use, psychiatric history, number of individuals in social network who encourage sobriety, marital status, AA participation (number of days attendance), total income measured as the sum of taxable income the subject earned over the past year (inflated/deflated) and neighborhood federal poverty level. At wave 3, contrary to our hypothesis, our estimate shows that individuals, if consistently exposed above the median cut-off for neighborhood AOD would experience a 12% (95% CI 0.01, 0.24) higher probability of past 30-day abstinence compared to the same group if constantly exposed below the cut-off. Results show that there was no difference at this time point with the unadjusted analysis (Table 2). However, the estimated associations between AOD and past 30-day abstinence at all other time points in this population were small and not statistically significant. A sensitivity analysis demonstrated that excluding subjects who never resided in areas with alcohol outlets yielded the same association estimates at all time points (Supplemental Table 1).

2.5 Discussion

The estimated association of neighborhood AOD exposure with past 30-day abstinence in this population was not statistically significant with the exception of at wave 3, 3 years after baseline. Specifically, our findings for that time point indicate that individuals consistently exposed to high neighborhood AOD would experience a higher probability of abstinence. This protective effect is contrary to our hypothesis and constitutes a surprising divergence from traditional theories. This finding may be attributed in part to certain factors that we could not incorporate in our models and that may have buffered the potential impact of high AOD.

To our knowledge, our study is the first to examine how neighborhood AOD influences abstinence in this population. We have applied advances in estimation of longitudinal interventions (*ltmle*) combined with data-adaptive estimation (SuperLearning) to estimate parameters targeting the impact of neighborhood AOD exposure on past 30-day abstinence among alcoholics in recovery. In our case, we defined the parameters of interest as the expected difference in the counterfactual probability of abstinence under sustained high versus sustained low AOD exposure.

To suggest that we can identify the causal effect of AOD on abstinence from the data requires strong assumptions, and we acknowledge that many of them will not be met. In addition, we acknowledge that the best estimation tools can still produce unreliable statistical estimates when data are inadequate. With this, we note several limitations. First, at baseline, we were unable to account for length of neighborhood residence. However, detailed tracking information allowed us to account for length of neighborhood exposure prior to each follow-up interview (61). Second, accurate measurement of drinking behavior is challenging, and measurement error could have been a major issue in this application. Given the time frame for the outcome (i.e. past 30 days), we did not have measures of abstention from alcohol use outside the 30-day window. By “sampling” within a very narrow window, our occasion-specific, situational approach necessarily constrains the extent of possible variation that can be observed in our outcome to one of

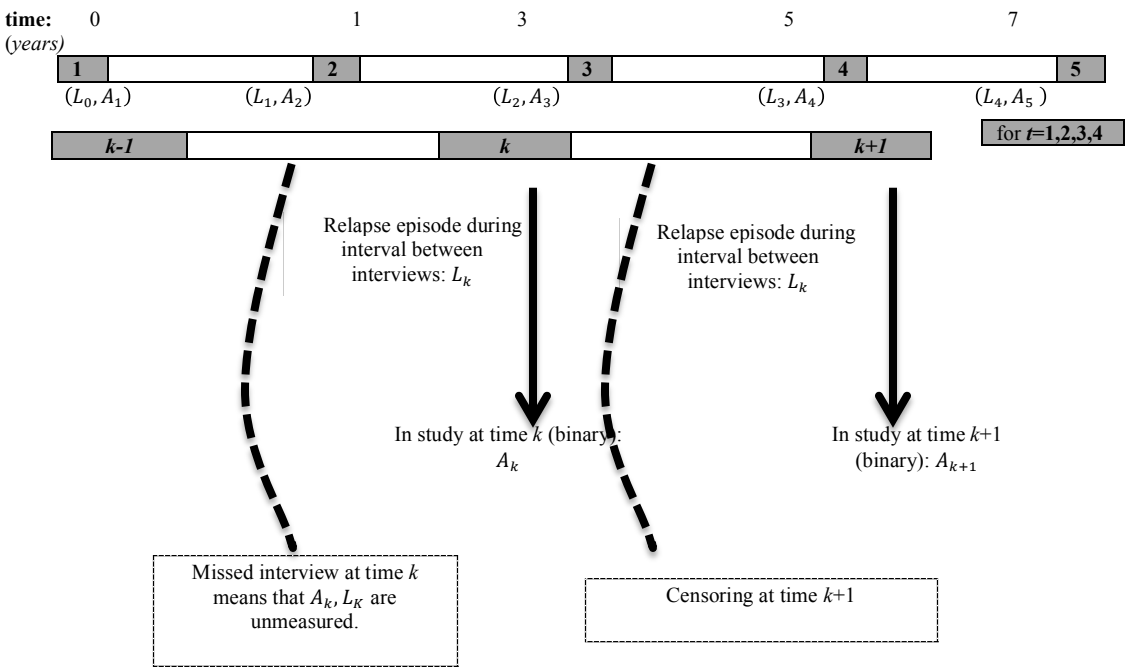
only two values: Either the outcome was present or it was not. However, drinking measures were developed through well-established and validated national alcohol surveys and clinical studies (74) and a substantive body of literature shows that as a group, alcoholics' self–reports of their drinking can be used with confidence (75-77). Third, our examination of AOD as a binary variable is unlikely to fully capture the relationship between the AOD values and shifts in past 30-day abstinence over time. It is unlikely that all individuals would have the same outcome had they been assigned to any exposure level above the cut-off that defined the category. Acknowledging this fact, we made a stronger consistency assumption of treatment variation irrelevance, or that the counterfactual outcome for each subject would be the same if they were exposed at any level within a treatment definition (78). The relevance of the causal model to our observed data depends on this somewhat dubious assumption, but acknowledging this, we nonetheless believe that the statistical parameters we estimate are informative for our primary question. We also tested multiple different definitions of our exposure using a mean cut-off and 90^{th} percentile cutoff, and our results were very similar. Fourth, we limited our analysis to a relatively small set of potential confounders. Some other potential confounders of interest that warrant future investigation with regard to AOD effects on abstinence include genetic factors, craving indicators, and community-level variables such as crime. In addition, there may be additional unmeasured time-dependent covariates that influence whether or not a participant was interviewed at time *t*. In other words, the sequential randomization assumption may not hold for the measurement process. There was some attrition over the seven-year follow-up period. While we controlled for the potentially informative censoring with *ltmle*, the wider confidence intervals at later time points reflect, in part, the smaller number of individuals interviewed in the later years of the study. Of course, that is one of the challenges of estimating ambitious parameters with relatively small sample sizes. Lastly, by implementing multiple imputation, we assumed missingness at random for the missing variables as well as a specific model form for the imputation model. Violations of this assumption or misspecification of the imputation model could result in bias (67).

Recognizing the limitations of this analysis, we have applied a framework for estimation of longitudinal interventions related to neighborhood AOD and abstinence from observational data, which might be useful for future work in this area. Strengths of this study include the use of alcohol outlet data for very small areas and the link between these data and data on a diverse group of individuals in alcohol recovery, and the longitudinal feature. By measuring neighborhood AOD over a longer time period, we are able to isolate the impact of sustained exposure. In addition, this study draws on novel methods that were specifically developed to adjust for possible time-varying confounders on the causal pathway. Traditional regression models are likely to be subject to bias from time-dependent confounding: we were able to much better control for these covariates using *ltmle*. Moreover, our use of SuperLearner for estimation of the outcome and exposure mechanisms guarded against the need to choose *a priori* a parametric model and allowed the combination of many data-adaptive estimators into one improved estimator, thereby minimizing the potential for bias in comparison with use of parametric regression (72).

Alcoholics in recovery tend to have a combination of internal and external precursors to relapse rather than just one prominent factor that precipitates a relapse episode (79). Thus, like other factors that influence substance use in general, environmental factors exert their influence in the context of a complex, dynamic multi-factor system. While our findings do not align with traditional theories, identifying factors that are associated with abstinence after treatment is likely to improve the effectiveness of treatment and prevent relapse in persons at risk. In addition, although we could not identify the causal effect of outlet density on abstinence, we emphasize that formal causal modeling, when used appropriately, can help navigate the tension between important causal questions and the shortcomings of available data and knowledge. Additional studies examining the extent to which neighborhood context impacts long term recovery among alcoholics using methods that account for time-varying covariates are warranted; our current study is a model of how future investigations can be approached using observational data.

2.6 Tables and Figures

Figure 1



t_0 denotes the date of enrollment into the study. A denotes neighborhood-level exposure and time between study entry and lost to follow-up. L denotes baseline and time-varying covariates and past 30-day abstinence history at each wave.

Table 1. Sample demographics and time-varying covariates by AOD exposure cut-off and exposure category at baseline

	Median AOD	
Exposure Status at Baseline	High	Low
N	363	401
Demographics		
Male (%)	58.7	58.6
Race (%)		
White	48.8	68.8
Black	35.5	16.0
Hispanic	6.6	7.5
Other	9.2	7.7
Age (mean, SE)	39.1 (10.6)	38.9 (12.0)
Education (%)		
<high school	22.3	15.7
high school	49.3	54.4
>high school	28.4	29.9
Family history of alcohol use	76.6	73.6
Age onset regular alcohol use	27.2 (10.0)	28.3 (11.2)
ASI Alcohol (mean, SE)	0.37 (0.33)	0.38 (0.33)
ASI Drug (mean, SE)	0.14 (0.14)	0.11 (0.13)
ASI Psych (mean, SE)	0.42 (0.25)	0.39 (0.24)
Time Varying Covariates		
Marital Status (%)		
Married/live with SO	29.5	41.4
Separated/divorced/widowed	41.6	30.7
Never married	28.9	27.9
AA attendance past 12 months (mean, SE)	30.5 (58.6)	23.1(57.8)
Support to abstain (mean, SE)	4.2 (4.7)	4.1 (4.8)
Income (%)		
<25K	62.5	39.2
25K+	37.5	60.9
Percent below poverty	15.5 (10.5)	8.2 (7.4)
Alcohol in past 30 days	78.2	76.1

Table 2. Subject treatment regime and past 30-day abstinence by year of follow-up and for all subjects and only subjects exposed consistently to either above or below the median neighborhood AOD.

	All Subjects		Constant High Median Exposure		Constant Low Median Exposure	
Time	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)
Baseline	764	175 (0.23)	363	79 (0.22)	401	96 (0.24)
Year 1	640	382 (0.60)	282	178 (0.63)	332	189 (0.57)
Year 3	567	244 (0.41)	191	119 (0.62)	232	117 (0.50)
Year 5	515	273 (0.53)	141	80 (0.57)	185	99 (0.54)
Year 7	467	248 (0.53)	116	68 (0.59)	144	82 (0.57)

Table 3. Estimates and expected differences in probability of past 30-day abstinence for subjects exposed consistently to above and below the median neighborhood AOD.

Time	$E[Y_{\bar{a}=1}(k)]$	$E[Y_{\bar{a}=0}(k)]$	$E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)]$
Baseline	0.25	0.24	0.01 (-0.05, 0.07)
Year 1	0.64	0.60	0.04 (-0.05, 0.13)
Year 3	0.62	0.49	0.12 (0.01, 0.24)
Year 5	0.58	0.54	0.04 (-0.08, 0.16)
Year 7	0.59	0.55	0.04 (-0.10, 0.17)

Supplemental Table 1. Estimates and expected differences in probability of past 30-day abstinence for subjects exposed consistently to above and below the median neighborhood AOD, excluding participants in neighborhoods without any alcohol outlets.

Time	$E[Y_{\bar{a}=1}(k)]$	$E[Y_{\bar{a}=0}(k)]$	$E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)]$
Baseline	0.25	0.25	0.01 (-0.06, 0.07)
Year 1	0.61	0.57	0.04 (-0.06, 0.14)
Year 3	0.62	0.49	0.13 (0.01, 0.24)
Year 5	0.56	0.51	0.04 (-0.09, 0.18)
Year 7	0.57	0.56	0.02 (-0.14, 0.17)

Chapter 3: Long-Term Effects of Alcohol Outlet Types on Relapse

3.1 Background

A substantial literature has shown that certain types of outlets confer distinct risks on drinking (54, 80-85). On-premise outlets, such as bars and restaurants, are licensed to sell alcohol for consumption on the premises, while off-premise outlets, such as liquor stores and convenience stores, are not, and this difference has the potential for differential effects on drinking behaviors. States vary widely in the specific mix of alcohol outlets, and use licensing as a means of regulating the makeup and number of each type of alcohol outlet. In 2015, the most recent year for which data are available, there were 361,928 on-premise licensed retail alcohol outlets and 646,010 off-premise licensed retail alcohol outlets in the United States (86).

Studies on the impact of on- vs. off-premise alcohol outlet density on alcohol consumption are inconsistent in their findings; some report positive relationships between higher on-premise—but not off-premise—outlet density and alcohol use, while others report the opposite pattern (87-90). For example, a study in New Orleans found that at-risk drinking was associated with liquor store densities but not on-premise density among African American drinkers (85). Another study found a strong non-linear effect between off-premise outlets and binge drinking in community districts with high densities (more than 80 outlets per square mile) (31). Lastly, a recent longitudinal study concluded that increases in liquor store densities were significantly associated with increases in weekly alcohol consumption (91). In contrast, other studies examining both on- and off-premise outlet densities have found on-premise alcohol density to be more predictive of excessive alcohol consumption than off-premise consumption. One large study that covered 50 cities in California found that on-premise densities, namely bars, were related to greater drinking frequencies and volume whereas no findings were reported for off-premise outlets (81). Another study using bar, restaurant and off-premise densities found that higher restaurant density was associated with greater self-reported drinking frequency whereas this was not the case with regard to bars or off-premise outlet densities (90).

While the impact of various outlet types on drinking has been examined extensively, there is a gap in the literature on how these outlets might influence relapse among alcoholics in recovery. Nonetheless drawing from the aforementioned studies and research on alcoholics' drinking preferences, a few hypotheses can be made. First, an alcoholic's choice of drink is often heavily influenced by economic considerations (92) and off-premise outlets typically sell alcohol in larger quantities for less money than in bars or restaurants. In addition, due to the stigma associated with "falling off the wagon", alcoholics may prefer off-premise outlets so that their drinking can take place away from watchful eyes. Thus, we would expect that higher off-premise densities to increase the risk of relapse. Second, social context may also be an inducing factor to drink and on premise-outlets, namely bars and pubs, are where social and cultural norms are more permissive of excess drinking (93). In addition, a limited research shows that alcoholics

frequent bars for drinking and drink in risky ways (81, 94). Thus, we would expect that higher bar and pub densities to increase the risk of relapse. Lastly, restaurants, given that the primary purpose is to serve food and alcohol is often priced higher than other establishments, might provide some level of protection for alcoholics. Thus we hypothesize that individuals living in neighborhoods with a higher density of restaurants would be more likely to abstain. Moreover, if there are effects in opposite directions for different kinds of outlets, this could explain our null and unexpected findings between overall AOD and abstinence in Chapter 2.

Building on previous work investigating the effects of on- and off-premise AOD on alcohol consumption, this study examines how specific types of alcohol outlets affect relapse, measured as past 30-day abstinence, among alcoholics in recovery. We begin by using a counterfactual framework to define our parameters of interest for the longitudinal effects of neighborhood AOD on abstinence. Then, with data from the Community Epidemiology Laboratory, we follow a prospective cohort of alcoholics in recovery, measuring neighborhood AOD five times over seven years, and estimate the expected difference in the counterfactual probability of past 30-day abstinence at sustained longitudinal exposures to high vs. low off-premise, bar and pub, and restaurant densities. The parameters of interest are estimated using longitudinal targeted maximum likelihood estimation (ltmle), incorporating data-adaptive estimation (SuperLearning), an estimation method that encourages an explicit process for specifying and estimating target parameters to address clearly defined questions while avoiding unnecessary assumptions about model form and accounting for time-dependent confounding (38).

3.2 Methods

Study Participants

From February 1995 to March 1996, respondents were recruited from ten public and private chemical dependency programs in Contra Costa county, excluding methadone maintenance programs and programs limited to aftercare, a stage that occurs after completion of a treatment program. Programs included two HMO's offering long-term outpatient treatment; two private hospital programs offering short-term detoxification, inpatient, day treatment and outpatient; and six public programs (2 detoxification, 2 inpatient, 2 outpatient). In-person interviews were conducted within the first three days of treatment or within the first three outpatient sessions. Contra Costa County, located east of San Francisco, was selected due to its diverse population and mix of rural and urban areas.

Respondents were interviewed with a structured questionnaire that included questions on demographic and socioeconomic characteristics, as well as substance use and treatment history. There were 926 respondents interviewed at baseline. Respondents were re-interviewed at 1, 3, 5 and 7 years post-baseline (58). An intensive effort to locate subjects led to the high response rate throughout the study of 80% at baseline, 80% at wave 2, 79% at wave 3, 78% at wave 4, and 75% at wave 5. Figure 1 provides a useful timeline.

For our analysis, we excluded those who moved out of the state (*n*=23), were in prison (*n*=3), were homeless (*n*=6), did not live independently (*n*=34), or lacked a valid address at baseline (*n*=19). We further limited the sample to exclude those with *intermittent* censoring over the study period (*n*=77). Our final sample included 764 respondents, roughly 80% of the original cohort.

Exposure
We calculated the median density within 0.5 miles for each outlet type at each wave and then averaged across all five waves. For off-premise outlets, the median density was 2. For on-premise outlets, we examined bars and pubs separately from restaurants. The median cut-off of was 1 for bars and pubs, and 3 for restaurants

Respondents provided information about their residential address or nearest cross-streets, which were geocoded and linked with Census geocodes for 1990, 2000, and 2010, which converts addresses to an approximate longitude and latitude coordinate and returns information about the address range that includes the address and the census geography the address is within. We used the best effective residential address for the majority of the time corresponding to the 12-month period referred to in the interview. All respondents' addresses in the U.S. were successfully geocoded (1 respondent had moved overseas), matching all to a valid tract geocode (4% were based on a ZIP code centroid associated with a PO Box) and 92% to a valid block group geocode (61). There was no clustering at the block group level, but 8% of respondents shared a tract with someone else (61).

Alcohol outlet data were compiled from the California Alcoholic Beverage Association (ABC) (62), and included license information by year, physical address, type of license (on- or off-premise, bar/pub/restaurant/liquor store) and status (active/not). All alcohol outlets were then geocoded and linked with longitude and latitude coordinates and a Census geocode to facilitate linkage with respondents' neighborhood addresses. All respondents' addresses and alcohol outlets were geocoded successfully using the ArcGIS software (63).

Outcome
We focused on abstinence from alcohol use, defined as the treatment goal of not consuming any alcohol, since the majority of substance use treatment centers in the United States, including Alcoholics Anonymous (AA), follow an abstinence-based model. The outcome was defined as past 30-day abstinence. The following question was used: 1) "Thinking of the past 30 days, on how many days did you drink any kind of alcoholic beverage – including beer, wine and/or liquor?". Respondent's answers to the survey question were dichotomized as "yes" if they completely abstained from any alcohol and "no" if they consumed any alcohol. Studies have shown greater reliability in recall when drinking is assessed over shorter intervals (64).

Covariates
Measured baseline covariates included gender, race/ethnicity, age at onset of problem drinking, parental and spousal history of alcohol use, education level, Addiction Severity Index measures for alcohol use, drug use, and psychiatric history. The ASI provides an overview of problems related to substance rather than focusing on any single area (65). A composite score, which ranges from 0.00 to 1.00 for each ASI problem area, is calculated

from interviewer severity ratings on a scale of 0- to 9-point estimates of problem severity, defined as the "need for additional treatment", and an objective composite score developed from a subset of items that reflect current status in a given problem area (66). At baseline, the ASI can provide a description of the study sample on a standard set of potentially important background characteristics over and above demographics (65).

Time-dependent variables included number of individuals in social network who encourage sobriety, marital status, AA participation (number of days attendance), total income measured as the sum of taxable income the subject earned over the past year (inflated/deflated) and neighborhood federal poverty level (percent below).

3.3 Statistical Analysis

We follow the targeted learning road map as presented by van der Laan and Rose (55) and Petersen and van der Laan (56). Our primary research question aimed to examine the causal effect of remaining in the same alcohol outlet exposure category throughout follow-up until the end of the study period on the counterfactual probability of past 30-day abstinence. An ideal experiment that would answer this question would be to randomize a cohort of alcoholics in recovery at baseline to each potential longitudinal pattern of outlet exposure, then follow up with them, ensuring perfect adherence and no attrition, until either relapse was observed or the maximum follow-up time (7 years) had passed without relapse. The causal inference estimation framework makes transparent the identifiability assumptions necessary to estimate such parameters from observational data.

Each observed subject history can be written as $O = (\bar{A}(K), \bar{L}(K+1))$, where the overbar represents the history of a random variable and where $k = 1$ indicates baseline, $k = 2$ indicates 1 year post-treatment, $k = 3$ indicates 3 years post-treatment, $k = 4$ indicates 5 years post-treament, and $k = 5$ indicates 7 years post-treatment. $K + 1$ denotes the maximum follow-up time (here equal to 5). $\bar{A}$ is defined as the full history of time-point specific exposure and censoring $A(k)$ up to time point K: $\bar{A} = A(0), \dots, A(K)$. For a given time point, $k, A(k)$ contains neighborhood exposure status $A_1(k)$ (defined as outlet density type above versus below the median) in the interval k and also includes a censoring indicator, $C(k)$, defined as an indicator that a subject has been lost to follow-up by the start of interval k. Similarly, $\bar{L}$ is defined as the history of covariates up to time point K: $\bar{L} = L(0), \dots, L(K)$, where baseline covariates are denoted $L(0)$, time-varying covariates measured in the interval k are denoted $L(k)$, and the outcome of interest, $Y(k)$, an indicator that a subject abstained from alcohol in the interval k, is included in $L(k)$. We assume the observed data over all subjects consists of n independent and identically distributed (i.i.d.) copies of the random (vector) variable O with some underlying probability distribution P_O.

The causal model, $\mathcal{M}^F$, is explicitly linked to our observed data, and thus reflects our beliefs about the time-ordering and relationships between the exposure, covariates, and the outcome of interest:

$$LL(k) = f_{L(k)}\big(Pa\big(L(k)\big), U_{L(k)}\big) \text{ for } k = 0, \dots K+1$$

$$A(k) = f_{A(k)}\big(Pa\big(A(k)\big), U_{A(k)}\big) \text{ for } k = 0, \dots K.$$

The functions f_A, f_L are non-parametric and deterministic. The U components denote unmeasured, independent (exogenous) variables, so that the variables that make up our data set are deterministic (but unknown) functions of the measured history, and some unmeasured error term.

The counterfactual outcomes of interest are $Y_{\bar{a}}(k), k = 1, \dots, K+1$ for $\bar{a}$ equal to $\overline{1}$ or $\overline{0}$, where $Y_{\bar{a}}(k)$ is interpreted as the counterfactual abstinence at time k under a hypothetical intervention to set AOD= $\bar{a}$. Our target parameter of interest,

$$E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)], k = 1, \dots, K+1,$$

was the expected difference in the counterfactual probability of being abstinent in the interval $k = 1, \dots$,5 among individuals consistently exposed to high versus low outlet density type.

An aspect of a statistical model is identifiable when the target causal parameter, which is a function of a data distribution we did not measure (i.e. a function of the counterfactual distribution), can be rewritten as a function of the observed data distribution (i.e. the two quantities will be equal under every data generating distribution compatible with the causal model). In order to estimate the marginal distribution of different counterfactuals from observed data, identifiability assumptions must be considered carefully to determine if the link can be made. Specifically, we need the sequential randomization and positivity assumptions to hold; that is, in each interval k, the counterfactual outcome $Y_k(A = a)$ is independent of the observation process at k, given the measured past, and there is a positive probability of being observed within all covariate-measurement histories. Additionally, we assume that ≥ X% of alcohol outlets in a neighborhood is considered "high." It does not matter for this analysis which X% of the neighborhood is considered because it can be interchangeable with a different X% of the neighborhood. Finally, special attention should be paid to the fact that the exposure in this causal question is a neighborhood-level variable, whereas the other covariates, and the outcome are measured at the individual level. Our statistical estimand was the longitudinal G-Computation formula (57), which will equal our causal parameter if the needed assumptions are met.

We used Longitudinal Targeted Maximum Likelihood Estimation (*ltmle*) to estimate the statistical parameter, best approximating our causal parameter of interest. *Ltmle* is an estimation method that encourages an explicit process for specifying and estimating target parameters to address questions that specifically incorporate time-dependent confounders and avoids modeling errors caused by incorrect parametric assumptions (38). The method also incorporates the possibility of including missing data and fixed (or dynamic) treatments of interest (70). Thus, *ltmle* allows for feasibility in the estimation of targeted statistical parameters based on potentially complex interventions. Specifically, for each time point, it requires estimates of the probability of being in the treatment group (e.g. high off-premise outlet density) given the past (that is, all past covariates, treatments, and outcomes) (71).

We incorporated data-adaptive methods using SuperLearner to reduce dependence on

correct parametric model specification when estimating outcome and treatment regressions. SuperLearner was used to build a library of candidate algorithms to provide a flexible, reasonable, and interpretable approach to fitting both the exposure and the outcome (72). Our pre-specified candidate SuperLearner library included main terms logistic regression, the mean estimate, multivariate adaptive regression spline models, generalized linear models, and generalized additive modeling. Given our modest sample size, we selected algorithms that allowed for flexible relationships and were not data-adaptive in a way that would invalidate reliable inference.

We used multiple imputation to account for our missing data in 10 datasets given that complete information was not available on all of the covariates of interest for all subjects. Multiple imputation was performed using the Amelia package in R, and included all variables used in our analysis in the prediction model (68). The procedure involves three phases: 1) the imputation phase in which missing values are imputed, forming 10 complete data sets; 2) the analysis phase in which each of the 10 complete data sets is analyzed using a statistical model; and 3) the pooling phase in which parameter estimates obtained from each analyzed data set are combined for inference (67). We used the Zelig package in R to combine estimates from the imputed datasets, calculated by Rubin's rules (69).

3.4 Results

We compared the baseline demographic characteristics of subjects by exposure categories defined by our median cut-offs for off-premise outlets (Table 1a), bars and pubs (Table 1b), and restaurants (Table 1c).

Off-premise outlets
The majority of participants residing in high-density neighborhoods at baseline were male (59%) whereas the majority of participants in low-density were female (59%). Black participants comprised 36% of participants residing in high-density neighborhoods compared to 19% in low-density neighborhoods. Nearly 62% of those in high-density neighborhoods reported incomes under 25K, with 16% in areas under the federal poverty level, compared to 43% and 9%, respectively, among those in low-density neighborhoods. Approximately 3/4 of participants in both groups reported having had alcohol in the past 30 days.

Bars/pubs
About 1/5 of participants at baseline were exposed to neighborhoods with high bar/pub density. There were a few notable differences between groups. White participants made up 48% of participants in high-density neighborhoods compared to 62% in low-density neighborhoods. About 69% of participants in high-density neighborhoods reported incomes below 25K compared to 45% in low-density neighborhoods, and 17% of those in high-density neighborhoods lived below the federal poverty line compared to 10% in low-density neighborhoods. Among those in high-density neighborhoods, 80% reported having had alcohol in the past 30 days compared to 76% of participants in low-density neighborhoods.

Restaurants
There were few differences between participants in neighborhoods with high vs. low restaurant density at baseline. Approximately 45% of study participants lived in high restaurant density neighborhoods. A slightly larger percentage (79%) of participants in high restaurant density neighborhoods reported having had alcohol in the past 30 days compared to participants in low-density neighborhoods (75%)

Tables 2a, 2b, and 2c present subjects and past 30-day abstinence counts by wave, with and without restriction to those following the treatment regimen of staying in the same exposure category by off-premise outlets, bars and pubs, and restaurants, respectively.

Off-premise outlets
By the end of the study period, 83 participants remained who were consistently exposed to high-density neighborhoods and among those, 53% reported being abstinent in the past 30 days. Nearly 201 participants remained who were consistently exposed to low-density neighborhoods at the end of the study period, and 54% reported being abstinent in the past 30 days.

Bars/pubs
At the end of the study period, only 31 participants remained who were consistently exposed to high-density neighborhoods and about 50% reported being abstinent for the past 30 days. Of the 294 participants remaining who were consistently exposed to low-density neighborhoods, 57% reported being abstinent in the past 30 days.

Restaurants
For restaurants, 89 participants remained in the constant high exposure and 55% reported being abstinent for the past 30 days. Of the 170 participants in sustained low exposure, approximately 55% reported being abstinent in the past 30 days.

Tables 3a, 3b, and 3c show the estimated differences in the probability of past 30-day abstinence for participants with sustained high exposure compared to sustained low exposure for off-premise outlet density, bar and pub density, and restaurant density, respectively, at each time point. Estimates are adjusted for gender, race/ethnicity, age at onset of problem drinking, parental and spousal history of alcohol use, education level, Addiction Severity Index measures for alcohol use, drug use, psychiatric history, number of individuals in social network who encourage sobriety, marital status, AA participation (number of days attendance), total income measured as the sum of taxable income the subject earned over the past year (inflated/deflated) and neighborhood federal poverty level. The estimated impacts of each exposure—off-premise, bars/pubs, and restaurant outlet density--on mean past 30-day abstinence seven years post-treatment in this population were all small and not statistically significant.

3.5 Discussion

No significant associations between alcohol outlet density and abstinence were found when data were examined stratified by type of alcohol outlet. We estimated parameters targeting the impact of various types of alcohol outlet densities on past 30-day abstinence

among alcoholics in recovery using advances in estimation of longitudinal interventions (*ltmle*) combined with data-adaptive estimation (SuperLearning). We validated the idea of categorizing alcohol outlets in our analytic models, because drinking patterns are strongly tied to the choice of drinking venue (90).

Research on different alcohol outlet types shows enormous diversity in findings, even within the same geographic region or across studies where comparable methodologies were used. For example, Picone *et al*. analyzed the number of bars in varying radii (e.g. 0.5 km) in four US cities including Oakland, CA looking at movers and those who stayed in a residence where the bar density changed, and found at most a very small positive effect on alcohol consumption between movers and non-movers (95). In contrast, the California 50 studies, which also included Oakland, CA concluded that greater proportions of bars among on-premise establishments were related to greater drinking frequencies, quantities, heavy drinking and volumes used (81).

Despite conflicting findings and our study's findings, some conclusions can nevertheless be drawn. First, there is surprisingly little evidence that outlet densities are strongly related to alcohol use by residents living nearby. It is possible that alcohol availability within an individual's residential area is not correlated with their actual exposure to alcohol outlets, but instead that individuals move to certain areas, where others meet or where they can consume alcohol discretely. Second, the use of a density measure, although common, does not allow for individual differences between outlet types. For example, in California, license data do not distinguish liquor stores from grocery stores. This system makes it difficult to disaggregate cleanly into off- and on-premise outlets and ignores the theoretical implications of how alcohol consumption might vary by outlet types. Moreover, although conceptually distinct, in practice, some establishments may share some common characteristics. For example, many restaurants have free-standing bars, and in fact, may transform into a bar during late hours. Finally, few studies have examined how outlet types are distributed or tested the non-linearity of findings rather than deducing effects from linearly estimated models. For example, a study of 82 neighborhoods in four northern/central California cities reported the most economically disadvantaged neighborhoods had three times as many off-premise outlets than that of the least deprived neighborhoods (96). Demonstrating non-linear relationships would facilitate an understanding of harmful outlet types and the scale of change required to reduce harm in different contexts among different groups (31).

As with all studies, there are limitations that need to be considered. First, at baseline, we were unable to account for length of neighborhood residence. The selection of drinkers into certain neighborhood contexts is critical for distinguishing endogenous factors (82). However, detailed tracking information allowed us to address endogeneity by accounting for length of neighborhood exposure prior to each follow-up interview (61). Second, our examination of AOD as a binary variable is unlikely to fully capture the relationship between the outlet density values and shifts in past 30-day abstinence over time. It is unlikely that all individuals would have the same outcome had they been assigned to any exposure level above the cut-off that defined the category. However, we also tested multiple different definitions of our exposure using a mean cut-off and 90^{th} percentile

cutoff, and our results were very similar. In addition, use of a binary variable reduces the increased likelihood of positivity violations and extrapolation that would occur when using a continuous variable. Third, our outcome measure relied exclusively on self-report of alcohol use. Given the time-frame for the outcome (i.e. alcohol past 30 days), we cannot verify that individuals abstained from alcohol use outside the 30-day window. By "sampling" within a very narrow window, our occasion- specific, situational approach necessarily constrains the extent of possible variation that can be observed in our outcome to one of only two values: Either the outcome was present or it was not. However, drinking measures were developed through well-established and validated national alcohol surveys and clinical studies (74). In addition, a substantive body of literature shows that as a group alcoholics' self–reports of their drinking can be used with confidence (75-77). Fourth, there may be additional unmeasured time-dependent covariates that influence whether or not a participant was interviewed at time *t*. In other words, the sequential randomization assumption may not hold for the measurement process. Finally, despite the study's best efforts, there was lost to follow-up. While we controlled for potentially informative censoring with ltmle, the wider confidence intervals at later time points reflect, in part, the smaller number of individuals interviewed in the later years of the study, which may also contribute to a higher potential for positivity violations. Lastly, by implementing multiple imputation, we assumed missingness at random for the missing variables as well as a specific model form for the imputation model (67). Violations of this assumption or misspecification of the imputation model could result in bias.

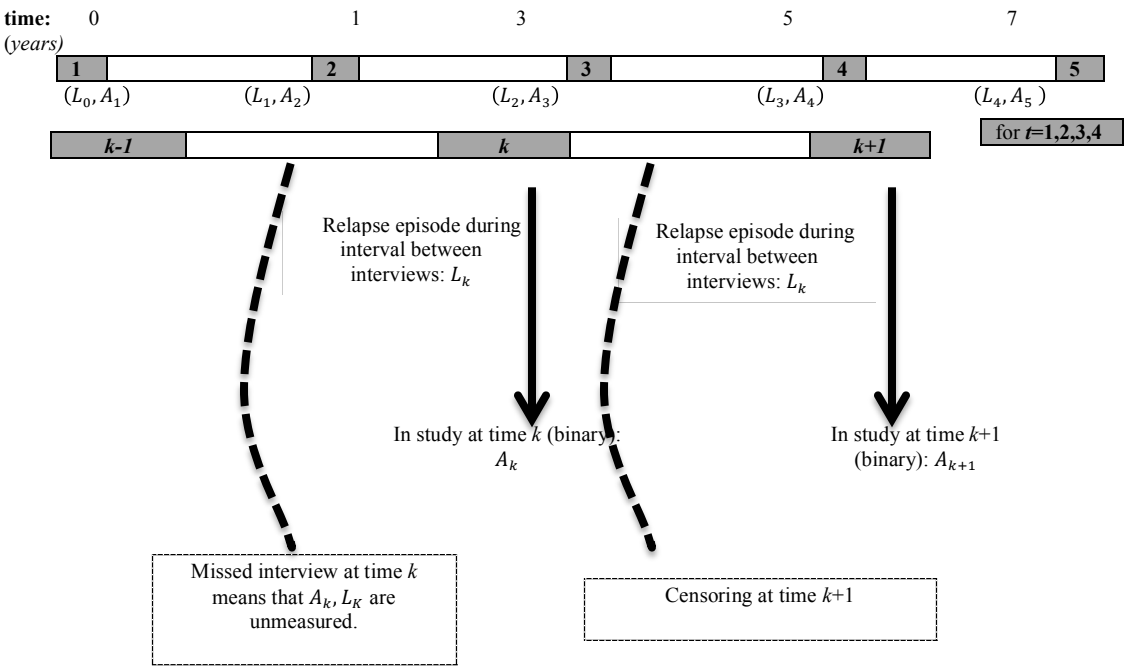
The strengths of this study include the use of alcohol outlet data for very small areas and the link between these data and data on a diverse group of individuals in alcohol recovery, and the longitudinal feature. In addition, this study extends research aiming to understand the effects of on- and off-premise alcohol outlet types on alcohol consumption, specifically among alcoholics in recovery. Previous studies have indicated that on-premise and off-premise outlet density have different impacts as do the different types of outlets within that dichotomy (e.g. bars vs. restaurants) on alcohol consumption in the general population. However, with the exception of young people (97, 98) and US ethnic groups (99, 100), the impacts of off- and on-premise outlets on population subgroups of interest are rarely explored. To our knowledge, our study is the first to directly examine how exposure to various alcohol outlet types may impact alcoholics in recovery. Lastly, this study draws on novel methods that were specifically developed to adjust for possible time-varying confounders on the causal pathway. Traditional regression models are likely to be subject to bias from time-dependent confounding: time-varying covariates that could influence variation in the outcome and the measurement process, and that are also affected by the baseline exposure. However, using our approach, we were able to much better control for these covariates using longitudinal-targeted maximum likelihood estimation (*ltmle*). Our use of SuperLearner for estimation of the outcome and exposure mechanisms guarded against the need to choose *a priori* a parametric model and allowed the combination of many data-adaptive estimators into one improved estimator, thereby minimizing bias in comparison with use of misspecified regressions (72). Additional studies examining the extent to which specific alcohol outlets are associated with drinking behavior using methods that account

for time-varying covariates are warranted; our current study is a model of how future investigations can be approached using observational data.

In summary, this analysis has demonstrated how a flexible and accessible 'causal' estimation method for estimation of longitudinal interventions can provide a way of estimating parameters with direct public health relevance within a large (honest) statistical model (38). We did not observe statistically significant differences in abstinence when examining different types of outlets. However, knowing more about how different outlets impact alcoholics in recovery, which coexist in most communities and together are the targets of preventive interventions, could help guide environmental strategies towards minimizing harm due to alcohol availability.

3.6 Tables and Figures

Figure 1



t_0 denotes the date of enrollment into the study. A denotes neighborhood-level exposure and time between study entry and lost to follow-up. L denotes baseline and time-varying covariates and past 30-day abstinence history at each wave.

Table 1a. Sample demographics and time-varying covariates by off-premise outlet density exposure category at baseline.

	Median Off-Premise Density	
Exposure Status at Baseline	High	Low
N	282	482
Demographics		
Male (%)	58.6	41.4
Race (%)		
White	48.6	65.6
Black	35.5	19.3
Hispanic	6.4	7.5
Other	9.6	7.7
Age (mean, SE)	38.9 (10.7)	39.0 (11.7)
Education (%)		
<high school	23.4	16.2
high school	49.3	53.5
>high school	27.3	30.3
Family history of alcohol use	75.2	74.9
Age onset regular alcohol use	27.1 (10.2)	28.2 (10.8)
ASI Alcohol (mean, SE)	0.35 (0.31)	0.39 (0.34)
ASI Drug (mean, SE)	0.14 (0.14)	0.11 (0.14)
ASI Psych (mean, SE)	0.42 (0.25)	0.40 (0.24)
Time Varying Covariates		
Marital Status (%)		
Married/live with SO	30.1	39.0
Separated/divorced/widowed	39.0	34.0
Never married	30.9	27.0
AA attendance past 12 months (mean, SE)	27.2 (53.4)	26.3 (61.0)
Support to abstain (mean, SE)	4.1 (4.8)	4.2 (4.8)
Income (%)		
<25K	62.4	43.2
25K+	37.6	56.9
Percent below poverty	15.7 (10.1)	9.4 (8.7)
Alcohol in past 30 days	78.0	76.6

Table 1b. Sample demographics and time varying covariates by bar and pub density exposure category at baseline.

	Median Bar/Pub Density	
Exposure Status at Baseline	High	Low
N	174	590
Demographics		
Male (%)	59.2	58.5
Race (%)		
White	48.3	62.5
Black	36.2	22.0
Hispanic	7.5	7.0
Other	8.1	8.5
Age (mean, SE)	39.0 (9.8)	38.9 (11.8)
Education (%)		
<high school	25.9	16.78
high school	51.2	52.2
>high school	23.0	31.0
Family history of alcohol use	77.6	74.24
Age onset regular alcohol use	27.4 (10.0)	27.9 (10.8)
ASI Alcohol (mean, SE)	0.39 (0.32)	0.37 (0.34)
ASI Drug (mean, SE)	0.14 (0.14)	0.12 (0.13)
ASI Psych (mean, SE)	0.45 (0.25)	0.39 (0.25)
Time Varying Covariates		
Marital Status (%)		
Married/live with SO	28.7	37.8
Separated/divorced/widowed	35.6	35.9
Never married	35.6	26.3
AA attendance past 12 months (mean, SE)	36.0 (65.0)	23.9 (55.9)
Support to abstain (mean, SE)	3.6 (3.3)	4.3 (5.1)
Income (%)		
<25K	69.0	44.8
25K+	31.0	55.2
Percent below poverty	17.1 (10.6)	10.1 (8.9)
Alcohol in past 30 days	80.5	76.1

Table 1c. Sample demographics and time-varying covariates by restaurant density exposure category at baseline.

	Median Restaurant Density	
Exposure Status at Baseline	High	Low
N	331	433
Demographics		
Male (%)	58.6	58.7
Race (%)		
White	55.9	61.9
Black	27.8	23.3
Hispanic	6.7	7.4
Other	9.7	7.4
Age (mean, SE)	38.8 (10.8)	39.1 (11.8)
Education (%)		
<high school	19.9	18.47
high school	51.4	52.4
>high school	29.3	29.1
Family history of alcohol use	77.6	73.0
Age onset regular alcohol use	27.2 (10.1)	28.2 (11.0)
ASI Alcohol (mean, SE)	0.38 (0.33)	0.37 (0.33)
ASI Drug (mean, SE)	0.13 (0.14)	0.11 (0.14)
ASI Psych (mean, SE)	0.42 (0.25)	0.39 (0.24)
Time Varying Covariates		
Marital Status (%)		
Married/live with SO	30.2	40.0
Separated/divorced/widowed	42.0	31.2
Never married	27.8	28.9
AA attendance past 12 months (mean, SE)	29.5 (58.9)	24.5 (57.7)
Support to abstain (mean, SE)	4.1 (4.8)	4.1 (4.8)
Income (%)		
<25K	58.0	44.3
25K+	42.0	55.7
Percent below poverty	13.5 (10.0)	10.3 (9.3)
Alcohol in past 30 days	79.5	75.3

Table 2a. Subject treatment regime and past 30-day abstinence by year of follow-up and for all subjects and only subjects exposed consistently to either above or below the median off-premise outlet density.

	All Subjects		Constant High Median Exposure		Constant Low Median Exposure	
Time	Subjects	Incident Cases (n,%)	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)
Baseline	764	175 (0.23)	314	66 (0.21)	433	107 (0.14)
Year 1	640	382 (0.60)	221	137 (0.62)	392	229 (0.58)
Year 3	567	244 (0.41)	148	88 (0.60)	290	155 (0.54)
Year 5	515	273 (0.53)	105	56 (0.53)	235	122 (0.52)
Year 7	467	248 (0.53)	83	44 (0.53)	201	109 (0.54)

Table 2b. Subject treatment regime and past 30-day abstinence by year of follow-up and for all subjects and only subjects exposed consistently to either above or below the median bar and pub density.

	All Subjects		Constant High Median Exposure		Constant Low Median Exposure	
Time	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)
Baseline	764	175 (0.23)	174	34 (0.20)	590	141 (0.24)
Year 1	640	382 (0.06)	131	77 (0.59)	486	293 (0.60)
Year 3	567	244 (0.41)	65	35 (0.54)	380	213 (0.56)
Year 5	515	273 (0.53)	40	25 (0.63)	334	186 (0.56)
Year 7	467	248 (0.53)	31	16 (0.52)	294	168 (0.57)

Table 2c. Subject treatment regime and past 30-day abstinence by year of follow-up and for all subjects and only subjects exposed consistently to either above or below the median restaurant density.

	All Subjects		Constant High Median Exposure		Constant Low Median Exposure	
Time	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)
Baseline	764	175 (0.23)	331	68 (0.21)	433	107 (0.25)
Year 1	640	382 (0.60)	256	168 (0.66)	356	198 (0.56)
Year 3	567	244 (0.41)	162	97 (59.9)	248	132 (0.53)
Year 5	515	273 (0.53)	115	65 (0.57)	197	111 (0.56)
Year 7	467	248 (0.53)	89	49 (0.55)	170	93 (0.55)

Table 3a. Estimates and expected differences in probability of past 30-day abstinence for subjects exposed consistently to above and below the median off-premise outlet density.

Time	$E[Y_{\bar{a}=1}(k)]$	$E[Y_{\bar{a}=0}(k)]$	$E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)]$
Baseline	0.26	0.24	0.02 (-0.04, 0.08)
Year 1	0.61	0.59	0.02 (-0.07, 0.11)
Year 3	0.60	0.55	0.05 (-0.05, 0.16)
Year 5	0.57	0.50	0.06 (-0.06, 0.18)
Year 7	0.52	0.53	-0.01 (-0.15, 0.14)

Table 3b. Estimates and expected differences in probability of past 30-day abstinence for subjects exposed consistently to above and below the median bar and pub density.

Time	$E[Y_{\bar{a}=1}(k)]$	$E[Y_{\bar{a}=0}(k)]$	$E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)]$
Baseline	0.24	0.25	-0.00 (-0.08, 0.07)
Year 1	0.54	0.61	-0.07 (-0.18, 0.04)
Year 3	0.52	0.56	-0.05 (-0.19, 0.10)
Year 5	0.55	0.55	0.01 (-0.16, 0.17)
Year 7	0.51	0.57	-0.06 (-0.29, 0.17)

Table 3c. Estimates and expected differences in probability of past 30-day abstinence for subjects exposed consistently to above and below the median restaurant density.

Time	$E[Y_{\bar{a}=1}(k)]$	$E[Y_{\bar{a}=0}(k)]$	$E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)]$
Baseline	0.24	0.25	-0.01 (-0.07, 0.04)
Year 1	0.64	0.57	0.08 (-0.01, 0.16)
Year 3	0.61	0.53	0.07 (-0.03, 0.17)
Year 5	0.56	0.54	0.02 (-0.10, 0.14)
Year 7	0.56	0.53	0.03 (-0.10, 0.16)

Chapter 4: Long-Term Effects of Alcoholics Anonymous on Relapse

4.1 Background

Establishing a social network that supports abstinence is a fundamental component of treatment success among alcoholics in recovery (29, 36, 101). Current conceptual models posit a reciprocal relationship between social networks and alcohol (29, 36, 101). Specifically, while social networks may both inhibit and promote alcohol consumption (102), alcohol consumption may also alter individuals' social networks. The former, a social causation perspective, emphasizes that social network norms determine individual drinking behaviors (36). On the other hand, a social selection perspective posits that individuals' alcohol consumption can have an impact on social networks (36). Taken as a whole, studies tend to support a social causation perspective. For example, Weisner and Matzger (2002) found that those with fewer heavy drinkers in their social network were less likely to have remained a problem drinker at follow-up (103). Similarly, a study by Rosenquist et *al.* (2010) found that for every social contact who abstained from alcohol, a person's likelihood of heavy drinking decreased by 10% (104). Lastly, among individuals who received treatment for alcohol abuse or dependence, Zywiak *et. al* (2002) found that clients who had social networks with a higher number of recovering alcoholics and abstainers had better outcomes 3 years after treatment completion (105).

Drinking cessation programs that provide peer support – that is, that modify the social network of the target – tend to provide the most promising chance for treatment success (29). The oldest peer social support network for alcohol recovery in the country, Alcoholics Anonymous (AA), remains the most widely used single intervention for alcoholism in the United States with the majority of treatment programs routinely referring patients to attend AA (106). As of January 2016, there were 60,698 AA groups and 1,262,542 members in the United States (27). Research has shown that the more involved subjects are with AA, the more likely they will abstain from alcohol (37, 107-109). For example, Moos *et. al* (2006) published results from a 16-year study of problem drinkers who had tried to quit on their own or who had sought help from AA, professional therapists or, in some cases, both, and found that individuals who participated in AA for 27 weeks or more had better 16-year outcomes (108). McKellar *et al.* (2003) studied a sample of 2,319 male alcohol-dependent patients in 15 Veterans Administration inpatient programs, and found that 1-year post-treatment levels of AA participation predicted lower alcohol-related problems at 2-year follow-up (110). A similar study by Magura et al. (2013) using multiple data waves in Project MATCH found support for the effectiveness of AA primarily in the context of primary outpatient treatment for alcoholism (111).

However, research evaluating the effect of AA participation and drinking is not definitive and subject to different interpretations (26, 37). With few exceptions, the studies that indicate a relationship between AA participation and abstinence from alcohol (26, 29, 32-35), are correlational in nature, making it difficult to discern the timing of life events versus levels of alcohol consumption. That is, it is not possible to determine if AA influences individual drinking behaviors, or if the actual direction of the effect may be the reverse, or in both directions (36). In addition, when longitudinal data have been

available, the data have been largely limited to shorter time periods (30) and report modest yet positive benefits associated with AA exposure (112). The most recent meta analysis determined that it is unclear from studies whether AA helps keep people sober, instead of other factors, including the fact that people more motivated to stay sober will go to more meetings, or that the group support helps alcoholics regardless of the actual program (37).

In this chapter, we aim to build on previous work investigating the effectiveness of AA on drinking and add strengths that prior studies lacked. Specifically, taking advantage of longitudinal data that span seven years, we examine whether the social causation perspective holds among a group of alcoholics in recovery. Using data from the Community Epidemiology Laboratory, a 7-year prospective cohort study of alcoholics in recovery, we estimate the longitudinal impact of AA participation on abstinence via a parameter motivated by the causal inference literature. In our case, we define the parameters of interest as the expected difference in the counterfactual probability of past 30-day abstinence among alcoholics in recovery if always exposed above and always exposed below an AA exposure cut-off. The parameters of interest are estimated using longitudinal targeted maximum likelihood estimation (*ltmle*), incorporating data-adaptive estimation (SuperLearner), an estimation method that encourages an explicit process for specifying and estimating target parameters to address clearly defined questions while avoiding unnecessary assumptions about model form and accounting for time-dependent confounding (38).

4.2 Methods

From February 1995 to March 1996, participants were recruited in Contra Costa County while seeking treatment at ten public and private chemical dependency programs, excluding methadone maintenance programs and programs limited to aftercare, a stage that occurs after completion of a treatment program. Contra Costa County, located east of San Francisco, was selected on the basis of its diverse population characteristics, mix of rural and urban areas and generalizability (74). Participants were interviewed with a structured questionnaire that included questions on demographic and socioeconomic characteristics, as well as substance use and treatment history. Trained research staff who were not employees of the treatment agencies administered a structured survey interview to all consenting participants by the end of their third day of residential treatment or third out-patient visit. Follow-up interviews were conducted 1, 3, 5, and 7 years following recruitment. An intensive effort to locate subjects led to the high response rate throughout the study of 80% at baseline, 80% at wave 2, 79% at wave 3, 78% at wave 4, and 75% at wave 5. No differences in income, psychiatric or alcohol problem severity were among those lost to follow-up; however, males and African Americans were under-represented at follow-up (29).

There were 926 participants interviewed at baseline. For our analysis, we excluded those who moved out of the state (n=23), were in prison (n=3), were homeless (n=6), did not live independently (n=34), or lacked a valid address at baseline (n=19). We further limited the sample to exclude those with intermittent censoring over the study period (n=77). Our final sample included 764 participants, roughly 80% of the original cohort.

Exposure
Exposure was treated as a binary variable to ensure that counterfactual intervention regimens were well represented in the cohort. Binary exposure was defined using a median cut-off where low AA participation was 6 or fewer meetings a year and high involvement was greater than 6 meetings a year across follow-up time.
Outcome
We focused on abstinence from alcohol use, defined as the treatment goal of not consuming any alcohol, since the majority of substance use treatment centers in the United States, including AA follow an abstinence-based model. The outcome was defined as past 30-day abstinence. The following question was used: 1) "Thinking of the past 30 days, on how many days did you drink any kind of alcoholic beverage – including beer, wine and/or liquor?". Respondent's answers to the survey question were dichotomized as "yes" if they completely abstained from any alcohol and "no" if they consumed any alcohol. Studies have shown greater reliability in recall when drinking is assessed over shorter intervals and the NIAAA uses this measure (64).

Covariates
Measured baseline covariates included gender, race/ethnicity, age at onset of problem drinking, parental and spousal history of alcohol use, education level, Addiction Severity Index measures for alcohol use, drug use, and psychiatric history. The ASI provides an overview of problems related to substance rather than focusing on any single area (65). A composite score, which ranges from 0.00 to 1.00 for each ASI problem area, is calculated from interviewer severity ratings on a scale of 0- to 9-point estimates of problem severity, defined as the "need for additional treatment", and an objective composite score developed from a subset of items that reflect current status in a given problem area (66). At baseline, the ASI can provide a description of the study sample on a standard set of potentially important background characteristics over and above demographics (65).

Time-dependent variables included number of individuals in social network who encourage sobriety, marital status, neighborhood alcohol outlet density (continuous within 0.5 mile), total income measured as the sum of taxable income the subject earned over the past year (inflated/deflated) and neighborhood federal poverty level (percent below).

4.3 Statistical Analysis

We used longitudinal targeted maximum likelihood estimation (*ltmle*) to estimate our parameter of interest. *Ltmle* is an estimation method that encourages an explicit process for specifying and estimating target parameters to address questions that specifically incorporate time-dependent confounders and avoids modeling errors caused by incorrect parametric assumptions (38). It also incorporates the possibility of missing data and fixed (or dynamic) treatments of interest (70). Thus, *ltme* allows for tremendous feasibility in the estimation of targeted statistical parameters based on potentially complex interventions. Specifically, for each time point, it requires estimates of the probability of being in the treatment group (e.g. high AA participation) given the past

(that is, all past covariates, treatments, and outcomes) (71). We used a dichotomous definition of exposure; AA participation above a cut-off was defined as "exposed" and that below the cut-off as "unexposed." A priori, we chose one cut-off at the median exposure. We estimated the effect of remaining in the same AA exposure category throughout follow-up until the end of the study.

We applied *ltmle* to estimate the expected difference in the counterfactual probability of past 30-day abstinence among alcoholics in recovery if, during each year of follow-up, they had all been exposed above the cut-off compared to if always exposed below the cut-off. In our study, censoring occurred at the time of the first missed interview.

Each observed subject history can be written as $O = (\bar{A}(K), \bar{L}(K+1))$, where the overbar represents the history of a random variable and where $k = 1$ indicates baseline, $k = 2$ indicates 1 year post-treatment, $k = 3$ indicates 3 years post-treatment, $k = 4$ indicates 5 years post-treament, and $k = 5$ indicates 7 years post-treatment. $K + 1$ denotes the maximum follow-up time (here equal to 5). $\bar{A}$ is defined as the full history of time-point specific exposure and censoring $A(k)$ up to time point K: $\bar{A} = A(0), \ldots, A(K)$. For a given time point, $k, A(k)$ contains AA exposure status $A_1(k)$ (defined as AA participation above versus below the median) in the interval k and also includes a censoring indicator, $C(k)$, defined as an indicator that a subject has been lost to follow-up by the start of interval k. Similarly, $\bar{L}$ is defined as the history of covariates up to time point K: $\bar{L} = L(0), \ldots, L(K)$, where baseline covariates are denoted $L(0)$, time-varying covariates measured in the interval k are denoted $L(k)$, and the outcome of interest, $Y(k)$, an indicator that a subject abstained from alcohol in the interval k, is included in $L(k)$. We assume the observed data over all subjects consists of n independent and identically distributed (i.i.d.) copies of the random (vector) variable O with some underlying probability distribution P_O.

For this analysis our causal question is: What is the average causal effect of consistent high compared to low AA participation on past 30-day abstinence? Our causal model, $\mathcal{M}^F$, is explicitly linked to our observed data, and thus reflects our beliefs about the time-ordering and relationships between the exposure, covariates, and the outcome of interest:

$$LL(k) = f_{L(k)}\big(Pa\big(L(k)\big), U_{L(k)}\big) \text{ for } k = 0, \ldots K+1$$
$$A(k) = f_{A(k)}\big(Pa\big(A(k)\big), U_{A(k)}\big) \text{ for } k = 0, \ldots K.$$

The functions f_A, f_L are non-parametric and deterministic. The U components denote unmeasured, independent (exogenous) variables, so that the variables that make up our data set are deterministic (but unknown) functions of the measured history, and some unmeasured error term.

The counterfactual outcomes of interest are $Y_{\bar{a}}(k), k = 1, \ldots, K+1$ for $\bar{a}$ equal to $\bar{1}$ or $\bar{0}$, where $Y_{\bar{a}}(k)$ is interpreted as the counterfactual abstinence at time k under a hypothetical intervention to set AOD= $\bar{a}$. Our target parameter of interest,

$$E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)], k = 1, \ldots, K+1,$$

was the expected difference in the counterfactual probability of being abstinent in the interval $k = 1, \ldots, 5$ among individuals consistently exposed to high versus low AA participation.

Our statistical estimand was the longitudinal G-Computation formula (57), which will equal our causal parameter if the needed assumptions are met. Specifically, we need the sequential randomization and positivity assumptions to hold; that is, at each time t, the counterfactual outcome $Y_t(A = a)$ is independent of the observation process at t, given the measured past, and there is a positive probability of being observed within al covariate-measurement histories.

We incorporated data-adaptive methods using SuperLearner to reduce dependence on correct parametric model specification when estimating outcome and treatment regressions. SuperLearner combines many different machine learning algorithms already available in R to provide a flexible, reasonable, and interpretable approach to fitting for both the exposure and the outcome. In this analysis, SuperLearner was used to build the best-weighted combination of candidate algorithms as measured by the cross-validated mean squared error (72). Our pre-specified candidate SuperLearner library included main terms logistic regression, the mean estimate, multivariate adaptive regression spline models, generalized linear models, and generalized additive modeling. Given our modest sample size, we selected algorithms that allowed for flexible relationships and were not data-adaptive in a way that would invalidate reliable inference.

We used multiple imputation to account for our missing data in 10 datasets given that complete information was not available on all of the covariates of interest for all subjects. Multiple imputation was performed using the Amelia package in R, and included all variables used in our analysis in the prediction model. The procedure involves three phases: 1) the imputation phase in which missing values are imputed, forming 10 complete data sets; 2) the analysis phase in which each of the 10 complete data sets is analyzed using a statistical model; and 3) the pooling phase in which parameter estimates obtained from each analyzed data set are combined for inference (67). We used the Zelig package in R to combine estimates from the imputed datasets using Rubin's rules to calculate adjusted point estimates and variances (69).

Sensitivity analysis. Some might argue that our median cut-off of 6 meetings per year was too infrequent. While AA strongly suggests that newcomers "make as many meetings as possible" during the first 3 months of sobriety and to keep coming thereafter, there appears to be a tendency to decrease attendance over time. Yet studies show that measures of AA engagement and commitment often are stronger and more consistent predictors of positive outcome than meeting attendance frequency in itself (113, 114). This may be due, for example, to the role of the AA "sponsor", an individual who takes it upon him- or herself to provide guidance for sobriety to another member regardless of AA meeting attendance (114-118). We therefore conduct sensitivity analysis using the same model specifications for the data comparing subjects exposed consistently to any AA participation (high) to subjects without any AA participation (low).

4.4 Results

Characteristics of the sample of participants at baseline are provided in Table 1. Approximately 60% of participants in the high AA participation were male compared to 56% in the low AA participation group, and the mean age in both groups was about 39. Nearly 75% of participants in the high AA participation group and 78% in the low AA participation group reported having had a drink in the past 30-days and both groups reported having 4 close social network contacts that supported abstinence. Notable differences include 39% of participants in the high AA participation group being in a relationship compared to 25% of participants in the low AA participation group. In addition, about 60% of participants in the high AA participation group reported incomes under 25K compared to 40% in the low AA participation group. Lastly, participants in the high AA participation group resided in areas with a mean density of 11.7 alcohol outlets within 0.5 miles whereas their counterpart resided in areas with a mean density of 9.2.

Table 2 contains participants and past 30-day abstinence counts by wave, with and without restriction to those following the treatment regimen of staying in the same exposure category of high or low AA participation. There was an approximately 30% decrease at each wave among participants with sustained high AA meeting involvement. By the end of the study period, participants with sustained high AA participation comprised about 18% of the original sample at baseline. Participants with sustained low AA participation steadily decreased at each wave, possibly indicating that some switched to higher AA participation.

Table 3 shows the estimated differences in the probability of past 30-day abstinence for participants with sustained high AA participation compared to sustained low AA participation at each time point. Estimates are after adjusted for gender, race/ethnicity, age at onset of problem drinking, parental and spousal history of alcohol use, education level, Addiction Severity Index measures for alcohol use, drug use, psychiatric history, number of individuals in social network who encourage sobriety, marital status, neighborhood alcohol outlet density (continuous within 0.5 mile), total income measured as the sum of taxable income the subject earned over the past year (inflated/deflated) and neighborhood federal poverty level. Our estimates show that individuals, if consistently exposed above the median cut-off for AA participation would experience a higher probability of past 30-day abstinence compared to the same group if constantly exposed below the cut-off. At baseline, the comparison for high versus low past year AA participation on abstinence was modest and not statistically significant (0.06; 95% CI 0.00, 0.13). However, the magnitude of the association at subsequent time points was notably large and statistically significant. At wave 2, the effect of AA on abstinence for high attendance compared with low attendance was estimated at 31% (95% CI 0.21, 0.42); 33% (95% 0.21, 0.45) at wave 3; and 34% (95% CI 0.21, 0.47) at wave 4. By wave 5, 7 years after treatment, individuals, if constantly exposed above the median cut-off of 6 AA meetings per year, would experience a 50% (95% CI 0.36, 0.64) higher probability of abstinence with the same cohort if constantly exposed below the cut-off.

Results show that there were not appreciable differences between estimates from unadjusted (Table 2) and adjusted analyses (Table 3). However, the unadjusted differences between groups underestimate the adjusted differences at all time points. For example, the unadjusted and adjusted differences between participants consistently exposed to high AA and consistently exposed to low AA at the end of the study was about 47% (Table 2) and 50% (Table 3), respectively.

Sensitivity Analysis

A sensitivity analysis where we defined high AA participation as >=1 AA meetings and low AA participation as 0 AA meetings were consistent with the main findings (Supplemental Table 3). In addition to the consistency of the direction across all time points, the effects were slightly stronger across waves 2, 3, and 4.

4.5 Discussion

These results provide evidence that increased abstinence is associated with AA participation. Specifically, our findings indicate that individuals consistently exposed to AA participation would experience a significantly higher probability of abstinence over time. Moreover, the association is of growing magnitude over time. Our findings also support a social causation perspective—that AA participation impacts drinking behavior. Previous studies have used this sample and found similar associations between AA participation and drinking. For example, Kaskutas and Weisner found that AA participation was a significant predictor of lower alcohol consumption and concluded that AA's primary mechanism of action is likely through helping to develop and encourage social network changes that facilitate sobriety (29). However, also with this sample, Weisner and Matzger (2002) found that those with fewer heavy drinkers in their social network were less likely to have remained a problem drinker at follow-up, and this result was not dependent on AA participation and was found even among those who had not gone to AA in the past 12 months (103).

We applied longitudinal TMLE (*ltmle*) to adjust for the time-varying confounders on the causal pathway. However, to suggest that we can identify the causal effect of the proposed interventions from the data requires strong assumptions, and we acknowledge that many of them will not be met. For example, there may be additional unmeasured time-dependent covariates that influence whether or not a participant was interviewed at time *t*. In other words, the sequential randomization assumption may not hold for the measurement process. Some other potential confounders of interest that warrant future investigation include co-morbid conditions, religious involvement (119), aspects of AA social networks (e.g., size) (120) and community-level variables such as distance to AA. However, there is greater potential for violating the positivity assumption with the addition of more covariates (121). In addition, despite the study's best efforts, there was loss to follow-up. While we controlled for the potentially informative measurement process with *ltmle*, the wider confidence intervals at later time points reflect, in part, the fewer number of participants interviewed in the later years of the study.

We also acknowledge that our examination of AA participation as a binary variable is unlikely to fully capture the relationship between the range of AA participation and shifts in drinking behavior over time. It is unlikely that all individuals would have the same outcome had they been assigned to any exposure level above the cut-off that defined the category. With this, we made a stronger consistency assumption of treatment variation irrelevance, or that the counterfactual outcome for each subject would be the same if they were exposed at any level within a treatment definition (78). The relevance of the causal model to our observed data depends on this somewhat dubious assumption, but acknowledging this, we nonetheless believe that the statistical parameters we estimate are informative for our primary question. We also limited our measure of AA participation to frequency of meeting attendance, which does not fully capture AA participation. Additionally, we were not able to determine how participants' reported AA attendance was distributed—some may have attended meetings sporadically over a year while others may have attended a lot of meetings over a shorter period, for example. Finally, our outcome measure relied exclusively on self-report of alcohol use. However, drinking measures were developed through well-established and validated national alcohol surveys and clinical studies (74). In addition, a substantive body of literature shows that as a group alcoholics' self–reports of their drinking can be used with confidence (75-77).

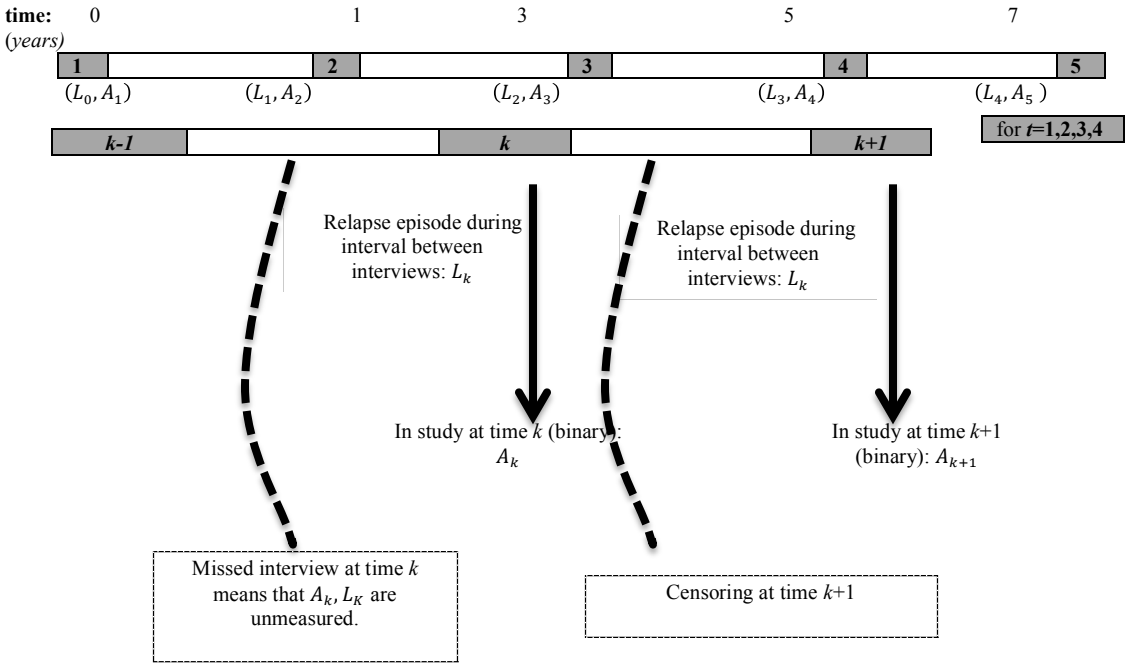
Our study has several strengths. We used a data set that includes a diverse group of individuals. In addition, this study extends research aiming to understand the effects of AA on relapse by drawing on novel methods that were specifically developed to adjust for possible time-varying confounders on the causal pathway. Traditional regression models are likely to be subject to bias from time-dependent confounding: time-varying covariates that could influence variation in the outcome and the measurement process, and that are also affected by the baseline exposure. However, using our approach, we were able to much better control for these covariates using *ltmle*. Moreover, estimators based on this methodology are double robust, in that they remain consistent if either the estimates of the outcome models or the exposure models are estimated consistently. These estimators are also efficient, in that if both the outcome models and the intervention models are consistently estimated they will have the lowest variance among all competitive estimators. In addition, our use of SuperLearner for estimation of the outcome and exposure mechanisms guarded against the need to choose *a priori* a parametric model and allowed the combination of many data-adaptive estimators into one improved estimator, thereby minimizing the potential for bias in comparison with use of parametric regression (72). Moreover, theory and simulation studies show that *ltmle* with SuperLearner is arguably the most reliable estimator and so we have reason to believe that the magnitude of the effect of AA on abstinence is actually larger than suggested by the methods that use parametric modeling (58).

In summary, our findings indicate that AA has a positive impact on long-term sobriety among alcoholics in recovery. Our findings were statistically significant and align with previous studies that support a social causation perspective of AA's impact on sobriety—that having a social network that supports sobriety has a positive impact upon the maintenance of sobriety. The mechanism of AA's action might revolve around AA's advocacy for changing "people, places, and things" that do not facilitate sobriety and, in

particular, limiting or eliminating contact with problematic drinkers and individuals who may exert pressure to drink (29). Therefore, treatment providers should help facilitate AA participation or at a minimum, help identify social networks supportive of abstinence. We applied *ltmle* in a longitudinal study to account for time-varying confounding and generated doubly-robust, efficient, substitution estimators of our parameters of interest. Our analysis has demonstrated how a flexible and accessible 'causal' estimation method for estimation of longitudinal interventions can provide a way of estimating parameters with direct public health relevance within a large (honest) statistical model (38).

4.6 Tables and Figures

Figure 1



t_0 denotes the date of enrollment into the study. A denotes AA exposure and time between study entry and lost to follow-up. L denotes baseline and time-varying covariates and past 30-day abstinence history at each wave.

Table 1. Sample demographics and time varying covariates by AA participation exposure category at baseline

	Median AA participation	
Exposure Status at Baseline	High	Low
N	359	405
Demographics		
Male (%)	61.6	56.1
Race (%)		
White	55.4	62.7
Black	26.5	24.2
Hispanic	7.8	6.4
Other	10.3	6.7
Age (mean, SE)	38.8 (10.4)	39.1 (12.1)
Education (%)		
<high school	22.0	16.1
high school	48.5	55.1
>high school	29.5	28.9
Family history of alcohol use	76.0	73.8
Age onset regular alcohol use	27.1 (10.7)	28.3 (10.5)
ASI Alcohol (mean, SE)	0.40 (0.33)	0.35 (0.33)
ASI Drug (mean, SE)	0.13 (0.14)	0.12 (0.13)
ASI Psych (mean, SE)	0.43 (0.24)	0.38 (0.25)
Time Varying Covariates		
Marital Status (%)		
Married/live with SO	29.0	41.7
Separated/divorced/widowed	39.8	32.4
Never married	31.2	25.9
AOD (mean, SE)	11.7 (24.9)	9.2 (24.3)
Support to abstain (mean, SE)	4.1 (4.9)	4.1 (4.6)
Income (%)		
<25K	61.0	40.7
25K+	39.0	59.3
Percent below poverty	13.2 (10.5)	10.4 (8.8)
Alcohol in past 30 days	75.4	77.9

Table 2. Subject treatment regime and past 30-day abstinence by year of follow-up and for all subjects and only subjects exposed consistently to either above or below AA participation category.

	All Subjects		Constant High Median Exposure		Constant Low Median Exposure	
Time	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)
Baseline	764	175 (0.23)	359	86 (0.24)	405	89 (0.22)
Year 1	640	382 (0.60)	227	162 (0.71)	225	98 (0.44)
Year 3	567	244 (0.41)	150	109 (0.73)	179	84 (0.47)
Year 5	515	273 (0.53)	99	69 (0.70)	158	56 (0.35)
Year 7	467	248 (0.53)	62	51 (0.82)	136	47 (0.35)

Table 3. Estimates and expected differences in probability of past 30-day abstinence for subjects exposed consistently to above and below for subjects exposed consistently to above and below the AA participation category.

Time	$E[Y_{\bar{a}=1}(k)]$	$E[Y_{\bar{a}=0}(k)]$	$E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)]$
Baseline	0.29	0.23	0.06 (0.00, 0.13)
Year 1	0.72	0.41	0.31 (0.21, 0.42)
Year 3	0.75	0.42	0.33 (0.21, 0.45)
Year 5	0.68	0.34	0.34 (0.21, 0.47)
Year 7	0.84	0.34	0.50 (0.36, 0.64)

Supplemental Table 1. Sample demographics and time-varying covariates by AA participation exposure category at baseline, comparing any AA participation (high) to no AA participation (low).

	Median AA participation	
Exposure Status at Baseline	High	Low
N	443	321
Demographics		
Male (%)	61.9	54.2
Race (%)		
White	54.0	66.7
Black	27.5	22.1
Hispanic	7.5	6.5
Other	11.1	4.7
Age (mean, SE)	39.1 (10.6)	38.7 (12.4)
Education (%)		
<high school	21.0	15.9
high school	50.1	54.5
>high school	30.6	29.6
Family history of alcohol use	75.6	74.1
Age onset regular alcohol use	27.0 (10.7)	28.9 (10.4)
ASI Alcohol (mean, SE)	0.41 (0.33)	0.33 (0.33)
ASI Drug (mean, SE)	0.13 (0.14)	0.12 (0.13)
ASI Psych (mean, SE)	0.42 (0.24)	0.37 (0.26)
Time Varying Covariates		
Marital Status (%)		
Married/live with SO	29.6	44.2
Separated/divorced/widowed	40.2	29.9
Never married	30.3	25.9
AOD within 0.5 mi (mean, SE)	12.1 (30.3)	6.5 (11.9)
Support to abstain (mean, SE)	4.0 (4.6)	4.3 (5.0)
Income (%)		
<25K	59.1	38.0
25K+	40.9	62.0
Percent below poverty	13.1 (10.5)	9.7 (8.0)
Alcohol in past 30 days	77.7	76.3

Supplemental Table 2. Subject treatment regime and past 30-day abstinence by year of follow-up and for all subjects and only subjects exposed consistently to any AA participation (high) compared to no AA participation (low).

	All Subjects		Constant High Median Exposure		Constant Low Median Exposure	
Time	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)	Subjects	Abstinent Cases (n,%)
Baseline	764	175 (0.23)	443	99 (0.22)	321	76 (0.24)
Year 1	640	382 (0.60)	355	231 (0.65)	180	71 (0.39)
Year 3	567	244 (0.41)	274	168 (0.61)	148	67 (0.45)
Year 5	515	273 (0.53)	229	129 (0.56)	130	40 (0.31)
Year 7	467	248 (0.53)	209	126 (0.60)	111	32 (0.29)

Supplemental Table 3. Estimates and expected differences in probability of past 30-day abstinence for subjects exposed consistently to any AA participation (high) to no AA participation (low).

Time	$E[Y_{\bar{a}=1}(k)]$	$E[Y_{\bar{a}=0}(k)]$	$E[Y_{\bar{a}=1}(k) - Y_{\bar{a}=0}(k)]$
Baseline	0.28	0.23	0.05 (-0.01, 0.11)
Year 1	0.74	0.35	0.39 (0.29, 0.49)
Year 3	0.73	0.39	0.34 (0.22, 0.46)
Year 5	0.68	0.29	0.38 (0.25, 0.51)
Year 7	0.78	0.28	0.50 (0.36, 0.64)

Chapter 5

Conclusion

5.1 Summary of Findings

While alcohol addiction is a debilitating and complex disease resulting in poor health outcomes, decreased quality of life, and death, few studies have utilized parameters based on the causal inference literature to examine the potential impacts of sustained exposure to environmental and social factors on relapse. Evidence supports the contribution of both environmental and social factors to success after treatment for alcohol addiction. Alcohol outlet density (AOD) has been implicated in excessive alcohol use; however, how AOD might impact long-term recovery among alcoholics after treatment has never been examined. In addition, while there is a substantive literature on Alcoholics Anonymous (AA) effectiveness, no studies have utilized parameters based on the causal inference literature to examine the potential impacts of long-term AA participation on recovery. This dissertation aimed to examine the association between AOD on recovery and AA on recovery using a longitudinal data sample of individuals treated for alcohol addiction.

Findings of Chapter 2: Sustained exposure to neighborhood AOD is not significantly associated with abstinence.

This chapter examined the longitudinal impact of sustained exposure to high neighborhood AOD compared to low neighborhood AOD on past 30-day abstinence via a parameter motivated by the causal inference literature, using non-parametric estimation approaches. The parameters of interest were estimated using longitudinal TMLE and SuperLearner. This study was the first to examine the longitudinal impact of AOD on relapse (past 30-day abstinence) among alcoholics in recovery. Contrary to our hypothesis, we found evidence of an association between high neighborhood AOD and past-30 day abstinence at wave 3, 3 years post-baseline. However, no significant association was found at other time points.

Findings of Chapter 3: Sustained exposure to alcohol outlets, whether on- or off-premise is not significantly associated with abstinence.

Chapter 2 estimated the association between sustained high compared to low exposure to high off-premise and on-premise (bars/pubs and restaurants) alcohol outlets. Using longitudinal TMLE and data-adpative methods via SuperLearner, no significant association was found between groups, regardless of outlet type. This study was the first to examine the longitudinal impact of various alcohol outlet types on relapse (past 30-day abstinence) among alcoholics in recovery.

Findings of Chapter 3: Longterm AA participation and abstinence: potential evidence for a protective association.

This study was the first to utilize parameters based on the causal inference literature to examine the potential impacts of AA on long term recovery from alcohol. Results from this chapter found evidence of an association between sustained AA participation and relapse (past-30 day abstinence) using advances in estimation of longitudinal interventions (ltmle) combined with data-adaptive estimation (SuperLearning). After baseline, a significant association was found, and the expected difference in the

estimated probability of past-30 days abstinence between groups increased over time.

5.2 Conclusions and Future Directions

This dissertation focused on 1) examining the role of neighborhood AOD as a risk factor for relapse and 2) examining the long-term impact of AA on relapse among alcoholics in recovery. Given the burden of disease attributable to alcohol in the U.S., exploration of modifiable factors that could influence risk associated with relapse among alcoholics in recovery is warranted.

We did not find a significant association between AOD and long term relapse and thus does not permit any concrete recommendation for policymaking. Some conclusions can nevertheless be drawn. First, it may not make sense to aggregate outlets based solely on proximity or density, or even by category of on- and off-premises. Alcohol outlets are heterogeneous and they confer different risks even at lower level categories (e.g. bars, restaurants). Future work might consider combining temporal and spatial characteristics of outlets into a single measure (e.g. 24-h outlet proximity). In addition future studies should explore which characteristics of outlet types (i.e heavily trafficked vs. secluded areas) may play a role in increased risk for alcohol consumption. Similarly, whether exposure to both high outlet density and high outlet proximity confers additive or multiplicative risks warrants further exploration. Second, neighborhood effects are particularly susceptible to unmeasured confounding and therefore difficult to parse out the dynamic processes that influence how a neighborhood's composition might shape individuals' behaviors and outcomes. If not adequately corrected for, this may yield biased results. For example, the neighborhood 'stickiness' problem, which refers to the idea that one's zip code nativity area (ZNA) plays a strong deterministic role for the life-course trajectory of health and well-being, can effect the relations between neighborhood context at birth and neighborhood context at study enrollment. This has several implications for causal inference in neighborhood research (122). Further research is needed to understand how these pathways operate to induce relapse susceptibility. Lastly, future work might examine the effect of AOD on specific subgroups of alcoholics in recovery based on severity of alcohol abuse and dependence. In addition, while abstinence is an ideal outcome, a contrasting approach would be to use more nuanced outcomes such as number of drinking occasion or volume of alcohol consumed. That might be a better indicator of the degree to which different alcohol outlet types confer different risks.

We did find a statistically significant association between AA participation and long-term recovery. It's worth noting that we focused on individuals who had already received treatment for their alcohol-related problems and were therefore more likely to initiate a search for help through AA. Accordingly, our findings may not generalize to individuals who have alcohol-related problems but have not received treatment. Future studies should examine the impact of AA attendance on long term relapse among untreated individuals. Similarly, if AA confers long-term benefits, it is worth examining whether individuals with court-mandated AA attendance or access to other 12-step programs have positive outcomes. In addition, we did not account for distance to AA meetings. It is quite

possible that one's proximity to AA meetings increases the likelihood of attendance.

The goal of our analyses was to estimate the causal effects of sustained exposure to AOD and AA on relapse, using statistical techniques that overcome limitations of past work. In an ideal world, we would conduct a randomized control trial which would allow us to nonparametrically identify the causal effects of AOD and AA on relapse under simple assumptions (123). But, for reasons of practicability and costs as well as ethical considerations, we instead relied upon a method that appropriately adjusts for time-dependent confounders. Under assumptions, these associations can be interpreted as causal effects, but in our application these assumptions were not met. Nonetheless, our approach provided a framework for estimation of parameters from observational data that correspond to longitudinal interventions related to exposures that may influence alcohol abstinence. Future studies should consider using longitudinal targeted maximum likelihood estimation (*ltmle*) to improve the inference that can be drawn from research by improving the control for confounding factors.

In conclusion, recovery from alcohol addiction is a lifelong dynamic process. This dissertation addresses aspects of the social context that may contribute to alcohol addiction and recovery. More knowledge on the myriad ways in which individuals might be impacted by contextual factors will enable a better understanding of how to help facilitate long-term recovery.

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