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Causal Inference in Longitudinal Studies with History-Restricted Marginal Structural Models

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Abstract

Causal Inference based on Marginal Structural Models (MSMs) is particularly attractive to subject-matter investigators because MSM parameters provide explicit representations of causal effects. We introduce History-Restricted Marginal Structural Models (HRMSMs) for longitudinal data for the purpose of defining causal parameters which may often be better suited for Public Health research. This new class of MSMs allows investigators to analyze the causal effect of a treatment on an outcome based on a fixed, shorter and user-specified history of exposure compared to MSMs. By default, the latter represents the treatment causal effect of interest based on a treatment history defined by the treatments assigned between the study's start and outcome collection. Beyond allowing a more flexible causal analysis, the proposed HRMSMs also mitigate computing issues related to MSMs as well as statistical power concerns when designing longitudinal studies. We develop three consistent estimators of HRMSM parameters under sufficient model assumptions: the Inverse Probability of Treatment Weighted (IPTW), G-computation and Double Robust (DR) estimators. In addition, we show that the assumptions commonly adopted for identification and consistent estimation of MSM parameters (existence of counterfactuals, consistency, time-ordering and sequential randomization assumptions) also lead to identification and consistent estimation of HRMSM parameters.

1 Introduction

Longitudinal epidemiological studies are increasingly becoming more interested in the time-dependent effects of various exposure on human health outcomes. This is particularly true for studies concerned with the effects of chronic exposure to ambient pollutants. Cohort studies with multiple time-specific estimates of exposure have been emphasized by the U.S. Environmental Protection Agency (EPA) as the preferred study design to address these issues [1]. Examples of such concerns can be found for other health relevant exposures, such as time-specific patterns of physical activity on cardiovascular outcomes and obesity [8].

Typically, cohort studies collect data at regular time intervals for all members of the cohort. In practice, each collection time represents a "window" of time over which data are collected. Information on the exposure of interest, also referred to as "treatment of interest", and other relevant covariates are obtained for the interval between successive data collection time points.

Currently, the principal tools used by epidemiologists for the analysis of cohort data are conditional, association, analyses (e.g., logistic regression, pool logistic regression, Cox proportional hazards). The time-dependence of exposure effects usually are addressed in one of several ways; 1) ignored, in that only baseline exposure is considered; and 2) risk-set sampling, in which exposure status is up-dated at specific time points and exposure effects estimated based on probability of exposure-outcome in the time interval. It is rare for cumulative exposures to be evaluated on their own or in conjunction with exposures over the entire person-time of the cohort and within shorter sub-intervals of time. Thus, the full complexity of the exposure history with respect to effects on a specific health outcome often is lost.

Conditional, association models have several limitations with respect to cohort data: they produce biased estimates in the face of time-dependent confounding and when factors "on the causal pathway" are included in the analysis. Moreover, these analyses generally are not well suited to adequate control of confounding, since confounders are evaluate either one at a time or in the model that includes the exposure. Finally, these models do not provide direct population estimates of exposure effects, which often are of most relevance to public health.

Marginal structural models are models that allow for direct causal inference. Moreover, these models can provide unbiased estimates in the presence of time-dependent confounding and the inclusion of covariates on the causal pathway between the exposure of interest and the health outcome. Of particular importance, these models address the history of the exposures with respect to the outcomes. Thus, it is possible to capture cumulating effects of exposure as well as exposures whose effects are observed over shorter time intervals. This has particular importance for exposures, such as ambient air pollutants, whose acute and chronic exposure effects lead to different health outcomes and/or contribute together in the occurrence of serious health outcomes such as heart attacks and deaths diseases of the heart and lung [1].

Current methods for the implementation of MSMs treat exposure histories over the

entire interval that precedes the occurrence of a time-specific health outcome. In cases where consideration of the entire time interval prior to an event occurrence may not be relevant, based on subject matter, this omnibus treatment of time possess an important limitation. This paper presents an extension of current MSM methodology to allow for more flexible analysis of time effects of exposure based on a priori or ad hoc considerations of specific periods of time antecedent to an event.

The present work was motivated by two specific research problems. First, we undertook a study to determine the extent to which reductions in ambient air pollution consequent to regulations propagated since 1980 by the California Air Resources Board to reduce air pollution in the Los Angeles Basin are associated with measurable health benefits. The basic time unit for the data was 3-monthly units, and we had 84 such time units. Geographic area of interest was divided into 150 10 x 10 km grids, based on know patterns of air pollutants and meteorology in the Basin. The exposures of interest were quarterly concentrations of ambient air pollutants-ozone, oxides of nitrogen, particulates with a median aerodynamic diameter # 10 m. A variety of health outcomes are being considered: quarterly hospital discharges and mortality rates for various chronic lung and cardiovascular diseases. Population denominators and demographic data are available on a quarter-spatial unit-specific basis. Over the 20 years encompassed by the study there have been large temporal trends in demography which has lead to changes in population susceptibility to certain diseases or interest. For example, there has been a large in flux of Mexicans into the study area. Mexicans are known to have decreased risks for asthma and increased risks for diabetes mellitus, an important underlying risk factor for cardiovascular disease. Moreover, since many of these immigrants are of low socioeconomic status, they may be more likely to live in closer proximity to sources of ambient pollutants (i.e., near Freeways). Thus, demography is an important temporal confounder. Changes in medical care over the study period also has affected the occurrence of health outcomes. In our descriptive analyses, important temporal trends for hospital discharges for asthma, chronic obstructive lung disease and various cardiovascular disease were observed. Temporal trends of disease-specific mortality are expected-i.e., there has been a decline in deaths from specific heart disease due to improvements in medical care. Based on the above, "time" becomes an important confounding variable to capture all of the unmeasured temporally-related factors that we have not measured and the residual temporal confounding for those factors that we have measured. Since our initial analysis focused on hospital discharges for asthma in children ages birth to 19 years, a central issue that emerged was the relevant exposure time for quarter-spatial-specific outcome rates. Based on available data on the effects of ambient air pollution on hospital discharges for asthma, it did not seem reasonable to extend the exposure period much beyond the 12 months prior to a given quarter. Consequently, there was a need to modify the how temporal history is handled in existing MSM estimation.

Second, the HRMSM methodology also has application to panel data that are being collected as part of as study of the relation between responses to short-term increases in ambient air pollutants and the long-term changes in symptoms and disease severity in children with asthma (Fresno Asthmatic Children's Environment Study - FACES). In

this study, subjects participate in up to 4 14-day panels during which time each subjects provides daily data on lung function, respiratory symptoms and daily activities. Analyses focus on the causal relation between daily symptoms and lung function and daily exposure to one or another pollutant over one or more days prior to any given day. Confounders for these analyses relate to meteorology and the effects of other pollutants not of primary interest in a given analysis. Virtually all studies to date evaluate the temporal relation between pollutants and symptoms/lung function through one of several methods: 1) tests of specific lag days (e.g., 1 or more days prior to a given day) ; 2) averages over several days before a given day ; or 3) polynomial distributed lag functions [3]. HRMSMs when coupled with a recently developed data-adaptive method for model fitting [10] provide greater flexibility in the evaluation of time lags. Once the investigator specifies a specific time frame over which the effect of the pollutant exposure is of interest, the data-adaptive model selection procedure for MSM can provide guidance on how each level of the pollutant during the specified time frame should enter the model of the causal relationship between the pollutant and asthma outcome.

2 History-Restricted Marginal Structural Model

2.1 Data structure and question of interest

For all experimental units in a random population sample of size n, we observe a treatment regimen $(A(0), \ldots, A(K))$ over time $t = 0, \ldots, K$ and a covariate process $(L(0), \ldots, L(K+1))$ measured at baseline and after a new treatment is assigned. The covariate $L(t)$ is measured after $A(t-1)$ and before $A(t)$. Note that $K+1$ represents the length of the treatment regimen in the appropriate unit of time and n the sample size.

In the formal counterfactual framework for longitudinal study [10], the data are represented as n independent and identically distributed (i.i.d) realizations of:

$$O = (L(0), A(0), L(1), A(1), \ldots, L(K), A(K), L(K+1)) = (\bar{A}(K), \bar{L}(K+1)) \sim P,$$

where P represents the distribution of the stochastic process O, referred to as the observed data, and the general notation $\bar{\cdot}(t)$ represents the history of the variable $\cdot$ between time 0 and t: a) $\bar{\cdot}(t) = (\cdot(0), \ldots, \cdot(t))$ if $t \geq 0$ and b) $\bar{\cdot}(t)$ is empty if $t < 0$. We extend this notation with the notation $\bar{\cdot}(t_-, t_+)$ to represent the history of the variable $\cdot$ between time points t_- and t_+: where a) $\bar{\cdot}(t_-, t_+) = (\cdot(t_-), \ldots, \cdot(t_+))$ if $t_- \leq t_+$, and b) $\bar{\cdot}(t_-, t_+)$ is empty otherwise. We thus have $\bar{\cdot}(t) = \bar{\cdot}(0, t)$.

We define V as a subset of the baseline covariates, $V \subset L(0)$ and we denote the time-dependent outcome with $Y(t)$. In addition, we define $V(t)$ as a subset of $(\bar{A}(t-s), \bar{L}(t-s+1))$, $V(t) \subset (\bar{A}(t-s), \bar{L}(t-s+1))$. We have $Y(t) \in L(t)$ for $t \in \mathcal{T}$, where $\mathcal{T}$ denotes the set of time points t such that the outcome, $Y(t+1)$, is of interest. We have $\mathcal{T} \subset \{0, \ldots, K\}$. Typically $\mathcal{T} = \{0, \ldots, K\}$ except when one is interested in the outcome collected at the end of the study only, i.e. when $\mathcal{T} = \{K\}$.

The question of interest is to investigate the causal effect of the treatment on the time-dependent outcomes of interest. In the literature, this problem has been addressed with MSMs. In MSM-based Causal Inference, the investigation of the causal relationship of interest relies on a representation of the effects of the treatment history $\bar{A}(t)$ on the time-dependent outcome, $Y(t+1) \in L(t+1)$, for all $t \in \mathcal{T}$ (see figure 1). We propose in this paper to address the same problem with the proposed HRMSMs. In HRMSM-based Causal Inference, the investigation of the causal relationship of interest relies on a representation of different causal effects. The effect of the treatment is investigated for a history of treatment that is restricted by the investigators based on considerations discussed later in this manuscript (see figure 2). In other words, MSMs and HRMSMs can be viewed as two different statistical strategies to investigate any given causal relationship, each providing different information and description of the causal effect of interest. We argue that an HRMSM-based causal inference strategy may often be more suitable than an MSM-based causal inference strategy for Public Health research.

2.2 Assumptions

Existence of counterfactuals: we assume the existence of the following treatment-specific processes, also referred to as a counterfactual processes, $\bar{L}_{\bar{a}(K)}(K+1)$ for every treatment regimen $\bar{a}(K) = (a(0), \ldots, a(K)) \in \mathcal{A}(K)$ where $\mathcal{A}(K)$ designates all possible treatment regimens between time points 0 and K, i.e. the support of the conditional distribution of $A(K)$ given V, $g(\bar{A}(K) \mid V)$. See Rubin (1976) [7] for details on the concept of counterfactuals. We denote the so-called full data process with $X = (\bar{L}_{\bar{a}(K)}(K+1))_{\bar{a}(K) \in \mathcal{A}(K)}$ and its distribution with F_X.

Note that the existence of the counterfactual process $\bar{L}_{\bar{a}(K)}(K+1)$ for every treatment regimen $\bar{a}(K) \in \mathcal{A}(K)$ implies the existence of the counterfactual processes $\bar{L}_{\bar{a}(t)}(t+1) \equiv \bar{L}_{\bar{a}(t),\bar{A}(t+1,K)}(t+1) \subset X$ for every $t = 0, \ldots, K-1$ and every treatment regimen $\bar{a}(t) = (a(0), \ldots, a(t)) \in \mathcal{A}(t)$ where $\mathcal{A}(t)$ designates all possible treatment regimens between time points 0 and t, i.e. the support of the conditional distribution of $A(t)$ given V, $g(\bar{A}(t) \mid V)$.

Consistency assumption: at any time point t, we assume the following link between the observed data and the counterfactuals: $L(t) = L_{\bar{A}(K)}(t)$. Under this assumption, we have: $O = (\bar{A}(K), \bar{L}_{\bar{A}(K)}(K+1)) \equiv \phi(\bar{A}(K), X)$, where ϕ is a specified function of the full data process X. This notation indicates that the problem can be treated as a missing data problem. Only the counterfactual associated with the observed treatment $\bar{A}(K)$ is observed; the others are missing.

Temporal Ordering assumption: at any time point t, we assume that any treatment specific variable can only be affected by past treatments: $L_{\bar{a}(K)}(t) = L_{\bar{a}(t-1)}(t)$ for $t = 0, \ldots, K+1$, where $L_{\bar{a}(-1)}(0) = L(0)$. This assumption is typically implied by the data collection procedure: the covariate $L(t)$ is measured after $A(t-1)$ and before $A(t)$.

Sequential Randomization Assumption (SRA): at any time point t, we assume that the observed treatment is independent of the full data given the data observed up to time point t: $A(t) \perp X \mid \bar{A}(t-1), \bar{L}(t)$. Under the SRA, the treatment mechanism, i.e. the conditional density or probability of $\bar{A}(K)$ given X: $g(\bar{A}(K) \mid X)$, becomes:

$$g(\bar{A}(K) \mid X) = \prod_{t=0}^{K} g(A(t) \mid \bar{A}(t-1), X) \overset{SRA}{=} \prod_{t=0}^{K} g(A(t) \mid \bar{A}(t-1), \bar{L}(t)).$$

The SRA implies coarsening at random [2] and thus the likelihood of the observed data factorizes into two parts: a so-called F_X and g part. The F_X part of the likelihood only depends on the full data process distribution, and the g part of the likelihood only depends on the treatment mechanism. As a consequence of this factorization of the likelihood under the SRA, we now denote the distribution of the observed data with $P_{F_X,g}$ and the likelihood of O is:

$$\mathcal{L}(O) \overset{SRA}{=} \overbrace{\underbrace{f(L(0)) \prod_{t=1}^{K+1} f(L(t) \mid \bar{L}(t-1), \bar{A}(t-1))}_{Q_{F_X}}}^{F_X \text{ part}} \overbrace{g(\bar{A}(K) \mid X)}^{g \text{ part}}.$$

In addition, we denote the set of conditional densities or probabilities that define the F_X part of the likelihood, except for $f(L(0))$ with Q_{F_X}.

2.3 HRMSM and causal parameter of interest

We define an HRMSM as a model of a feature (e.g. expectation) of the marginal distribution of the following counterfactuals: $Y_{\bar{A}(t-s),\bar{a}(t-s+1,t)}(t+1)$ possibly conditional on the covariates $V(t)$, for $t \in \mathcal{T}_s$ where 1) $s > 0$ is specified by the investigators and referred to as the (treatment) history size of interest, and 2) $\mathcal{T}_s$ represents the set of time points t such that the outcome $Y(t+1)$ is of interest and $t \geq s-1$, $\mathcal{T}_s = \{t \in \mathcal{T} : t \geq s-1\}$. We have $\mathcal{T}_s \subset \{s-1, \ldots, K\}$. Typically we will have $\mathcal{T}_s = \{s-1, \ldots, K\}$.

In the next section, we discuss the interpretation of HRMSM parameters and how they represent the causal relationship of interest for a given value for s compared to MSM parameters. By convention in this paper, the random portion of the treatment history defining counterfactuals is excluded from the counterfactual notation and thus we adopt the following notations $Y_{\bar{A}(t-s),\bar{a}(t-s+1,t)}(t+1) \equiv Y_{\bar{a}(t-s+1,t)}(t+1)$.

Typically and specifically in this paper, one is interested in average causal effects per stratum $V(t)$ of the population which can be represented by causal parameters defined by HRMSMs of $E_{F_X,g}(Y_{\bar{a}(t-s+1,t)}(t+1) \mid V(t))$ for $t \in \mathcal{T}_s$. We denote a causal parameter defined by an HRMSM with $\beta_t(F_X, g \mid \cdot)$ to indicate that it is a mapping from the space of distributions (F_X, g) to the space of real numbers and that this mapping is a function of modeling assumptions represented by $\cdot$.

Note that unlike the class of MSMs, HRMSMs are introduced as a class of mixed full and observed data models since an HRMSM models the marginal distribution of

counterfactuals where part of the treatment history is left random. The distribution of the random portion of the treatment history is defined by the treatment mechanism, g, and is thus identified with the observed data.

3 When and why prefer HRMSM-based versus MSM-based causal inference in practice?

3.1 MSM parameters: interpretation and causal effect representation

MSMs were introduced as a class of full data models which define parameters based on a feature of the marginal distribution of the following counterfactual outcomes: $Y_{\bar{a}(t)}(t+1)$ possibly conditional on the baseline covariates V. Typically and specifically in this paper, one is interested in average causal effects per stratum V of the population which can be represented by causal parameters defined by MSMs of $E_{F_X}(Y_{\bar{a}(t)}(t+1) \mid V)$ for $t \in \mathcal{T}$. We denote a causal parameter defined by an MSM with $\beta_t(F_X \mid \cdot)$ to indicate that it is a mapping from the space of full data distribution F_X to the space of real numbers and that this mapping is a function of modeling assumptions represented by $\cdot$.

Two approaches to causal inference based on MSM have been proposed. They provide different representations of causal effects with distinct causal parameters. Initially, a parametric MSM approach to causal inference was developed and rely on correct specification of a parametric MSM while, recently, a new approach based on nonparametric MSM was introduced [4] that does not require to assume a correctly specified MSM and that generalizes the definition of causal parameters. This later approach is more realistic if one believes that correct specification of a parametric MSM is unlikely in practice.

In addition, both MSM approaches can be based on either a stratified or a pooled analysis, i.e. distinct models, $m_t(\bar{a}(t), V \mid \beta_t)$, or a single model, $m(t, \bar{a}(t), V \mid \beta)$, for $E_{F_X}(Y_{\bar{a}(t)}(t+1) \mid V)$ for $t \in \mathcal{T}$.

Independently of the MSM approach chosen (nonparametric versus parametric and pooled versus stratified), MSM parameters represents the causal effects of the treatment history, $\bar{A}(t)$, on the outcome, $Y(t+1)$. Note that this implies that in MSM-based Causal Inference, the causal effect of the treatment on the outcome collected at time point t is always investigated for a treatment history of size t. As a result, the causal effect on the outcome collected at time t, $Y(t)$, is defined based on larger treatment histories as t increases, i.e. as the outcome is collected later in the longitudinal study. This feature of this causal analysis is illustrated in figure 1. The figure illustrates how causal effects are investigated in practice based on a MSM approach for a study where $K = 5$, i.e. where the observed data is:

$$O = (L(0), A(0), L(1), A(1), L(2), A(2), L(3), A(3), L(4), A(4), L(5), A(5), L(6)).$$

For instance, the causal effect of the treatment on the outcome collected at time point $t = 6$ is investigated for a treatment history of size 6: $(A(0), A(1), A(2), A(3), A(4), A(5))$

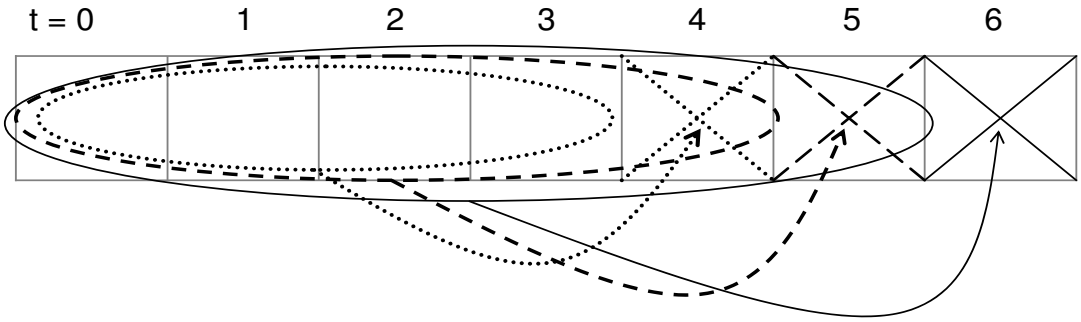

Figure 1: Illustration of the MSM representation of causal effects in a longitudinal study with time-dependent outcomes.

as represented on figure 1 by the ellipse that covers time point 0 to 5 and the arrow that connects the ellipse to the outcome collected at time point 6 represented by a cross.

The investigation of causal effects with MSMs (see figure 1) raises three *potential* concerns that are likely to become more significant for longitudinal studies with longer follow-ups:

- a computing obstacle when proceeding to MSM estimation with the G-computation estimator
- a disbelief about the subject-matter relevance of the causal effects investigated
- a statistical power problem

The first issue is directly related to the implementation of the G-computation estimator. We illustrate it with the following example. Consider a longitudinal study where data are collected over 20 time points: $t = 0, \ldots, 19$ (K=18), where the outcome of interest is collected at each time point. Assume that at each time point, the treatment assigned can take on two values with a non-null probability, i.e. there are $\text{Card}(\mathcal{A}(K)) = 2^{19} = 524,288$ possible treatment regimens that can be assigned between $t = 0, \ldots, 18$, where $\text{Card}(\mathcal{A}(K))$ represents the cardinal of $\mathcal{A}(K)$. For each of these potential treatment regimens, implementation of the G-computation estimator requires to draw by Monte Carlo simulation N_g realizations of the outcome $Y_{\bar{a}(18)}(19)$ based on the G-computation formula. In practice, N_g should be large enough, at least 1,000. Based on this recommendation, the G-computation estimate of MSM parameters in a stratified analysis would be obtained by performing a regression using the MSM and the simulated data that consists of $\text{Card}(\mathcal{A}(K)) * N_g = 524,288,000$. Such a regression could not be handled successfully in most standard statistical packages with the computing resources available to most investigators. In addition, most investigators would also adopt a pooled MSM approach, i.e. the number of observations in the final regression leading to the G-computation estimator would be at least: $\sum_{t=0}^{18} \text{Card}(\mathcal{A}(t)) * N_g = 1,048,574,000$. Such

a pooled analysis is even more unlikely to be successfully handled by most investigators. This example should clearly underline the computing limitation associated with analysis based on MSMs in longitudinal studies with long follow-ups.

The second issue can easily be illustrated with the following hypothetical study. Consider a longitudinal study during which individuals are treated or not every day over three months (90 days) with a new medication for headache relief and monitored for headache symptoms. Now consider the last outcome, $Y(90)$, collected after a treatment history of 89 days, $\bar{A}(89)$. In MSM-based Causal Inference, the investigation of treatment effect on the last outcome measured would be based on the estimation of a causal parameter representing the effect of the treatment history $\bar{A}(89)$ on $Y(90)$. Most investigators would argue that looking a the effect of such a medication taken 3-month prior outcome report is likely to be of little interest for most Public Health questions of interest since 1) the relief effect of such medication usually does not carry over such a long period of time and 2) because the drug effect that is pursued, i.e. of interest, for such a treatment is a short-term relief. In other words, investigating the effect of a headache reliever absorbed 3-month prior outcome report is not of primary interest and it may often make no sense to look at such a long lag effect in practice if the treatment is known to act over a short-term time scale exclusively. Note however that the conventional approach still allows correct investigation of such effects, for example a parametric MSM of $Y_{\bar{a}(89)}(90)$ may only rely on the last two treatments absorbed to explain the outcome, e.g. $E(Y_{\bar{a}(89)}(90)) = \beta_0 + \beta_1 a(88) + \beta_2 a(89)$. However, we argue in this manuscript that the MSM approach can be improved to better identify causal effects that are truly of interest from a subject-matter point of view. The HRMSM proposed in this manuscript addresses this issue and mitigates the other two concerns discussed here.

The third issue is not illustrated with a concrete example but should be obvious to the reader. If the causal relationship that is of interest for Public Health purposes provides support for a statistical analysis based on MSMs, then the investigator may be faced with a serious statistical power problem. The longer the treatment history, i.e. the study follow-up, the more complex the effect of the treatment on the outcome may be. Thus, it is likely that the information required to understand the exact impact of a treatment that was assigned long before outcome report will be very important and beyond the reach of most investigators. As a result, even when it is sensible to investigate causal effects based on MSMs, the investigator may still wish to revise their study aims and lower their research ambition for the sake of practicability.

3.2 HRMSM parameters: interpretation and causal effect representation

Both the parametric and nonparametric MSM [4] approaches to Causal Inference that have been proposed for MSM-based Causal Inference can be directly extended to HRMSM-based Causal Inference. Similarly, the corresponding parametric and nonparametric HRMSM approaches to Causal Inference provide different representations of causal effects with distinct causal parameters.

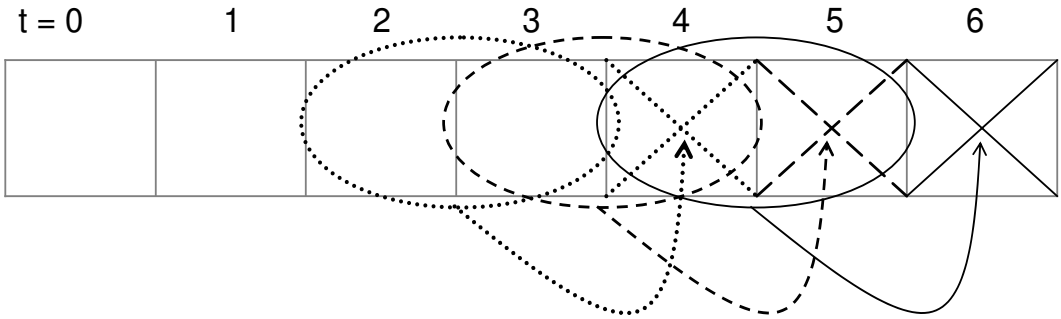

Figure 2: Illustration of the HRMSM representation of causal effects in a longitudinal study with time-dependent outcomes.

In addition, both HRMSM approaches can be based on either a stratified or a pooled analysis, i.e. distinct models, $m_t(\bar{a}(t-s+1,t), V(t) \mid \beta_t)$, or a single model, $m(t, \bar{a}(t-s+1,t), V(t) \mid \beta)$, for $E_{F_X,g}(Y_{\bar{a}(t-s+1,t)} \mid V(t))$ for $t \in \mathcal{T}_s$.

Independently of the HRMSM approach chosen (nonparametric versus parametric and pooled versus stratified), the causal effect of the treatment on the outcome is always investigated for a treatment history of fixed size, s, in HRMSM-based Causal Inference. As a result, the causal effect on the outcome collected at time t, $Y(t)$, is defined based on a fixed treatment history even as t increases, i.e. as the outcome is collected later in the longitudinal study. This feature of this causal analysis is illustrated in figure 2. It illustrates how causal effects are investigated in practice with HRMSMs for a study where $K = 5$ and $s = 2$, i.e. where the data collected is:

$$(L(0), A(0), L(1), A(1), L(2), A(2), L(3), A(3), L(4), A(4), L(5), A(5), L(6)).$$

For instance, the causal effect of the treatment on the outcome collected at time point $t = 6$ is investigated for a treatment history of size 2: $(A(4), A(5))$ as represented on figure 2 by the ellipse that covers time points 4 to 5 and the arrow that connects the ellipse to the outcome collected at time point 6 represented by a cross.

The following three practical considerations may often lead Public Health investigators to prefer a causal analysis based on HRMSMs above an analysis based on MSMs for causal inference problems based on longitudinal data:

- HRMSM-based Causal Inference mitigates the computing limitations associated with MSM estimation in longitudinal studies with long follow-ups based on the G-computation estimator (and thus the Double Robust estimator).
- HRMSMs allows a different investigation of causal relationships and can thus be more relevant to Public Health research in general.

- HRMSM-based Causal Inference alleviates potential statistical power concerns.

Support for these claims can be found in section 1 and 3.1 where the limitations of MSM-based Causal Inference are underlined.

4 HRMSM estimation: the time-specific counterfactual framework

In this section, we introduce the time-specific (t-specific) counterfactual framework which can be viewed as an extension of the conventional counterfactual framework on which MSM-based Causal Inference is based (see sections 2.1 and 2.2). This latter mathematical construct provided the rigorous framework to define, identify and estimate MSM parameters with the full and observed data based on a sufficient set of assumptions developed in section 2.2. We introduce the t-specific counterfactual framework as a statistical artifice that allows us to generalize the estimation procedures that were developed for MSM parameters to procedures for the estimation of HRMSM parameters with minimum effort. In addition, we prove in this section that the assumptions sufficient for estimation of MSM parameters are also sufficient for estimation of HRMSM parameters based on the t-specific counterfactual framework.

4.1 Data structures

In this section, we adopt the notations introduced in the previous section to represent the treatments, covariates and outcomes collected at each time point $t = 0, \ldots, K+1$ on each of the n experimental units: $A(t)$, $L(t)$, Y(t) respectively. We also adopt the notation $V(t)$ to designate a subset of $(\bar{A}(t-s), \bar{L}(t-s+1))$, $V(t) \subset (\bar{A}(t-s), \bar{L}(t-s+1))$.

In the t-specific counterfactual framework, the representation of the data collected during a longitudinal study between time points 0 and $K+1$ is based on a user-specified choice of a fixed treatment history size $s > 0$. We already discussed the interpretation of this parameter, s. In the discussion section of this paper, we discuss the decision making about its value in practice.

In the t-specific counterfactual framework and for a given treatment history size s, the data are represented as n i.i.d realizations of $K - s$ data structures:

$$\begin{aligned} O^t &= (L^t(t-s+1), A^t(t-s+1), L^t(t-s+2), A^t(t-s+2), \ldots, L^t(t), A^t(t), \\ &\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad L^t(t+1)) \\ &= (\bar{A}^t(t-s+1,t), \bar{L}^t(t-s+1,t+1)) \sim P^t, \text{ for all } t \text{ such that } s-1 \leq t \leq K, \end{aligned}$$

where

- P^t represents the distribution of the stochastic process O^t referred to as one of the t-specific observed data,

- $\bar{A}^t(t-s+1,t)$ represents the t-specific treatment process defined as

$$A^t(j) = A(j) \text{ for all } j \text{ such that } t-s+1 \leq j \leq t, \tag{1}$$

- $\bar{L}^t(t-s+1,t+1)$ represents the t-specific covariate process defined by:

a) $L^t(j) = L(j)$ for all j such that $t-s+1 < j \leq t+1$ (2)

b) $L^t(t-s+1) = (\bar{A}(0,t-s), \bar{L}(0,t-s+1))$ (3)

In other words, we have $\bar{L}^t(t-s+1,t+1) = (\bar{A}(t-s), \bar{L}(t+1))$

We define V^t as a subset of the baseline covariates in the t-specific observed data, O^t, $V^t \subset L^t(t-s+1)$, such that:

$$V^t \equiv V(t). \tag{4}$$

We define Y^t as the t-specific outcome of interest, $Y^t \in L^t(t+1)$, such that:

$$Y^t \equiv Y(t+1). \tag{5}$$

In addition, we denote with $\mathcal{T}_s$ the set of time points t such that the outcome in the t-specific observed data, Y^t, is of interest. We have $\mathcal{T}_s \subset \{s-1,\ldots,K\}$. Typically we will have $\mathcal{T}_s = \{s-1,\ldots,K\}$.

Like in the conventional counterfactual framework, the question of interest is to investigate the causal effect of treatment A on the time-dependent outcome, $Y \in L$. In the t-specific counterfactual framework, this problem is addressed through the investigation of the causal effects of the treatment histories $\bar{A}^t(t-s+1,t)$ on the outcomes $Y^t \in L^t(t+1)$ for all $t \in \mathcal{T}_s$.

Note that in this approach and for a given $t \in \mathcal{T}_s$, the outcome Y^t is not defined as a time-dependent variable in the sense that it corresponds with a variable measured at a unique time-point, specifically the last time-point $t+1$ associated with the corresponding t-specific observed data, O^t. That is why, although $Y^t = Y(t)$, we adopt a separate notation Y^t to designate the outcome. It is not to be confused with the notation Y introduced for the conventional counterfactual framework and which designates a time-dependent variable. Indeed, $Y(j)$ can be regarded in the t-specific counterfactual framework both as any covariate $Y(j) \in L^t(j)$ and the outcome Y^t when $j = t+1$. Similarly, note that we adopt a distinct notation, A^t, to unambiguously represent the treatment of interest in the t-specific observed data $O(t)$. This notation is not to be confused with A which refer to a variable that can be regarded both as a covariate L^t and a treatment variable A^t in the t-specific counterfactual framework.
Note that if $s = 2$ for example, then $Y(1)$ cannot be of interest since at time point 1 each unit has been treated with a treatment history of size 1 and it is thus not possible to look at the effect of a treatment history of size 2 on $Y(1)$. That is why we use the notation $\mathcal{T}_s$ to indicate that the set of outcomes of interest depends on the investigator's choice for s.

4.2 Assumptions

In the t-specific counterfactual framework, we adopt the same set of assumptions as described for the conventional counterfactual framework with the exception that each assumption is made relative to each t-specific observed data of interest, O^t for $t \in \mathcal{T}_s$. In other words, we make the following t-specific assumptions **for all t** $\in \mathcal{T}_\mathbf{s}$.

Existence of counterfactuals: we assume the existence of the following t-specific treatment specific processes, $\bar{L}^t_{\bar{a}^t(t-s+1,t)}(t-s+1,t+1)$, also referred to as t-specific counterfactual processes, for every treatment regimen $\bar{a}^t(t-s+1,t) = (a(t-s+1),\ldots,a(t)) \in \mathcal{A}(t-s+1,t)$ where $\mathcal{A}(t-s+1,t)$ designates all possible treatment regimens between time points $t-s+1$ and t, i.e. the support of the conditional distribution of $\bar{A}(t-s+1,t)$ given $\bar{A}(t-s)$ and V^t, $g(\bar{A}(t-s+1,t) \mid \bar{A}(t-s), V^t)$. We denote the so-called t-specific full data process associated with O^t with $X^t = (\bar{L}^t_{\bar{a}^t(t-s+1,t)}(t-s+1,t+1))_{\bar{a}^t(t-s+1,t)\in\mathcal{A}(t-s+1,t)}$ and its distribution with F_{X^t}.

Note that the existence of the t-specific counterfactual process $\bar{L}^t_{\bar{a}^t(t-s+1,t)}(t-s+1,t+1)$ for every treatment regimen $\bar{a}^t(t-s+1,t) \in \mathcal{A}(t-s+1,t)$ implies the existence of the t-specific counterfactual processes $\bar{L}^t_{\bar{a}^t(t-s+1,j)}(t-s+1,j+1) \equiv \bar{L}^t_{\bar{a}^t(t-s+1,j),A^t(j+1),\ldots,A^t(t)}(t-s+1,j+1) \subset X^t$ for every $j = t-s+1,\ldots,t-1$ and every treatment regimen $\bar{a}^t(t-s+1,j) = (a(t-s+1),\ldots,a(j)) \in \mathcal{A}(t-s+1,j)$ where $\mathcal{A}(t-s+1,j)$ designates all possible treatment regimens between time points t-s+1 and j, i.e. the support of the conditional distribution of $A(t-s+1,j)$ given $\bar{A}(t-s)$ and V^t, $g(\bar{A}(t-s+1,j) \mid \bar{A}(t-s), V^t)$.

Consistency assumption: at any time point j such that $t-s+1 \leq j \leq t+1$, we assume the following link between the t-specific observed data and the t-specific counterfactuals: $L^t(j) = L^t_{\bar{A}^t(t-s+1,t)}(j)$. Under this assumption, we have: $O^t = (\bar{A}^t(t-s+1,t), \bar{L}^t_{\bar{A}^t(t-s+1,t)}(t-s+1,t+1)) \equiv \phi^t(\bar{A}^t(t-s+1,t), X^t)$, where ϕ^t is a specified function of the t-specific full data process X^t. This notation indicates that the problem can be treated as multiple (for each $t \in \mathcal{T}_s$) missing data problems. Indeed, for each $t \in \mathcal{T}_s$, only the t-specific counterfactual associated with the observed treatment $\bar{A}^t(t-s+1,t)$ is observed; the others are missing.

Temporal Ordering assumption: at any time point j such that $t-s+1 \leq j \leq t+1$, we assume that any treatment specific variable can only be affected by past treatments: $L^t_{\bar{a}^t(t-s+1,t)}(j) = L^t_{\bar{a}^t(t-s+1,j-1)}(j)$ for $j = t-s+1,\ldots,t+1$, where $L^t_{\bar{a}^t(t-s+1,t-s)}(t-s+1) = L^t(t-s+1)$. This assumption is typically implied by the data collection procedure: the covariate $L^t(t)$ is measured after $A^t(t-1)$ and before $A^t(t)$.

Sequential Randomization Assumption (SRA): at any time point j such that $t-s+1 \leq j \leq t+1$, we assume that the t-specific observed treatment is independent of the t-specific full data given the t-specific data observed up to time point j: $A^t(j) \perp X^t \mid \bar{A}^t(t-s+1,j-1), \bar{L}^t(t-s+1,j)$. Under the SRA, the t-specific treatment mechanism, i.e. the conditional density or probability of $\bar{A}^t(t-s+1,t)$ given X^t: $g(\bar{A}^t(t-s+1,t) \mid X^t)$,

becomes:

$$\begin{aligned} g(\bar{A}^t(t-s+1,t) \mid X^t) &= \prod_{j=t-s+1}^{t} g(A^t(j) \mid \bar{A}^t(t-s+1,j-1), X^t) \\ &\overset{SRA}{=} \prod_{j=t-s+1}^{t} g(A^t(j) \mid \bar{A}^t(t-s+1,j-1), \bar{L}^t(t-s+1,j)). \end{aligned}$$

The SRA implies coarsening at random [2] and thus the t-specific likelihood of the t-specific observed data factorizes into two parts: a so-called F_{X^t} and g^t part. The F_{X^t} part of the likelihood only depends on the t-specific full data process distribution, and the g^t part of the likelihood only depends on the t-specific treatment mechanism. As a consequence of this factorization of the t-specific likelihood under the SRA, we now denote the distribution of the t-specific observed data with $P_{F_{X^t},g^t}$ and the likelihood of O^t is:

$$\mathcal{L}(O^t) \overset{SRA}{=} \overbrace{\underbrace{f(L^t(t-s+1)) \prod_{j=t-s+2}^{t+1} f(L^t(j) | \bar{L}^t(t-s+1,j-1), \bar{A}^t(t-s+1,j-1))}_{Q_{F_{X^t}}}}^{F_{X^t} \text{ part}} \overbrace{g(\bar{A}^t(t-s+1,t) | X^t)}^{g^t \text{ part}}.$$

In addition, we denote the set of conditional densities or probabilities that define the F_{X^t} part of the likelihood, except for $f(L^t(t-s+1))$ with $Q_{F_{X^t}}$.

4.3 Equivalence between MSM parameters in the t-specific counterfactual framework and HRMSM parameters in the conventional counterfactual framework

Like in the conventional counterfactual framework, causal effects can be represented based on parameters defined by MSMs in the t-specific counterfactual framework. Indeed MSM approach can be applied to all t-specific observed data, O^t. We refer to an MSM associated with a given t-specific full data as a t-specific MSM. These t-specific MSMs are t-specific full data models, i.e. model of F_{X^t}, which define parameters based on a feature of the distribution of the following counterfactual outcomes: $Y^t_{\bar{a}^t(t-s+1,t)}$. Typically and specifically in this paper, one is interested in average causal effects per stratum V^t of the population which can be represented by causal parameters defined by MSMs of $E_{F_{X^t}}(Y^t_{\bar{a}^t(t-s+1,t)} \mid V^t)$ for $t \in \mathcal{T}_s$. We denote a causal parameter defined by an MSM with $\beta_t(F_{X^t} \mid \cdot)$ to indicate that it is a mapping from the space of t-specific full data distribution F_{X^t} to the space of real numbers and that this mapping is a function of modeling assumptions represented by $\cdot$.

We have by definition from (4): $V^t \equiv V(t)$ and we can show as follows that $Y^t_{\bar{a}^t(t-s+1,t)} = Y_{\bar{a}(t-s+1,t)}(t+1)$ for $t \in \mathcal{T}_s$:

$$\begin{aligned} Y^t_{\bar{a}^t(t-s+1,t)} &= Y^t_{\bar{a}(t-s+1,t)} \text{ from (1)} \\ &= Y_{\bar{a}(t-s+1,t)} \text{ from (5)} \end{aligned}$$

Thus we have $E_{F_{X^t}}(Y^t_{\bar{a}^t(t-s+1,t)} \mid V^t) = E_{F_X,g}(Y_{\bar{a}(t-s+1,t)}(t+1) \mid V(t))$ and $F_{X^t} = \psi(F_X, g)$ for some specified function ψ.

In general, one can show that HRMSM parameters defined in the conventional counterfactual framework, $\beta_t(F_X, g \mid \cdot)$, corresponds to MSM parameters defined in the t-specific counterfactual framework, $\beta_t(F_{X^t} \mid \cdot)$:

$$\beta_t(F_X, g \mid \cdot) = \beta_t(F_{X^t} \mid \cdot) \tag{6}$$

4.4 Link between the conventional and t-specific counterfactual frameworks

Figure 3 illustrates based on an example of a longitudinal study with short follow-up the link between the longitudinal data representation in the conventional counterfactual framework and its representation in the time-specific counterfactual framework. Note that in the conventional counterfactual framework the data are approached as a single entity, O, in the sense that the treatment is defined once and for all as a history $\bar{A}(K)$ and the outcome is time-dependent, $Y(t) \in L(t)$. On the other hand, in the t-specific counterfactual framework the data are viewed as layers of separate entities, O^t. For each entity, the treatment and outcome of interest are redefined along with the baseline covariates (highlighted in yellow on figure 3). Note that for a given entity, the outcome is no longer time-dependent but correspond with the last outcome collected, $Y^t \in L^t(t+1)$, (highlighted in orange on figure 3) and the treatment history size is fixed to a user-specified value s. In the conventional counterfactual framework, the investigator examines the effect of $\bar{A}(K)$ on $Y(t)$ for all $t \in \mathcal{T}$ based on MSMs of the full data associated with O whereas in the t-specific counterfactual framework, the investigator examines the effect of $\bar{A}^t(t-s+1,t)$ on Y^t for $t \in \mathcal{T}_s$ based on MSMs of the t-specific full data associated with O^t. We have shown earlier the equivalence between t-specific MSM parameters and HRMSM parameters. Thus both the t-specific and conventional counterfactual approaches lead to a different representation of the causal effect of A on Y, we argued that the t-specific counterfactual framework (i.e. HRMSM-based Causal Inference) leads to a representation of causal effects that may often be more relevant to Public Health research.

In short, figure 3 illustrates how the t-specific counterfactual framework can be viewed as a collection of conventional counterfactual sub-frameworks with distinct definition of the outcome, treatment and baseline covariates. These conventional counterfactual sub-frameworks differ from the conventional counterfactual framework in the sense that the treatment history is of size $s \neq K+1$ and the outcome of interest is no longer time-dependent. The MSM approach developed for the conventional counterfactual framework can now, under the appropriate assumptions, be directly applied to all the conventional counterfactual sub-frameworks.

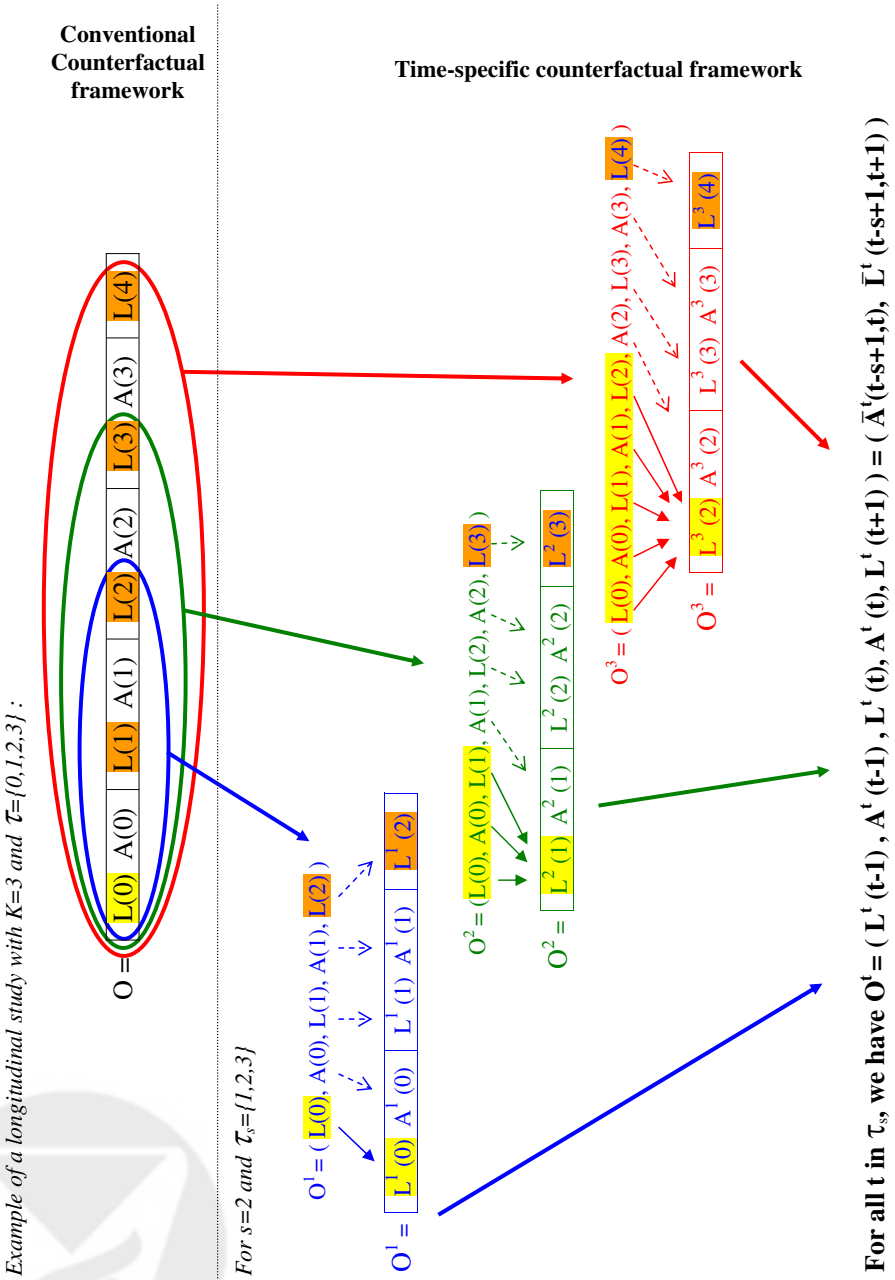

Figure 3: Link between the data representations in the conventional and t-specific counterfactual frameworks illustrated with data from a longitudinal study with short follow-up.

4.5 HRMSM estimators

Under the assumptions presented earlier in section 4.2 and from equality (6), the HRMSM parameters, $\beta_t(F_X, g \mid \cdot)$, can be identified and consistently estimated with the t-specific observed data and three estimators of the t-specific MSM parameters: the Inverse Probability of Treatment Weighted, the G-computation, and Double Robust estimators. The implementation procedures for these three estimators of HRMSM parameters correspond with the procedures developed for MSM-based Causal Inference except that they are applied not to the observed data, O, with treatment, A, and time-dependent outcomes of interest, $Y(t)$ for $t \in \mathcal{T}$, but to all t-specific observed data, O^t, of interest, i.e. for $t \in \mathcal{T}_s$, with treatment A^t and outcome Y^t.

The consistency and efficiency properties of these three estimators along with their implementation procedures have been thoroughly studied in the literature [10, 6, 11, 5].

5 Sufficient assumptions for consistent HRMSM estimation

We now formally establish that the seemingly larger set of t-specific assumptions (see section 4.2) required to investigate causal effects in the t-specific counterfactual framework is implied by the set of assumptions (see section 2.2) required to investigate causal effects in the conventional counterfactual framework. The important practical consequence of both of these results is that successful investigation of causal effects based on HRMSM parameters can be achieved based on the same model assumptions leading to successful investigation of causal effects based on MSMs. Thus, the choice of HRMSM-based causal analysis over MSM-based causal analysis is only a matter of practical considerations (statistical power and computing issues) and above all subject-matter considerations, e.g. the relevance of the causal effect representation to Public Health research.

Theorem 5.1 *We adopt the notations introduced previously for the conventional and t-specific counterfactual frameworks. Based on these notations we have:*

i. the assumption of existence of counterfactuals defined in the conventional counterfactual framework implies the t-specific assumptions of existence of counterfactuals defined in the t-specific counterfactual framework:

$$\forall\ \bar{a}(K) \in \mathcal{A}(K) \quad \bar{L}_{\bar{a}(K)}(K+1) \implies \forall\ t \in \{s-1, \ldots, K\} \quad \forall\ \bar{a}^t(t-s+1,t) \in \mathcal{A}(t-s+1,t) \quad \bar{L}^t_{\bar{a}^t(t-s+1,t)}(t-s+1, t+1)$$

ii. the consistency assumption in the conventional counterfactual framework implies the t-specific consistency assumptions in the t-specific counterfactual framework:

$$\forall\ t \in \{0, \ldots, K+1\} \quad L(t) = L_{\bar{A}(K)}(t) \implies \forall\ t \in \{s-1, \ldots, K\} \quad \forall\ j \in \{t-s+1, \ldots, t+1\} \quad L^t(j) = L^t_{\bar{A}^t(t-s+1,t)}(j)$$

iii. the temporal ordering assumption in the conventional counterfactual framework implies the t-specific temporal ordering assumptions in the t-specific counterfactual framework:

$$\forall\, t \in \{0,\ldots,K+1\} \quad L_{\bar{a}(K)}(t) = L_{\bar{a}(t-1)}(t) \implies \forall\, t \in \{s-1,\ldots,K\} \quad \forall\, j \in \{t-s+1,\ldots,t+1\} \quad L^t_{\bar{a}^t(t-s+1,t)}(j) = L^t_{\bar{a}^t(t-s+1,j-1)}(j)$$

iv. the SRA in the conventional counterfactual framework implies the t-specific SRAs in the t-specific counterfactual framework:

$$\forall\, t \in \{0,\ldots,K\} \quad A(t) \perp X \mid \bar{A}(t-1), \bar{L}(t) \implies \forall\, t \in \{s-1,\ldots,K\} \quad \forall\, j \in \{t-s+1,\ldots,t\} \quad A^t(j) \perp X^t \mid \bar{A}^t(t-s+1, j-1), \bar{L}^t(t-s+1, j)$$

Proof. For $t \in \{s-1,\ldots,K\}$ and $j \in \{t-s+1,\ldots,t+1\}$ we have:

iv.

$$\begin{aligned}
X^t &= \left(\bar{L}^t_{\bar{a}^t(t-s+1,t)}(t-s+1,t+1)\right)_{\bar{a}^t(t-s+1,t)\in\mathcal{A}(t-s+1,t)} \\
&= \left(\bar{L}^t_{\bar{a}(t-s+1,t)}(t-s+1,t+1)\right)_{\bar{a}(t-s+1,t)\in\mathcal{A}(t-s+1,t)} \text{ from (1)} \\
&= \left(L^t_{\bar{a}(t-s+1,t)}(t-s+1), \bar{L}^t_{\bar{a}(t-s+1,t)}(t-s+2,t+1)\right)_{\bar{a}(t-s+1,t)\in\mathcal{A}(t-s+1,t)} \\
&= \left(\bar{A}(t-s), \bar{L}_{\bar{a}(t-s+1,t)}(t-s+1), \bar{L}_{\bar{a}(t-s+1,t)}(t-s+2,t+1)\right)_{\bar{a}(t-s+1,t)\in\mathcal{A}(t-s+1,t)} \\
&\quad \text{from (2) and (3)} \\
&= \left(\bar{A}(t-s), \bar{L}_{\bar{a}(t-s+1,t)}(t+1)\right)_{\bar{a}(t-s+1,t)\in\mathcal{A}(t-s+1,t)} \\
&= \left(\bar{A}(t-s), \left(\bar{L}_{\bar{a}(t-s+1,t)}(t+1)\right)_{\bar{a}(t-s+1,t)\in\mathcal{A}(t-s+1,t)}\right) \\
X^t &= (\bar{A}(t-s), X^t_L) \text{ where } X^t_L = \left(\bar{L}_{\bar{a}(t-s+1,t)}(t+1)\right)_{\bar{a}(t-s+1,t)\in\mathcal{A}(t-s+1,t)} \qquad (7)
\end{aligned}$$

In addition, we have:

$$\begin{aligned}
X^t_L &= \left(\bar{L}_{\bar{a}(t-s+1,t)}(t+1)\right)_{\bar{a}(t-s+1,t)\in\mathcal{A}(t-s+1,t)} \\
&= \left(\bar{L}_{\bar{A}(t-s),\bar{a}(t-s+1,t),\bar{A}(t+1,K)}(t+1)\right)_{\bar{a}(t-s+1,t)\in\mathcal{A}(t-s+1,t)} \\
&\subset X = \left(\bar{L}_{\bar{a}(K)}(K+1)\right)_{\bar{a}(K)\in\mathcal{A}(K)} \\
X^t_L &\subset X \qquad (8)
\end{aligned}$$

Based on these previous two results, we obtain:

$$
\begin{aligned}
& g\Big(A^t(j), X^t \mid \bar{A}^t(t-s+1, j-1), \bar{L}^t(t-s+1, j)\Big) \\
&= g\Big(A(j), X^t \mid \bar{A}(t-s+1, j-1), L^t(t-s+1), \bar{L}^t(t-s+2, j)\Big) \text{ from (1)} \\
&= g\Big(A(j), X^t \mid \bar{A}(t-s+1, j-1), \bar{A}(t-s), \bar{L}(t-s+1)\bar{L}(t-s+2, j)\Big) \text{ from (2) and (3)} \\
&= g\Big(A(j), X^t \mid \bar{A}(j-1), \bar{L}(j)\Big) \\
&= g\Big(A(j), \bar{A}(t-s), X_L^t \mid \bar{A}(j-1), \bar{L}(j)\Big) \text{ from (7)} \\
&= g\Big(A(j), X_L^t \mid \bar{A}(j-1), \bar{L}(j)\Big) \text{ since } \bar{A}(t-s) \subset \bar{A}(j-1) \\
&= g\Big(A(j) \mid \bar{A}(j-1), \bar{L}(j)\Big) \text{ from the SRA and (8)} \\
&= g\Big(A^t(j) \mid \bar{A}^t(t-s+1, j-1), \bar{L}^t(t-s+1, j)\Big) \text{ from (1), (2) and (3)}
\end{aligned}
$$

This last equality is equivalent to $A^t(j) \perp X^t \mid \bar{A}^t(t-s+1, j-1), \bar{L}^t(t-s+1, j)$. We also have:

- if $j \neq t-s+1$:

  i.

$$
\begin{aligned}
L^t_{\bar{a}^t(t-s+1,t)}(j) &= L^t_{\bar{a}(t-s+1,t)}(j) \text{ from (1)} \\
&= L_{\bar{a}(t-s+1,t)}(j) \text{ from (2)} \\
&= L_{A(0),\ldots,A(t-s),\bar{a}(t-s+1,t),A(t+1),\ldots,A(K)}(j)
\end{aligned}
$$

  ii.

$$
\begin{aligned}
L^t(j) &= L(j) \text{ from (2)} \\
&= L_{\bar{A}(K)}(j) \text{ from the consistency assumption} \\
&= L_{\bar{A}(t-s),\bar{A}(t-s+1,t),\bar{A}(t+1,K)}(j) \\
&= L_{\bar{A}(t-s+1,t)}(j) \\
&= L_{\bar{A}^t(t-s+1,t)}(j) \text{ from (1)} \\
&= L^t_{\bar{A}^t(t-s+1,t)}(j) \text{ from (2)}
\end{aligned}
$$

  iii.

$$
\begin{aligned}
L^t_{\bar{a}^t(t-s+1,t)}(j) &= L_{\bar{a}(t-s+1,t)}(j) \text{ from (1) and (2)} \\
&= L_{\bar{A}(t-s),\bar{a}(t-s+1,t),\bar{A}(t+1,K)}(j) \\
&= L_{\bar{A}(t-s),\bar{a}(t-s+1,j-1)}(j) \text{ from the temporal ordering assumption} \\
&= L_{\bar{a}(t-s+1,j-1)}(j) \\
&= L^t_{\bar{a}^t(t-s+1,j-1)}(j) \text{ from (1) and (2)}
\end{aligned}
$$

- if $j = t - s + 1$:

  i.

$$\begin{aligned} L^t_{\bar{a}^t(t-s+1,t)}(j) &= L^t_{\bar{a}(t-s+1,t)}(j) \text{ from (1)} \\ &= \left(\bar{A}(0,t-s), \bar{L}(0,t-s+1)\right)_{\bar{a}(t-s+1,t)} \text{ from (3)} \\ &= \left(\bar{A}(t-s), \bar{L}_{\bar{a}(t-s+1,t)}(t-s+1)\right) \\ &= \left(\bar{A}(t-s), \bar{L}_{A(0),\ldots,A(t-s),\bar{a}(t-s+1,t),A(t+1),\ldots,A(K)}(t-s+1)\right) \end{aligned}$$

  ii.

$$\begin{aligned} L^t(j) &= \left(\bar{A}(0,t-s), \bar{L}(0,t-s+1)\right) \text{ from (3)} \\ &= \left(\bar{A}(0,t-s), \bar{L}_{\bar{A}(K)}(0,t-s+1)\right) \text{ from the consistency assumption} \\ &= \left(\bar{A}(0,t-s), \bar{L}_{\bar{A}(t-s),\bar{A}(t-s+1,t),\bar{A}(t+1,K)}(0,t-s+1)\right) \\ &= \left(\bar{A}(0,t-s), \bar{L}_{\bar{A}(t-s+1,t)}(0,t-s+1)\right) \\ &= \left(\bar{A}(0,t-s), \bar{L}(0,t-s+1)\right)_{\bar{A}(t-s+1,t)} \\ &= L^t_{\bar{A}(t-s+1,t)}(j) \text{ from (3)} \\ &= L^t_{\bar{A}^t(t-s+1,t)}(j) \text{ from (1)} \end{aligned}$$

  iii.

$$\begin{aligned} L^t_{\bar{a}^t(t-s+1,t)}(j) &= \left(\bar{A}(0,t-s), \bar{L}(0,t-s+1)\right)_{\bar{a}(t-s+1,t)} \text{ from (1) and (3)} \\ &= \left(\bar{A}(0,t-s), \bar{L}_{\bar{a}(t-s+1,t)}(0,t-s+1)\right) \\ &= \left(\bar{A}(0,t-s), \bar{L}_{\bar{A}(t-s),\bar{a}(t-s+1,t),\bar{A}(t+1,K)}(0,t-s+1)\right) \\ &= \left(\bar{A}(0,t-s), \bar{L}_{\bar{A}(t-s)}(0,t-s+1)\right) \text{ from the temporal ordering assumption} \\ &= \left(\bar{A}(0,t-s), \bar{L}(0,t-s+1)\right) \\ &= L^t(j) \text{ from (3)} \\ &= L^t_{\bar{a}^t(t-s+1,j-1)}(j) \text{ since } \bar{a}^t(t-s+1,t-s) \text{ is empty by definition} \square \end{aligned}$$

Theorem 5.2 *We adopt the notations introduced previously for the conventional and t-specific counterfactual frameworks. Based on these notations we have:*

i. $\forall\ t \in \{s-1,\ldots,K\} \quad \forall\ j \in \{t-s+2,\ldots,t+1\}$
$f(L^t(j) \mid \bar{L}^t(t-s+1,j-1), \bar{A}^t(t-s+1,j-1)) = f(L(j) \mid \bar{L}(j-1), \bar{A}(j-1))$

ii. $\forall\ t \in \{s-1,\ldots,K\} \quad \forall\ j \in \{t-s+1,\ldots,t\}$
$g(A^t(j) \mid \bar{A}^t(t-s+1,j-1), \bar{L}^t(t-s+1,j)) = g(A(j) \mid \bar{A}(j-1), \bar{L}(j))$

Proof.
For $t \in \{s-1,\ldots,K\}$ we have

i. for $j \in \{t-s+2,\ldots,t+1\}$:

$$
\begin{aligned}
& f\Big(L^t(j) \mid \bar{L}^t(t-s+1,j-1), \bar{A}^t(t-s+1,j-1)\Big) \\
&= f\Big(L^t(j) \mid L^t(t-s+1), \bar{L}^t(t-s+2,j-1), \bar{A}(t-s+1,j-1)\Big) \text{ from (1)} \\
&= f\Big(L(j) \mid L^t(t-s+1), \bar{L}(t-s+2,j-1), \bar{A}(t-s+1,j-1)\Big) \text{ from (2)} \\
&= f\Big(L(j) \mid \bar{A}(t-s), \bar{L}(t-s+1), \bar{L}(t-s+2,j-1), \bar{A}(t-s+1,j-1)\Big) \text{ from (3)} \\
&= f\Big(L(j) \mid \bar{L}(j-1), \bar{A}(j-1)\Big)
\end{aligned}
$$

ii. for $j \in \{t-s+1,\ldots,t\}$:

$$
\begin{aligned}
& g\Big(A^t(j) \mid \bar{A}^t(t-s+1,j-1), \bar{L}^t(t-s+1,j)\Big) \\
&= g\Big(A(j) \mid \bar{A}(t-s+1,j-1), L^t(t-s+1), \bar{L}^t(t-s+2,j)\Big) \text{ from (1)} \\
&= g\Big(A(j) \mid \bar{A}(t-s+1,j-1), L^t(t-s+1), \bar{L}(t-s+2,j)\Big) \text{ from (2)} \\
&= g\Big(A(j) \mid \bar{A}(t-s+1,j-1), \bar{A}(t-s), \bar{L}(t-s+1), \bar{L}(t-s+2,j)\Big) \text{ from (3)} \\
&= g\Big(A(j) \mid \bar{A}(j-1), \bar{L}(j)\Big)
\end{aligned}
$$

6 Discussion

In this manuscript, we introduced HRMSMs as a new class of MSMs to investigate the causal effects of exposure to a treatment over time on time-dependent outcomes. HRMSMs can be viewed as alternative Causal Inference tools to MSMs. We argued based on practical considerations that an HRMSM-based Causal Inference strategy may often be more suitable than an MSM-based Causal Inference strategy for Public Health research. We believe these considerations should motivate the use of this methodology in many

practical applications. We developed an extension of the conventional counterfactual framework that we called the t-specific counterfactual framework. This framework was solely introduced as a statistical artifice to provide the rigorous mathematical framework to develop consistent estimators of HRMSM parameters with minimal effort: the IPTW, G-computation and DR estimators. We have shown that these estimators of HRMSM parameters are consistent under the same model assumptions commonly adopted in the conventional counterfactual framework: existence of counterfactuals, consistency, time-ordering and sequential randomization assumptions. We now discuss the decision making about the history size, s, to consider in practice when applying the proposed HRMSM-based causal analysis.

Decision about the value for the history size, s, should be based on the combination of considerations about the analysis aims and a priori knowledge about the problem studied. This decision however cannot ignore practical considerations like implementation issues and statistical power concerns.

For instance, if the longitudinal study aims at investigating the causal effect of a new medication for headache relief whose action is likely not to carry over time beyond a few hours then it will not make sense to choose a history size that extends well beyond the known lag effect of similar medication. Even when the treatment effect of interest is likely to carry over long periods of time, the subject-matter focus may be the investigation of short-term effects in which case the investigators should consider small values for s. In addition, note that the larger s is, the more complex may the causal effect of interest be. As a result, the statistical power to investigate the causal effect of interest will likely decrease when considering larger history sizes s. Moreover, the larger s is, the more challenging may HRMSM estimation based on the G-computation (and thus DR) estimator be.

Nevertheless, choosing a suitable value for s based on these guidelines remain subjective and may lead to two situations: 1) the chosen history size, s, is larger than the maximum time interval over which the treatment of interest has an effect on the outcome, and 2) the chosen history size, s, is smaller than the maximum time interval over which the treatment of interest has an effect on the outcome. In the first case scenario, the model selection procedure for MSMs proposed by van der Laan and Dudoit (2003) [9] can be used to identify the smaller component of the treatment history that is causally relevant. The second case scenario is most likely to occur in practice since statistical power and implementation considerations will often prevent investigators to study causal effects of treatment histories that are too long. In that case, an HRMSM-based causal analysis will still provide valuable answers to the Public Health questions of interest based on the available data even if the causal effect of the treatment over time will not be completely described (e.g. the maximum lag effect will remain unknown). The HRMSM approach is to be compared to the MSM approach which will consider the effect of longer treatment histories even when the statistical power may not allow identification of significant results.

References

[1] U.S. Environmental Protection Agency. Air quality criteria for particulate matter. Report EPA/600/P-95-001bF, Washington, D.C, 1996.

[2] R.D. Gill, M.J. van der Laan, and J.M. Robins. Coarsening at random: Characterizations, conjectures and counter-examples. In D.Y. Lin and T.R. Fleming, editors, *Proceedings of the First Seattle Symposium in Biostatistics, 1995*, Lecture Notes in Statistics, pages 255–294, New York, 1997. Springer.

[3] P.G. Goodman, D.W. Dockery, and L. Clancy. Cause-specific mortality and the extended effects of particulate pollution and temperature exposure. *Environ Health Perspect*, 112(2):179–185, 2004.

[4] R. Neugebauer and M.J. van der Laan. Locally efficient estimation of nonparametric causal effects on mean outcomes in longitudinal studies. Working paper 134, U.C. Berkeley Division of Biostatistics Working Paper Series, 2003. [www http://www.bepress.com/ucbbiostat/paper134/].

[5] R. Neugebauer and M.J. van der Laan. Why prefer double robust estimators in causal inference? *Journal of Statistical Planning and Inference*, 129:405–426, February 2005. [www http://www.sciencedirect.com/science/article/B6V0M-4D5X61S-1/2/b7d0d4635a72e22ee511cce500b33901].

[6] J.M. Robins, M.A. Hernàn, and B. Brumback. Marginal structural models and causal inference in epidemiology. *Epidemiology*, 11(5):550–560, 2000.

[7] D.B. Rubin. Inference and missing data. *Biometrika*, pages 581–590, 1976.

[8] I.B. Tager, T. Haight, B. Sternfeld, Z. Yu, and M. van der Laan. Effects of physical activity and body composition on functional limitation in the elderly: application of the marginal structural model. *Epidemiology*, 15(4):479–493, 2004.

[9] M.J. van der Laan and S. Dudoit. Unified cross-validation methodology for selection among estimators: finite sample results, asymptotic optimality, and applications. Working paper 130, U.C. Berkeley Division of Biostatistics Working Paper Series, 2003. [www http://www.bepress.com/ucbbiostat/paper130/].

[10] M.J. van der Laan and J.M. Robins. *Unified Methods for Censored Longitudinal Data and Causality*. Springer, New York, 2002.

[11] Z. Yu and M.J. van der Laan. Double robust estimation in longitudinal marginal structural models. Working paper 132, U.C. Berkeley Division of Biostatistics Working Paper Series, 2002. [www http://www.bepress.com/ucbbiostat/paper132/].