The Annals of Applied Statistics
2021, Vol. 15, No. 2, 747–767
https://doi.org/10.1214/20-AOAS1427

CAUSAL MEDIATION ANALYSIS FOR SPARSE AND IRREGULAR LONGITUDINAL DATA

BY SHUXI ZENG[1,*], STACY ROSENBAUM[2,4], SUSAN C. ALBERTS[3], ELIZABETH A. ARCHIE[4] AND FAN LI[1,†]

[1]*Department of Statistical Science, Duke University,* [*]*zengshx777@gmail.com;* [†]*fl35@duke.edu*
[2]*Department of Anthropology, University of Michigan, rosenbas@umich.edu*
[3]*Departments of Biology and Evolutionary Anthropology, Duke University, alberts@duke.edu*
[4]*Department of Biological Sciences, University of Notre Dame, earchie@nd.edu*

Causal mediation analysis seeks to investigate how the treatment effect of an exposure on outcomes is mediated through intermediate variables. Although many applications involve longitudinal data, the existing methods are not directly applicable to settings where the mediator and outcome are measured on sparse and irregular time grids. We extend the existing causal mediation framework from a functional data analysis perspective, viewing the sparse and irregular longitudinal data as realizations of underlying smooth stochastic processes. We define causal estimands of direct and indirect effects accordingly and provide corresponding identification assumptions. For estimation and inference, we employ a functional principal component analysis approach for dimension reduction and use the first few functional principal components instead of the whole trajectories in the structural equation models. We adopt the Bayesian paradigm to accurately quantify the uncertainties. The operating characteristics of the proposed methods are examined via simulations. We apply the proposed methods to a longitudinal data set from a wild baboon population in Kenya to investigate the causal relationships between early adversity, strength of social bonds between animals and adult glucocorticoid hormone concentrations. We find that early adversity has a significant direct effect (a 9–14% increase) on females' glucocorticoid concentrations across adulthood but find little evidence that these effects were mediated by weak social bonds.

1. Introduction. Mediation analysis seeks to understand the role of an intermediate variable (i.e., mediator) M that lies on the causal path between an exposure or treatment Z and an outcome Y. The most widely used mediation analysis method, proposed by Baron and Kenny (1986), fits two linear structural equation models (SEMs) between the three variables and interprets the model coefficients as causal effects. There is a vast literature on the Baron–Kenny framework across a variety of disciplines, including psychology, sociology and epidemiology (see MacKinnon (2012)). A major advancement in recent years is the incorporation of the potential-outcome-based causal inference approach (Neyman (1923), Rubin (1974)). This led to a formal definition of relevant causal estimands, clarification of identification assumptions and new estimation strategies beyond linear SEMs (Daniels et al. (2012), Pearl (2001), Robins and Greenland (1992), Sobel (2008), Tchetgen Tchetgen and Shpitser (2012), VanderWeele (2016)). In particular, Imai, Keele and Yamamoto (2010) proved that the Baron–Kenny estimator can be interpreted as a special case of a causal mediation estimator given additional assumptions. These methodological advancements opened up new application areas, including imaging, neuroscience and environmental health (Lindquist (2012),

Received September 2020; revised December 2020.
Key words and phrases. Causal inference, functional principal component analysis, mediation, longitudinal data, sparse and irregular data.

Lindquist and Sobel (2011), Zigler, Dominici and Wang (2012), Kim et al. (2019)). Comprehensive reviews on causal mediation analysis are given in Nguyen, Schmid and Stuart (2020), VanderWeele (2015).

In the traditional settings of mediation analysis, exposure Z, mediation M and outcome Y are all univariate variables at a single time point. Recent work has extended to time-varying cases, where at least one of the triplet (Z, M, Y) is longitudinal. This line of research has primarily focused on cases with time-varying mediators or outcomes that are observed on sparse and regular time grids (Lin et al. (2017a), Roth and MacKinnon (2012), van der Laan and Petersen (2008)). For example, VanderWeele and Tchetgen Tchetgen (2017) developed a method for identifying and estimating causal mediation effects with time-varying exposures and mediators based on marginal structural models (Robins, Hernan and Brumback (2000)). Some researchers also investigated the case with time-varying exposure and mediator for the survival outcome (Lin et al. (2017b), Zheng and van der Laan (2017)). Another stream of research, motivated by applications in neuroimaging, focuses on cases where mediators or outcomes are densely recorded continuous functions, for example, the blood-oxygen-level-dependent (BOLD) signal collected in a functional magnetic resonance imaging (fMRI) session. In particular, Lindquist (2012) introduced the concept of *functional mediation* in the presence of a functional mediator and extended causal SEMs to functional data analysis (Ramsay and Silverman (2005)). Zhao et al. (2018) further extended this approach to functional exposure, mediator and outcome.

Sparse and irregularly-spaced longitudinal data are increasingly available for causal studies. For example, in electronic health records (EHR) data, the number of observations usually varies between patients and the time grids are uneven. The same situation applies in animal behavior studies due to the inherent difficulties in observing wild animals. Such data structure poses challenges to existing causal mediation methods. First, one cannot simply treat the trajectories of mediators and outcomes as functions, as in Lindquist (2012), because the sparse observations render the trajectories volatile and nonsmooth. Second, with irregular time grids the dependence between consecutive observations changes over time, making the methods based on sparse and regular longitudinal data such as VanderWeele and Tchetgen Tchetgen (2017) not applicable. A further complication arises when the mediator and outcome are measured with different frequencies even within the same individual.

In this paper we propose a causal mediation analysis method for sparse and irregular longitudinal data that address the aforementioned challenges. Similar to Lindquist (2012) and Zhao et al. (2018), we adopt a functional data analysis perspective (Ramsay and Silverman (2005)), viewing the sparse and irregular longitudinal data as realizations of underlying smooth stochastic processes. We define causal estimands of direct and indirect effects accordingly and provide assumptions for nonparametric identification (Section 3). For estimation and inference, we proceed under the classical two-SEM mediation framework (Imai, Keele and Yamamoto (2010)) but diverge from the existing methods in modeling (Section 4). Specifically, we employ the functional principal component analysis (FPCA) approach (Yao, Müller and Wang (2005), Jiang and Wang (2010, 2011), Han et al. (2018)) to project the mediator and outcome trajectories to a low-dimensional representation. We then use the first few functional principal components (instead of the whole trajectories) as predictors in the structural equation models. To accurately quantify the uncertainties, we employ a Bayesian FPCA model (Kowal and Bourgeois (2020)) to simultaneously estimate the functional principal components and the structural equation models. Though the Bayesian approach to mediation analysis has been discussed before (Daniels et al. (2012), Kim et al. (2017), Kim et al. (2018)), it has not been developed for the setting of sparse and irregular longitudinal data.

Our motivating application is the evaluation of the causal relationships between early adversity, social bonds and physiological stress in wild baboons (Section 2). Here, the exposure

is early adversity (e.g., drought, maternal death before reaching maturity), the mediators are the strength of adult social bonds and the outcomes are adult glucocorticoid (GC) hormone concentrations, which is a measure of an animal's physiological stress level. The exposure, early adversity, is a binary variable measured at one time point, whereas both the mediators and outcomes are sparse and irregular longitudinal variables. We apply the proposed method to a prospective and longitudinal observational data set from the Amboseli Baboon Research Project located in the Amboseli ecosystem, Kenya (Alberts and Altmann (2012)) (Section 5). We find that experiencing one or more sources of early adversity leads to significant direct effects (a 9–14% increase) on females" GC concentrations across adulthood but find little evidence that these effects were mediated by weak social bonds. Though motivated from a specific application, the proposed method is readily applicable to other causal mediation studies with similar data structure, including EHR and ecology studies. Furthermore, our method is also applicable to regularly spaced longitudinal observations.

2. Motivating application: Early adversity, social bond and stress.

2.1. *Biological background.* Conditions in early life can have profound consequences for individual development, behavior and physiology across the life course (Bateson et al. (2004), Gluckman et al. (2008), Lindström (1999)). These early life effects are important, in part, because they have major implications for human health. One leading explanation for how early life environments affect adult health is provided by the biological embedding hypothesis, which posits that early life stress causes developmental changes that create a "proinflammatory" phenotype and elevated risk for several diseases of aging (Miller, Chen and Parker (2011)). The biological embedding hypothesis proposes at least two, nonexclusive causal pathways that connect early adversity to poor health in adulthood. In the first pathway, early adversity leads to altered hormonal profiles that contribute to downstream inflammation and disease. Under this scenario, stress in early life leads to dysregulation of hormonal signals in the body"s main stress response system, leading to the release of GC hormone, which engages the body"s fight-or-flight response. Chronic activation is associated with inflammation and elevated disease risk (McEwen (1998, 2008), Miller, Cohen and Ritchey (2002)). In the second causal pathway, early adversity hampers an individual's ability to form strong interpersonal relationships. Under this scenario the social isolation contributes to both altered GC profiles and inflammation.

Hence, the biological embedding hypothesis posits that early life adversity affects both GC profiles and social relationships in adulthood and that poor social relationships partly mediate the connection between early adversity and GCs. Importantly, the second causal pathway, mediated through adult social relationships, suggests an opportunity to transmit the negative health effect of early adversity. Specifically, strong and supportive social relationships may dampen the stress response or reduce individual exposure to stressful events, which in turn reduces GCs and inflammation. For example, strong and supportive social relationships have repeatedly been linked to reduced morbidity and mortality in humans and other social animals (Holt-Lunstad, Smith and Layton (2010), Silk (2007)). In addition to the biological embedding hypothesis, this idea of social mediation is central to several hypotheses that propose causal connections between adult social relationships and adult health, even independent of early life adversity; these hypotheses include the stress buffering and stress prevention hypotheses (Cohen and Wills (1985), Landerman et al. (1989), Thorsteinsson and James (1999)) and the social causation hypothesis (Anderson and Marmot (2011), Marmot et al. (1991)).

Despite the aforementioned research, the causal relationships among early adversity, adult social relationships and HPA (hypothalamic–pituitary–adrenal) axis dysregulation remain the subject of considerable debate. While social relationships might exert direct effects on stress

and health, it is also possible that poor health and high stress limit an individual's ability to form strong and supportive relationships. As such, the causal arrow flows backward, from stress to social relationships (Case and Paxson (2011)). In another causal scenario, early adversity exerts independent effects on social relationships and the HPA axis, and correlations between social relationships and GCs are spurious, arising solely as a result of their independent links to early adversity (Marmot et al. (1991)).

2.2. *The data*. In this paper we test whether the links between early adversity, the strength of adult social bonds and GCs are consistent with predictions derived from the biological embedding hypothesis and other related theories. Specifically, we use data from a well-studied population of savannah baboons in the Amboseli ecosystem in Kenya. Founded in 1971, the Amboseli Baboon Research Project has prospective longitudinal data on early life experiences and fine-grained longitudinal data on adult social bonds and GC hormone concentrations, a measure of the physiological stress response (Alberts and Altmann (2012)).

Our study sample includes 192 female baboons. Each baboon entered the study after becoming mature at age 5, and we had information on its experience of six sources of early adversity (i.e., exposure) (Tung et al. (2016), Zipple et al. (2019)): drought, maternal death, competing sibling, high group density, low maternal rank and maternal social isolation. Table 1 presents the number of baboons that experienced each early adversity. Overall, while only a small proportion of subjects experienced any given source of early adversity, most subjects experienced at least one source of early adversity. Therefore, in our analysis we also create a cumulative exposure variable that summarizes whether a baboon experienced any source of the adversity.

Each baboon's adult social bonds (i.e., mediators) and fecal GC hormone concentrations (i.e., outcomes) are measured repeatedly throughout its life on the same grid. Social bonds are measured using the dyadic sociality index with females (DSI-F) (Silk, Altmann and Alberts (2006)). The indices are calculated for each female baboon separately based on all visible observations for social interactions between the baboon and other members in the entire social group within a given period. Larger values mean stronger social bonds. We normalized the DSI-F measurements, and the normalized DSI-F values range from -1.47 to 3.31 with mean value at 1.04 and standard deviation 0.51. The fecal GC concentrations were collected opportunistically, and the values range from 7.51 to 982.87 with mean 74.13 and standard deviation 38.25. Age is used to index within-individual observations on both social bond and GC concentrations. Only about 20% baboons survive until age 18, and, thus, data on females older than 18 years are extremely sparse and volatile. Therefore, we truncated all trajectories at age 18, resulting in a final sample with 192 female baboons and 9878 observations.

TABLE 1

Sources of early adversity and the number of baboons experienced each type of early adversity. The last row summarizes the number of baboons had at least one of six individual adversity sources

Early adversity	No. subjects did not experience (control)	No. subjects did experience (exposure)
Drought	164	28
Competing sibling	153	39
High group density	161	31
Maternal death	157	35
Low maternal rank	152	40
Maternal social isolation	140	52
At least one	48	144

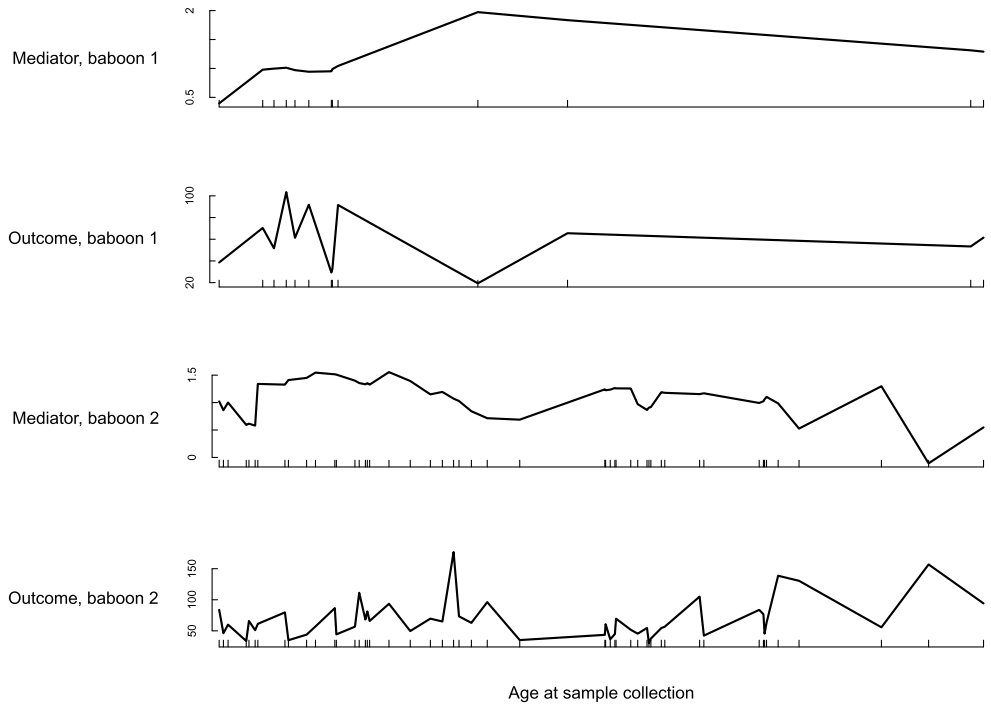


FIG. 1. *Observed trajectories of social bonds and GC hormone as a function of age of two randomly selected female baboons in the study sample.*

For wild animals the observations usually made on irregular or opportunistic basis. We have on average 51.4 observations of each baboon for both social bonds and GC concentrations, but the number of observations of a single baboon ranges from three to 113. Figure 1 shows the mediator and outcome trajectories as a function of age of two randomly selected baboons in the sample. We can see that the frequency of the observations and time grids of the mediator or outcome trajectories vary significantly between baboons.

We also have a set of static and time-varying covariates that are deemed important to wild baboons' physiology and behavior. These include reproductive state (i.e., cycling, pregnant or lactating), density of the social group, max temperature in the last 30 days before the fecal sample was collected, whether the sample is collected in wet or dry season, the amount of rainfall, relative dominance rank of a baboon and number of coresident adult maternal relatives. More information on the covariates' exposure, mediator and outcomes can be found in Rosenbaum et al. (2020).

3. Causal mediation framework.

3.1. *Setup and causal estimands.* Suppose we have a sample of N units (in the use case described here, baboons); each unit i ($i = 1, 2, \ldots, N$) is assigned to a treatment ($Z_i = 1$) or a control ($Z_i = 0$) group. For each unit i, we make observations at T_i different time points $\{t_{ij} \in [0, T], j = 1, 2, \ldots, T_i\}$, and T_i can vary between units. At each time point t_{ij}, we measure an outcome Y_{ij} and a mediator M_{ij} prior to the outcome and a vector of p time-varying covariates $\mathbf{X}_{ij} = (X_{ij,1}, \ldots, X_{ij,p})'$. For each unit the observations points are sparse along the time span and irregularly spaced. For simplicity, we assume the observed time grids for the outcome and the mediator are the same within one unit. However, our method is directly applicable when the observation grids for the outcome and the mediator are different for a given individual.

A key to our method is to view the observed mediator and outcome values drawn from a smooth underlying process $M_i(t)$ and $Y_i(t)$, $t \in [0, T]$ with Normal measurement errors, respectively,

$$M_{ij} = M_i(t_{ij}) + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma_m^2), \tag{3.1}$$

$$Y_{ij} = Y_i(t_{ij}) + \nu_{ij}, \quad \nu_{ij} \sim \mathcal{N}(0, \sigma_y^2). \tag{3.2}$$

Hence, instead of directly exploring the relationship between the treatment Z_i, mediators M_{ij} and outcomes Y_{ij}, we investigate the relationship between Z_i and the stochastic processes $M_i(t_{ij})$ and $Y_i(t_{ij})$. In particular, we wish to answer two questions: (a) how big is the causal impact of the treatment on the outcome process, and (b) how much of that impact is mediated through the mediator process?

To be consistent with the standard notation of potential outcomes in causal inference (Imbens and Rubin (2015)), from now on we move the time index of the mediator and outcome process to the superscript: $M_i(t) = M_i^t$, $Y_i(t) = Y_i^t$. Also, we use the following bold font notation to represent a process until time t: $\mathbf{M}_i^t \equiv \{M_i^s, s \le t\} \in \mathcal{R}^{[0,t]}$, and $\mathbf{Y}_i^t \equiv \{Y_i^s, s \le t\} \in \mathcal{R}^{[0,t]}$. Similarly, we denote covariates between the jth and $j+1$th time point for unit i as $\mathbf{X}_i^t = \{X_{i1}, X_{i2}, \ldots, X_{ij'}\}$ for $t_{ij'} \le t < t_{ij'+1}$.

We extend the definition of potential outcomes to define the causal estimands. Specifically, let $\mathbf{M}_i^t(z) \in \mathcal{R}^{[0,t]}$ for $z = 0, 1, t \in [0, T]$; denote the potential values of the underlying mediator process for unit i until time t under the treatment status z; let $\mathbf{Y}_i^t(z, \mathbf{m}) \in \mathcal{R}^{[0,t]}$ be the potential outcome for unit i until time t under the treatment status z and the mediator process taking value of $\mathbf{M}_i^t = \mathbf{m}$ with $\mathbf{m} \in \mathcal{R}^{[0,t]}$. The above notation implicitly makes the stable unit treatment value assumption (SUTVA) (Rubin (1980)), which states that: (i) there is no different version of the treatment and (ii) there is no interference between the units, more specifically, the potential outcomes of one unit do not depend on the treatment and mediator values of other units. SUTVA is plausible in our application. First, there is unlikely different versions of the early adversities. Second, though baboons live in social groups, it is unlikely a baboon's long-term GC concentration (outcome) was much affected by the early adversities experienced by other cohabitant baboons in its social group, particularly considering the fact that only a small proportion of baboons experienced any given early adversity. Moreover, the social bond index (mediator) summarizes the interaction between a focal baboon and other members in a social group, and, thus, we can view the impact from other baboons as constant while examining the variation of social bond for the focal baboon. The notation of $\mathbf{Y}_i^t(z, \mathbf{m})$ makes another implicit assumption that the potential outcomes are determined by the mediator values $\mathbf{m}$ before time t but not after t. For each unit we can only observe one realization from the potential mediator or outcome process,

$$\mathbf{M}_i^t = \mathbf{M}_i^t(Z_i) = Z_i \mathbf{M}_i^t(1) + (1 - Z_i)\mathbf{M}_i^t(0), \tag{3.3}$$

$$\mathbf{Y}_i^t = \mathbf{Y}_i^t\big(Z_i, \mathbf{M}_i^t(Z_i)\big) = Z_i \mathbf{Y}_i^t\big(1, \mathbf{M}_i^t(1)\big) + (1 - Z_i)\mathbf{Y}_i^t\big(0, \mathbf{M}_i^t(0)\big). \tag{3.4}$$

We define the total effect (TE) of the treatment Z_i on the outcome process at time t as

$$\tau_{\mathrm{TE}}^t = E\big\{Y_i^t\big(1, \mathbf{M}_i^t(1)\big) - Y_i^t\big(0, \mathbf{M}_i^t(0)\big)\big\}. \tag{3.5}$$

When there is a mediator, the TE can be decomposed into direct and indirect effects. Below, we extend the framework of Imai, Keele and Yamamoto (2010) to formally define these effects. First, we define the average causal mediation (or indirect) effect (ACME) under treatment z at time t by fixing the treatment status while altering the mediator process,

$$\tau_{\mathrm{ACME}}^t(z) \equiv E\big\{Y_i^t\big(z, \mathbf{M}_i^t(1)\big) - Y_i^t\big(z, \mathbf{M}_i^t(0)\big)\big\}, \quad z = 0, 1. \tag{3.6}$$

The ACME quantifies the difference between the potential outcomes, given a fixed treatment status z, corresponding to the potential mediator process under treatment $\mathbf{M}_i^t(1)$ and that under control $\mathbf{M}_i^t(0)$. In the previous literature, variants of the ACME are also called the *natural indirect effect* (Pearl (2001)) or the *pure indirect effect* for $\tau_{\text{ACME}}^t(0)$ and *total indirect effect* for $\tau_{\text{ACME}}^t(1)$ (Robins and Greenland (1992))

Second, we define the average natural direct effect (ANDE) (Imai, Keele and Yamamoto (2010), Pearl (2001)) of treatment on the outcome at time t by fixing the mediator process while altering the treatment status,

$$\tau_{\text{ANDE}}^t(z) \equiv E\{Y_i^t(1, \mathbf{M}_i^t(z)) - Y_i^t(0, \mathbf{M}_i^t(z))\}. \tag{3.7}$$

The ANDE quantifies the portion in the TE that does not pass through the mediators.

It is easy to verify that the TE is the sum of ACME and ANDE,

$$\tau_{\text{TE}}^t = \tau_{\text{ACME}}^t(z) + \tau_{\text{ANDE}}^t(1-z), \quad z = 0, 1. \tag{3.8}$$

This implies we only need to identify two of the three quantities τ_{TE}, $\tau_{\text{ACME}}^t(z)$, $\tau_{\text{ANDE}}^t(z)$. In this paper we will focus on the estimation of τ_{TE} and $\tau_{\text{ACME}}^t(z)$. Because we only observe a portion of all the potential outcomes, we cannot directly identify these estimands from the observed data, which would require additional assumptions.

3.2. *Identification assumptions*. In this subsection we list the causal assumptions necessary for identifying the ACME and ANDEs with sparse and irregular longitudinal data. There are several sets of identification assumptions in the literature (Imai, Keele and Tingley (2010), Pearl (2001), Robins and Greenland (1992), Shpitser and VanderWeele (2011), Forastiere, Mattei and Ding (2018)) with subtle distinction (Ten Have and Joffe (2012)). Here we follow the similar set of assumptions in Imai, Keele and Yamamoto (2010).

The first assumption extends the standard ignorability assumption and rules out the unmeasured treatment-outcome confounding.

ASSUMPTION 1 (Ignorability). Conditional on the observed covariates, the treatment is unconfounded with respect to the potential mediator process and the potential outcomes process,

$$\{\mathbf{Y}_i^t(1, \mathbf{m}), \mathbf{Y}_i^t(0, \mathbf{m}), \mathbf{M}_i^t(1), \mathbf{M}_i^t(0)\} \perp\!\!\!\perp Z_i \mid \mathbf{X}_i^t,$$

for any t and $\mathbf{m} \in \mathcal{R}^{[0,t]}$.

In our context, Assumption 1 indicates that there is no unmeasured confounding, besides the observed covariates, between the sources of early adversity and the processes of social bonds and GCs. In other words, early adversity is randomized among the baboons with the same covariates. This assumption is plausible given the early adversity events considered in this study are largely imposed by nature.

The second assumption extending the sequential ignorability assumption in Imai, Keele and Yamamoto (2010) to the functional data setting.

ASSUMPTION 2 (Sequential ignorability). There exists $\varepsilon > 0$ such that, for any $0 < \Delta < \varepsilon$, the increment of the mediator process is independent of the increment of potential outcomes process from time t to $t + \Delta$, conditional on the observed treatment status, covariates and the mediator process up to time t,

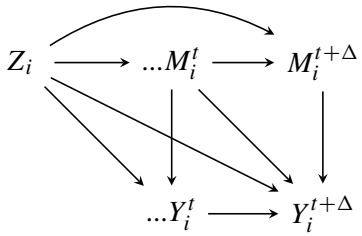
$$\{Y_i^{t+\Delta}(z, \mathbf{m}) - Y_i^t(z, \mathbf{m})\} \perp\!\!\!\perp \{M_i^{t+\Delta}(z') - M_i^t(z')\} \mid \{Z_i, \mathbf{X}_i^t, \mathbf{M}_i^t\},$$

for any $z, z', 0 < \Delta < \varepsilon, t, t + \Delta \in [0, T]$, $\mathbf{m} \in \mathcal{R}^{[0,T]}$.

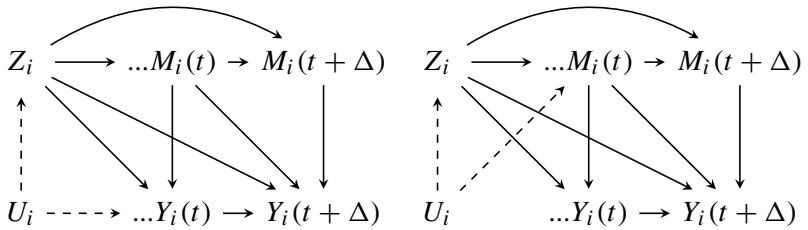
In our application, Assumption 2 implies that conditioning on the early adversity status, covariates and the potential social bond history up to a given time point, any change in the social bond values within a sufficiently small time interval Δ is randomized with respect to the change in the potential outcomes. Namely, there are no unobserved mediator-outcomes confounders in a sufficiently small time interval. Though it differs in the specific form, Assumption 2 is in essence the same sequential ignorability assumption used for the regularly spaced observations in Bind et al. (2016) and VanderWeele and Tchetgen Tchetgen (2017). This is a crucial assumption in mediation analysis but is strong and generally untestable in practice because it is usually impossible to manipulate the mediator values, even in randomized trials.

Assumptions 1 and 2 are illustrated by the directed acyclic graphs (DAG) in Figure 2(a) which condition on the covariates $\mathbf{X}_i^t$ and a window between two sufficiently close time points t and $t + \Delta$. The arrows between Z_i, M_i^t, Y_i^t represent a causal relationship (i.e., nonparametric structural equation model), with solid and dashed lines representing measured and unmeasured relationships, respectively. Figures 2(b) and 2(c) depict two possible scenarios where Assumptions 1 and 2 are violated, respectively, where U_i represents an unmeasured confounder.

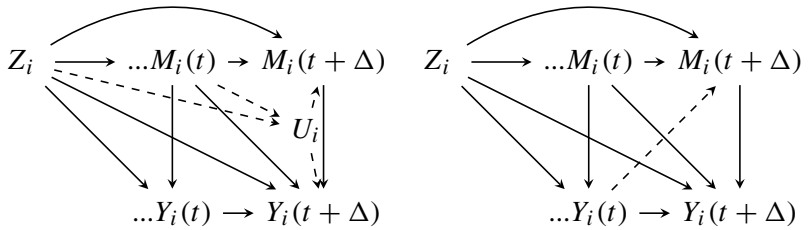
Assumptions 1 and 2 allow nonparametric identification of the TE and ACME from the observed data, as summarized in the following theorem.



(a) DAG of Assumption 1 and 2.



(b) DAG of two examples of violation to Assumption 1 (ignorability).



(c) DAG of two examples of violation to Assumption 2 (sequential ignorability).

FIG. 2. *Directed acyclic graphs (DAG) of Assumptions 1, 2 and examples of possible violations. The arrows between variables represent a causal relationship, with solid and dashed lines representing measured and unmeasured relationships, respectively.*

THEOREM 1. *Under Assumption 1, 2 and some regularity conditions* (*specified in the Supplementary Material* (*Zeng et al.* (2021))), *the TE, ACME and ANDE can be identified nonparametrically from the observed data*: *for* $z = 0, 1$, *we have*

$$\tau^t_{\mathrm{TE}} = \int_X \{E(Y_i^t | Z_i = 1, \mathbf{X}_i^t = \mathbf{x}^t) - E(Y_i^t | Z_i = 0, \mathbf{X}_i^t = \mathbf{x}^t)\} \, \mathrm{dF}_{\mathbf{X}_i^t}(\mathbf{x}^t),$$

$$\tau^t_{\mathrm{ACME}}(z) = \int_{\mathcal{X}} \int_{R^{[0,t]}} E(Y_i^t | Z_i = z, \mathbf{X}_i^t = \mathbf{x}^t, \mathbf{M}_i^t = \mathbf{m}) \, \mathrm{dF}_{\mathbf{X}_i^t}(\mathbf{x}^t) \times \mathrm{d}\{\mathrm{F}_{\mathbf{M}_i^t | Z_i = 1, \mathbf{X}_i^t = \mathbf{x}^t}(\mathbf{m}) - \mathrm{F}_{\mathbf{M}_i^t | Z_i = 0, \mathbf{X}_i^t = \mathbf{x}^t}(\mathbf{m})\},$$

where $F_W(\cdot)$ *and* $F_{W|V}(\cdot)$ *denote the cumulative distribution of a random variable or a vector* W *and the conditional distribution given another random variable or vector* V, *respectively.*

The proof of Theorem 1 is provided in the Supplementary Material (Zeng et al. (2021)). Theorem 1 implies that estimating the causal effects requires modeling two components: (a) the conditional expectation of observed outcome process, given the treatment, covariates, and the observed mediator process, $E(Y_i^t | Z_i, \mathbf{X}_i^t, \mathbf{M}_i^t)$, and (b) the distribution of the observed mediator process, given the treatment and the covariates, $\mathrm{F}_{\mathbf{M}_i^t | Z_i, \mathbf{X}_i^t}(\cdot)$. These two components correspond to the two linear structural equations in the classic mediation framework of Baron and Kenny (1986). In the setting of functional data, we can employ more flexible models, instead of linear regression models, and express the TE and ACME as functions of the model parameters. Theorem 1 can be readily extended to more general scenarios such as discrete (i.e., as opposed to continuous) mediators and time-to-event outcomes.

4. Modeling mediator and outcome via functional principal component analysis. In this section we propose to employ the functional principal component analysis (FPCA) approach to infer the mediator and outcome processes from sparse and irregular observations (Yao, Müller and Wang (2005), Jiang and Wang (2010, 2011)). In order to take into account the uncertainty due to estimating the functional principal components (Goldsmith, Greven and Crainiceanu (2013)), we adopt a Bayesian model to jointly estimate the principal components and the structural equation models. Specifically, we impose a Bayesian FPCA model similar to that in Kowal and Bourgeois (2020) to project the observed mediator and outcome processes into lower-dimensional representations and, then, take the first few dominant principal components as the predictors in the structural equation models.

We assume the potential processes for mediators $\mathbf{M}_i^t(z)$ and outcomes $\mathbf{Y}_i^t(z, \mathbf{m})$ have the following Karhunen–Loeve decomposition:

$$M_i^t(z) = \mu_M(\mathbf{X}_i^t) + \sum_{r=1}^{\infty} \zeta_{i,z}^r \psi_r(t), \tag{4.1}$$

$$Y_i^t(z, \mathbf{m}) = \mu_Y(\mathbf{X}_i^t) + \int_0^t \gamma(s, t)\mathbf{m}(s) \, ds + \sum_{s=1}^{\infty} \theta_{i,z}^s \eta_s(t), \tag{4.2}$$

where $\mu_M(\cdot)$ and $\mu_Y(\cdot)$ are the mean functions of the mediator process $\mathbf{M}_i^t$ and outcome process $\mathbf{Y}_i^t$, respectively; $\boldsymbol{\psi}_r(t)$ and $\boldsymbol{\eta}_s(t)$ are the Normal orthogonal eigenfunctions for $\mathbf{M}_i^t$ and $\mathbf{Y}_i^t$, respectively, and $\zeta_{i,z}^r$ and $\theta_{i,z}^s$ are the corresponding principal scores of unit i. The above model assumes that the treatment affects the mediation and the outcome processes only through the principal scores. We represent the mediator and outcome process of each unit with its principal score $\zeta_{i,z}^r$ and $\theta_{i,z}^s$. Given the principal scores, we can transform back to the smooth process with a linear combination. As such, if we are interested in the differences in the process, it is equivalent to investigate the difference in the principal scores. Also, as we

usually require only three or four components to explain most of the variation, we reduce the dimensions of the trajectories effectively by projecting the difference to the principal scores. With the model specification in (4.2), we make an implicit assumption that the ACME and ANDE are the same in the treatment and control groups in our application, $\tau^t_{\text{ACME}}(0) = \tau^t_{\text{ACME}}(1)$, $\tau^t_{\text{ANDE}}(0) = \tau^t_{\text{ANDE}}(1)$, and, thus, there are no interactions between the treatment and the mediator. This assumption leads to a unique decomposition of the TE for simple interpretations (VanderWeele (2014)).

The underlying processes $\mathbf{M}^t_i$ and $\mathbf{Y}^t_i$ are not directly observed. Instead, we assume the observations M_{ij}'s and Y_{ij}'s are randomly sampled from the respective underlying processes with errors. For the observed mediator trajectories, we posit the following model that truncates to the first R principal components of the mediator process:

$$M_{ij} = X'_{ij}\beta_M + \sum_{r=1}^{R} \zeta_i^r \psi_r(t_{ij}) + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma_m^2), \tag{4.3}$$

where $\psi_r(t)$ $(r = 1, \ldots, R)$ are the orthogonormal principal components, ζ_i^r $(r = 1, \ldots, R)$ are the corresponding principal scores and ε_{ij} is the measurement error. With similar parametrization that used in Kowal and Bourgeois (2020), we express the principal components as a linear combination of the spline basis $\mathbf{b}(t) = (1, t, b_1(t), \ldots, b_L(t))'$ in $L + 2$ dimensions and choose the coefficients $\mathbf{p}_r \in \mathcal{R}^{L+2}$ to meet the normal orthogonality constraints of the rth principal component,

$$\psi_r(t) = \mathbf{b}(t)'\mathbf{p}_r, \quad \text{subject to } \int_0^T \psi_r^2(t)\,dt = 1, \int_0^T \psi_{r'}(t)\psi_{r''}(t)\,dt = 0, r' \neq r''. \tag{4.4}$$

We assume the principal scores ζ_i^r are randomly drawn from normal distributions with different means in the treatment and control groups, χ_1^r and χ_0^r, and diminishing variance as r increases,

$$\zeta_i^r \sim \mathcal{N}(\chi^r_{Z_i}, \lambda_r^2), \quad \lambda_1^2 \geq \lambda_2^2 \geq \cdots \lambda_R^2 \geq 0. \tag{4.5}$$

We select the truncation term R based on the fraction of explained variance (FEV), $\sum_{r=1}^{R} \lambda_r^2 / \sum_{r=1}^{\infty} \lambda_r^2$ being greater than 90%.

For the observed outcome trajectories, we posit a similar model that truncates to the first S principal components of the outcome process,

$$Y_{ij} = X_{ij}^T\beta_Y + \int_0^{t_{ij}} \gamma(u,t)M_i^u\,\mathrm{d}u + \sum_{s=1}^{S} \eta_s(t)\theta_i^s + \nu_{ij}, \quad \nu_{ij} \sim N(0, \sigma_y^2). \tag{4.6}$$

We express the principal components η_s as a linear combination of the spline basis $\mathbf{b}(t)$, with the normal orthogonality constraints,

$$\eta_s(t) = \mathbf{b}(t)'\mathbf{q}_s, \quad \text{subject to } \int_0^T \eta_s(t)^2\,dt = 1, \int_0^T \eta_{s'}(t)\eta_{s''}(t)\,dt = 0, s' \neq s''. \tag{4.7}$$

Similarly, we assume that the principal scores of the outcome process for each unit come from two different normal distributions in the treatment and control group with means ξ_1^s and ξ_0^s, respectively, and a shrinking variance ρ_s^2,

$$\theta_i^s \sim \mathcal{N}(\xi^s_{Z_i}, \rho_s^2), \quad \rho_1^2 \geq \rho_2^2 \geq \cdots \rho_S^2 \geq 0. \tag{4.8}$$

We select the truncation term S, based on the FEV being greater than 90%, namely, $\sum_{s=1}^{S} \rho_s^2 / \sum_{s=1}^{\infty} \rho_s^2 \geq 90\%$.

We assume the effect of the mediation process on the outcome is concurrent, namely, the outcome process at time t does not depend on the past value of the mediation process. As such, $\gamma(u,t)$ can be shrunk to γ, instead of the integral in Model (4.6),

$$Y_{ij} = X_{ij}^T \beta_Y + \gamma M_{ij} + \sum_{s=1}^{S} \eta_s(t)\theta_i^s + \nu_{ij}, \quad \nu_{ij} \sim N(0, \sigma_y^2). \tag{4.9}$$

The causal estimands, the TE and ACME can be expressed as functions of the parameters in the above mediator and outcome models,

$$\tau_{\mathrm{TE}}^t = \sum_{s=1}^{S} (\xi_1^s - \xi_0^s)\eta_s(t) + \gamma \sum_{r=1}^{R} (\chi_1^r - \chi_0^r)\psi_r(t), \tag{4.10}$$

$$\tau_{\mathrm{ACME}}^t = \sum_{r=1}^{R} \gamma(\chi_1^r - \chi_0^r)\psi_r(t). \tag{4.11}$$

To account for the uncertainty in estimating the above models, we adopt the Bayesian paradigm and impose prior distributions for the parameters (Kowal and Bourgeois (2020)). For the basis function $\mathbf{b}(t)$ to construct principal components, we choose the thin-plate spline, which takes the form $\mathbf{b}(t) = (1, t, (|t-k_1|)^3, \ldots, |t-k_L|^3)' \in \mathcal{R}^{L+2}$, where the k_l $(l = 1, 2, \ldots, L)$ are the predefined knots on the time span. We set the values of knots k_l with the quantiles of observation time grids. For the parameters of the principal components, taking the mediator model as an example, we impose the following priors on the parameters in (4.4):

$$\mathbf{p}_r \sim N(0, h_r^{-1}\Omega^{-1}), \quad h_r \sim \mathrm{Uniform}(\lambda_r^2, 10^4),$$

where $\Omega \in \mathcal{R}^{(L+2)\times(L+2)}$ is the roughness penalty matrix and $h_r > 0$ is the smooth parameter. The implies a Gaussian process prior on $\psi_r(t)$ with mean function zero and covariance function $\mathrm{Cov}\,\psi_r(t), \psi_r(s)) = h_r \mathbf{b}'(s)\Omega\mathbf{b}(t)$. We choose the Ω such that $[\Omega_r]_{l,l'} = (k_l - k_l)^2$,when $l, l' > 2$, and $[\Omega_r]_{l,l'} = 0$ when $l, l' \le 2$. For the distribution of principal scores in (4.5), we specify a multiplicative Gamma prior (Bhattacharya and Dunson (2011), Montagna et al. (2012)) on the variance to encourage shrinkage as r increases,

$$\chi_0^r, \chi_1^r \sim N(0, \sigma_{\chi_r}^2), \qquad \sigma_{\chi_r}^{-2} = \prod_{l \le r} \delta_{\chi l}, \quad \delta_{\chi 1} \sim \mathrm{Ga}(a_{\chi 1}, 1), \delta_{\chi l} \sim \mathrm{Ga}(a_{\chi 2}, 1), l \ge 2,$$

$$\lambda_r^{-2} = \prod_{l \le r} \delta_l, \qquad \delta_1 \sim \mathrm{Ga}(a_1, 1), \qquad \delta_l \sim \mathrm{Ga}(a_2, 1), \quad l \ge 2,$$

$$a_1, a_{\chi 1} \sim \mathrm{Ga}(2, 1), \qquad a_2, a_{\chi 2} \sim \mathrm{Ga}(3, 1).$$

Further details on the hyperparameters of the priors can be found in Bhattacharya and Dunson (2011) and Durante (2017). For the coefficients of covariates β_M, we specify a diffused normal prior $\beta_M \sim \mathcal{N}(0, 100^2 * \mathrm{I}_{\dim(X)})$. We impose similar prior distributions for the parameters in the outcome model.

Posterior inference can be obtained by Gibbs sampling. The credible intervals of the causal effects τ_{TE}^t and τ_{ACME}^t can be easily constructed using the posterior sample of the parameters in the model. Details of the Gibbs sampler are provided in the Supplementary Material (Zeng et al. (2021)).

5. Empirical application.

5.1. *Results of FPCA.* We apply the method and models proposed in Sections 3 and 4 to the data described in Section 2.2 to investigate the causal relationship between early adversity, social bonds and stress in wild baboons. Here, we first summarize the results of FPCA of the observed trajectories. We posit Model (4.3) for the social bonds and Model (4.9) for the GC

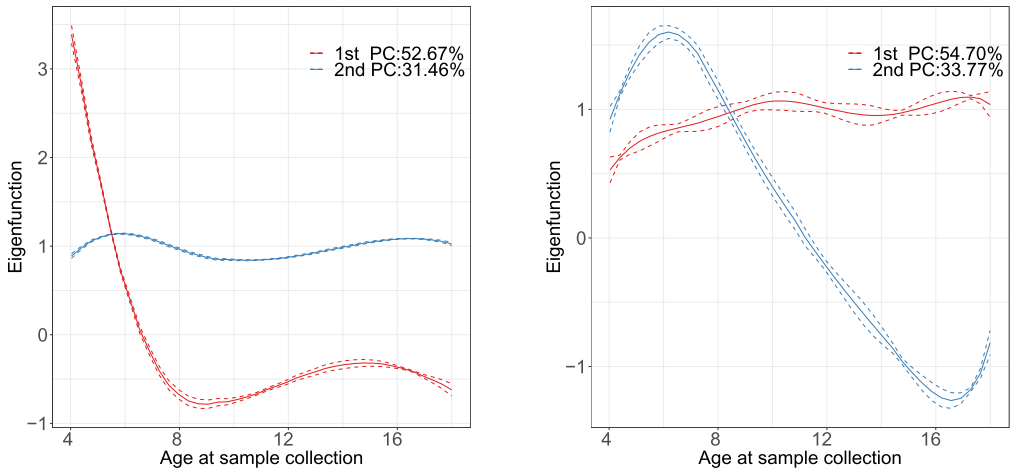


FIG. 3. *The first two functional principal components of the process of the mediator, that is, social bonds (left panel) and the outcome, that is, GC concentrations (right panel).*

concentrations, with some modifications. First, we added two random effects, one for social group and one for hydrological year, in both models. Second, in the outcome model we use the log transformed GC concentrations instead of the original scale as the outcome, which allows us to interpret the coefficient as the percent difference in GC concentrations between the treatment and control groups. For both the mediator and outcome processes, the first three functional principal components explain more than 90% of the total variation, and, thus, we use them in the structural equation model for mediation analysis. Figure 3 shows the first two principal components extracted from the mediator (left panel) and outcome (right panel) processes. For the social bond process the first two principal components explain 53% and 31% of the total variation, respectively. The first component depicts a drastic change in the early stage of a baboon's life and stabilizes afterward. The second component is relatively stable across the life span. For the GC process the first two functional principal components explain 54% and 34% of the total variation, respectively. The first component depicts a stable trend throughout the life span. The second component shows a quick rise, then steady drop pattern across the lifespan.

The left panel of Figure 4 displays the observed trajectory of GCs vs. the posterior mean of the imputed smooth process of three baboons who experienced zero (EAG), one (OCT) and two (GUI) sources of early adversity, respectively. We can see that the imputed smooth process generally captures the overall time trend of each subject while reducing the noise in the observations. The pattern is similar for the animals' social bonds, which is shown in the Supplementary Material (Zeng et al. (2021)) with a few more randomly selected subjects. Recall that each subject's observed trajectory is fully captured by its vector of principal scores, and, thus, the principal scores of the first few dominant principal components adequately summarize the whole trajectory. The right panel of Figure 4 shows the principal scores of the first (X-axis) vs. second (Y-axis) principal component for the GC process of all subjects in the sample, plotted in clusters based on the number of early adversities experienced. We can see that significant differences exist in the distributions of the first two principal scores between the group who experienced no early adversity and the groups experienced one or more sources of adversity.

5.2. *Results of causal mediation analysis.* We perform a separate causal mediation analysis for each source of early adversity. Table 2 presents the posterior mean and 95% credible interval of the total effect (TE), direct effect (ANDE) and indirect effect mediated through

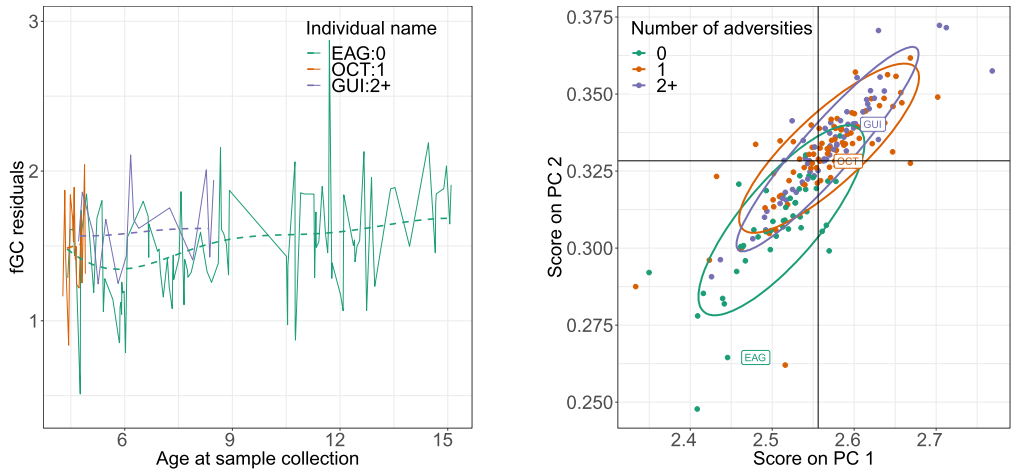


FIG. 4. *Left panel*: *Observed trajectory of GCs vs. the posterior mean of its imputed smooth process of three baboons who experienced zero* (*EAG*), *one* (*OCT*) *and two* (*GUI*) *sources of early adversity, respectively. Right panel*: *Principal scores of the first* (*X-axis*) *vs. second* (*Y-axis*) *principal component for the GC process of all subjects in the sample, plotted in clusters based on the number of early adversities experienced.*

social bonds (ACME) of each source of early adversity on adult GC concentrations as well as the effects of early adversity on the mediator (social bonds). First, from the first column of Table 2 we can see that experiencing any source of early adversity would reduce the strength of a baboon's social bond strength with other baboons in adulthood. The negative effect is particularly severe for those who experienced drought, high group density or maternal death in early life. For example, compared with the baboons who did not experience any early adversity, the baboons who experienced maternal death have a 0.221 unit decrease in social bonds, translating to a 0.4 standard deviation difference in social bond strength in this population. Overall, experiencing at least one source of early adversity corresponds to social bonds that are 0.2 standard deviations weaker in adulthood.

TABLE 2

Total, direct and indirect causal effects of individual and cumulative sources of early adversity on social bonds and GC concentrations in adulthood in wild female baboons. 95% credible intervals are in the parentheses

Source of adversity	Effect on mediator	τ_{TE}	τ_{ACME}	τ_{ANDE}
Drought	−0.164 (−0.314, −0.014)	0.124 (0.007, 0.241)	0.009 (0.000, 0.017)	0.114 (0.005, 0.222)
Competing sibling	−0.106 (−0.249, 0.030)	0.084 (−0.008, 0.172)	0.006 (0.003, 0.009)	0.078 (−0.012, 0.163)
High group density	−0.271 (−0.519, −0.023)	0.123 (−0.052, 0.281)	0.015 (0.000, 0.029)	0.108 (−0.053, 0.252)
Maternal death	−0.221 (−0.423, −0.019)	0.061 (−0.006, 0.129)	0.011 (0.005, 0.014)	0.049 (−0.014, 0.113)
Low maternal rank	−0.052 (−0.298, 0.001)	0.134 (0.011, 0.256)	0.008 (0.005, 0.011)	0.126 (0.008, 0.244)
Maternal social isolation	−0.040 (−0.159, 0.095)	0.035 (−0.045, 0.116)	0.002 (0.000, 0.005)	0.033 (−0.044, 0.111)
At least one	−0.102 (−0.195, −0.008)	0.092 (0.005, 0.178)	0.007 (0.002, 0.009)	0.084 (0.009, 0.159)

Second, from the second column of Table 2 we can see a strong total effect of early adversity on female baboon's GC concentrations across adulthood. Baboons who experienced at least one source of adversity had GC concentrations that were approximately 9% higher than their peers who did not experience any adversity. Although the range of total effect sizes across all individual adversity sources varies from 4% to 14%, the point estimates are consistently toward higher GC concentrations, even for the early adversity sources for which the credible interval includes zero. Among the individual sources of adversity, females who were born during a drought, into a high-density group or to a low-ranking mother had particularly elevated GC concentrations (12–14%) in adulthood, although the credible interval of high group density includes zero.

Third, while female baboons who experienced harsh conditions in early life show higher GC concentrations in adulthood, we found no evidence that these effects were significantly mediated by the absence of strong social bonds. Specifically, the mediation effect τ_{ACME} (third column in Table 2) is consistently small; the strength of females' social bonds with other females accounted for a difference in GCs of only 0.85% when averaged across the six individual adversity sources, even though the credible intervals did not include zero for five of the six individual adversity sources. On the other hand, the direct effects τ_{ANDE} (fourth column in Table 2) are much stronger than the mediation effects. When averaged across the six adversity sources, the direct effect of early adversity on GC concentrations was 11.6 times stronger than the mediation effect running through social bonds. For example, for females who experienced at least one source of early adversity, the direct effect explain an 8.4% difference in GC concentrations, while the mediation effect only takes up 0.7% for the difference in GCs.

We also assess the plausibility of the key causal assumptions in the application. One possible violation can be due to "feedback" between the social bond and GC processes, as is shown in Figure 2(c). We performed a sensitivity analysis by adding: (a) the most recent prior observed GC value or (b) the average of all past observed GC values, as a predictor in the mediation model, which led to little difference in the results and thus bolsters sequential ignorability. Though we are not aware of the existence of other sequential confounders, we also cannot rule them out.

The above findings on the causal relationships among early adversity, social bonds and GC concentrations in wild baboons are compatible with observations in many other species that early adversity and weak relationships both give rise to poor health and that early adversity predicts various forms of social dysfunction, including weaker relationships. However, they call into question the notion that social bonds play a major role in mediating the effect of early adversity on poor health. In wild female baboons any such effect appears to be functionally biologically irrelevant or minor.

6. Simulations. In this section, we conduct simulations to further evaluate the operating characteristics of the proposed method and compare it with two standard methods.

6.1. *Simulation design.* We generate 200 units to approximate the sample size in our application. For each unit we make T_i observations at the time grid $\{t_{ij} \in [0,1], j = 1,2,\ldots,T_i\}$. We draw T_i from a Poisson distribution with mean T and randomly pick t_{ij} uniformly,

$$T_i \sim \text{Poisson}(T), \qquad t_{ij} \sim \text{Uniform}(0,1), \quad j = 1,2,\ldots,T_i.$$

For each unit i and time j, we generate three covariates from a trivariate Normal distribution, $\mathbf{X}_{ij} = (X_{ij1}, X_{ij2}, X_{ij3}) \sim \mathcal{N}([0,0,0]^T, \sigma_X^2 \mathrm{I}_3)$. We simulate the binary treatment indicator

from $Z_i = \mathbf{1}\{c_{i1} > 0\}$, where $c_{i1} \sim \mathcal{N}(0, 1)$. To simulate the sparse and irregular mediator trajectories, we first simulate a smooth underlying process $M_i^t(z)$ for the mediators,

$$M_i^t(z) = 0.2 + \{0.2 + 2t + \sin(2\pi t)\})(z + 1) - X_{ij1} + 0.5X_{ij2} + \varepsilon_i^m(t) + c_{i2},$$

where the error term $\varepsilon_i^m(t) \sim \mathrm{GP}(0, \sigma_m^2 \exp\{-8(s-t)^2\})$ is drawn from a Gaussian process (GP) with an exponential kernel and σ_m^2 controlling the volatility of the realized curves and $c_{i2} \sim \mathcal{N}(0, \sigma_m^2)$ to represent the individual random intercepts. The mean value of the mediator process depends on the covariates and time index t. The polynomial term and the trigonometric function of t introduce the long-term growth trend and periodic fluctuations, respectively. Also, the coefficient of z evolves as the time changes, implying a time-varying treatment effect on the mediator. Similarly, we specify a GP model for the outcome process,

$$\begin{aligned} Y_i^t(z, \mathbf{m}) = \mathbf{m}^t + \cos(2\pi t) + 0.1t^2 + 2t + \{\cos(2\pi t) + 0.2t^2 + 3t\}z \\ - 0.5X_{ij2} + X_{ij3} + \varepsilon_i^y(t) + c_{i3}, \end{aligned}$$

where the error term $\varepsilon_i^y(t) \sim \mathrm{GP}(0, \sigma_y^2 \exp\{-8(s-t)^2\})$ is drawn from a GP and $c_{i3} \sim \mathcal{N}(0, \sigma_y^2)$ controls the individual random effects for the outcome process.

The above settings imply nonlinear true causal effects (τ_{TE}^t and τ_{ACME}^t) in time, which are shown as the dashed lines in Figure 5. Upon simulating the processes, we evaluate the potential values of the mediators and outcomes at the sampled time point t_{ij} to obtain the observed trajectories with measurement error,

$$M_{ij} \sim \mathcal{N}\big(\mathbf{M}_i^{t_{ij}}(Z_i), 1\big), \qquad Y_{ij} \sim \mathcal{N}\big(\mathbf{Y}_i^{t_{ij}}(Z_i, \mathbf{M}_i^{t_{ij}}(Z_i)), 1\big).$$

We control the sparsity of the mediator and outcome trajectories by varying the value of T in the grid of $(15, 25, 50, 100)$, namely, the average number of observations for each individual.

We compare the proposed method in Section 4 (abbreviated as MFPCA) with two standard methods in longitudinal data analysis: the random effects model (Laird and Ware (1982)) and the generalized estimating equations (GEE) (Liang and Zeger (1986)). To facilitate the comparisons, we aggregate the time-varying mediation effects into the following scalar values:

$$\tau_{\mathrm{ACME}} = \int_0^T \tau_{\mathrm{ACME}}^t \, \mathrm{d}t, \qquad \tau_{\mathrm{TE}} = \int_0^T \tau_{\mathrm{TE}}^t \, \mathrm{d}t.$$

The true values for τ_{ACME} and τ_{TE} in the simulations are 1.20 and 2.77, respectively.

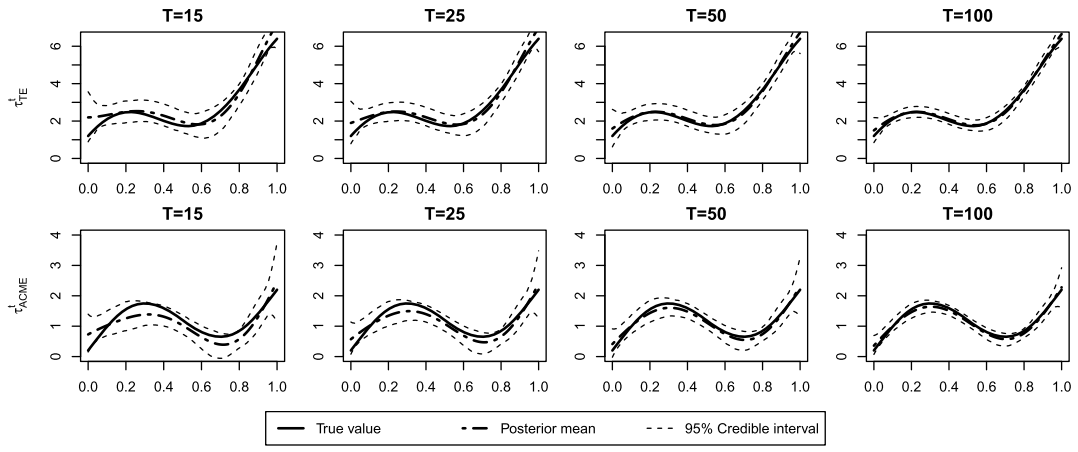


FIG. 5. *Posterior mean of τ_{TE}^t, τ_{ACME}^t and 95% credible intervals in one simulated dataset under each level of sparsity with 200 units. The solid lines are the true surfaces for τ_{TE}^t and τ_{ACME}^t.*

For the random effects approach, we fit the following two models:

$$M_{ij} = X_{ij}^T \beta_M + s_m(T_{ij}) + \tau_m Z_i + r_{ij}^m + \varepsilon_{ij}^m, \tag{6.1}$$

$$Y_{ij} = X_{ij}^T \beta_Y + s_y(T_{ij}) + \tau_y Z_i + \gamma M_{ij} + r_{ij}^y + \varepsilon_{ij}^y, \tag{6.2}$$

where r_{ij}^m and r_{im}^y are normally distributed random effects with zero means, $s_m(T_{ij})$ and $s_y(T_{ij})$ are thin plate splines to capture the nonlinear effect of time. To model the time dependency, we specify an AR(1) correlation structure for the random effects, thus $\text{Corr}(r_{ij}^m, r_{ij+1}^m) = p_1$, $\text{Corr}(r_{ij}^y, r_{ij+1}^y) = p_2$, namely, the correlation decay exponentially within the observations of a given unit. Given the above random effects model, the mediation effect and TE can be calculated as: $\hat{\tau}_{\text{ACME}}^{\text{RD}} = \hat{\gamma}\hat{\tau}_m$, $\hat{\tau}_{\text{TE}}^{\text{RD}} = \hat{\gamma}\hat{\tau}_m + \hat{\tau}_y$.

For the GEE approach, we specify the following estimation equations:

$$E(M_{ij}|X_{ij}, Z_i) = X_{ij}^T \beta_M + \tau_m Z_i, \tag{6.3}$$

$$E(Y_{ij}|M_{ij}, X_{ij}, Z_i) = X_{ij}^T \beta_M + \tau_y Z_i + \gamma M_{ij}. \tag{6.4}$$

For the working correlation structure we consider the AR(1) correlation for both the mediators and outcomes. Similarly, we obtain the estimations through $\hat{\tau}_{\text{ACME}}^{\text{GEE}} = \hat{\gamma}\hat{\tau}_m$, $\hat{\tau}_{\text{TE}}^{\text{GEE}} = \hat{\gamma}\hat{\tau}_m + \hat{\tau}_y$ with two different correlation structures.

It is worth noting that both the random effects model and the GEE model generally lack the flexibility to accommodate irregularly-spaced longitudinal data, which renders specifying the correlation between consecutive observations difficult. For example, though the AR(1) correlation takes into account the temporal structure of the data, it still requires the correlation between any two consecutive observations to be constant, which is unlikely to be the case in use cases with irregularly-spaced data. Nonetheless, we compare the proposed method with these two models, as they are the standard methods in longitudinal data analysis.

6.2. *Simulation results*. We apply the proposed MFPCA method, the random effects model and the GEE model in Section 6.1 to the simulated data $\{Z_i, \mathbf{X}_{ij}, M_{ij}, Y_{ij}\}$, to estimate the causal effects τ_{TE} and τ_{ACME}.

Figure 5 shows the causal effects and associated 95% credible interval estimated from MFPCA in one randomly selected simulated dataset under each of the four levels of sparsity T. Regardless of T, MFPCA appears to estimate the time-varying causal effects satisfactorily, with the 95% credible interval covering the true effects at any time. As expected, the accuracy of the estimation increases as the frequency of the observations increases.

Table 3 presents the absolute bias, root mean squared error (RMSE) and coverage rate of the 95% confidence interval of τ_{TE} and τ_{ACME} under the MFPCA, the random effects model and the GEE model based on 1000 simulated datasets for each level of sparsity T in $[15, 25, 50, 100]$. The performance of all three methods improves as the frequency of observations increases. With low frequency ($T < 100$), that is, sparse observations, MFPCA consistently outperforms the random effects model, which in turn outperforms GEE in all measures. The advantage of MFPCA over the other two methods diminishes as the frequency increases. In particular, with dense observations ($T = 100$), MFPCA leads to similar results as random effects, though both still outperform GEE. The simulation results bolster the use of our method in the case of sparse data.

We also conducted the same simulations with larger sample sizes, $N = 500, 1000$. MFPCA's advantage over the random effects and GEE models in terms of bias and RMSE increases as the sample size increases. With $N = 500$, MFPCA already achieves a coverage rate close to the nominal level. We leave the detailed results to the Supplementary Material (Zeng et al. (2021)).

TABLE 3

Absolute bias, RMSE and coverage rate of the 95% confidence interval of MFPCA, the random effects model and the generalized estimating equation (GEE) model under different frequency of observations in the simulations

	τ_{TE}			τ_{ACME}		
Method	Bias	RMSE	Coverage	Bias	RMSE	Coverage
			$T = 15$			
MFPCA	0.103	0.154	88.4%	0.134	0.273	86.4%
Random effects	0.165	0.208	78.2%	0.883	1.673	69.5%
GEE	0.183	0.304	77.6%	0.987	2.051	61.8%
			$T = 25$			
MFPCA	0.092	0.123	92.3%	0.102	0.246	90.6%
Random effects	0.124	0.165	81.2%	0.679	1.263	72.3%
GEE	0.152	0.273	80.3%	0.860	1.753	64.4%
			$T = 50$			
MFPCA	0.087	0.112	93.5%	0.094	0.195	92.3%
Random effects	0.109	0.134	90.3%	0.228	0.497	88.8%
GEE	0.121	0.175	83.5%	0.236	0.493	80.8%
			$T = 100$			
MFPCA	0.053	0.089	94.3%	0.064	0.163	93.1%
Random effects	0.046	0.093	93.1%	0.053	0.154	92.8%
GEE	0.093	0.124	90.5%	0.098	0.161	90.3%

7. Discussion. We proposed a framework for conducting causal mediation analysis with sparse and irregular longitudinal mediator and outcome data. We defined several causal estimands (total, direct and indirect effects) in such settings and specified structural assumptions to nonparametrically identify these effects. For estimation and inference, we combine functional principal component analysis (FPCA) techniques and the standard two structural-equation-model system. In particular, we use a Bayesian FPCA model to reduce the dimensions of the observed trajectories of mediators and outcomes. We applied the proposed method to analyze the causal effects of early adversity on adult social bonds and adult GC hormone concentrations in a sample of wild female baboons. We found that experiencing adversity before maturity generally hampers a baboon's ability to build social bonds with other baboons and increases GC hormone concentrations in adulthood. Chronically elevated stress hormones have been linked to disease in many species. However, the effect of early adversity on adult GC concentrations does not appear to be mediated by the strength of the animals' social bonds, at least in wild baboons.

Identification of the causal effects in our method relies a set of structural assumptions. In particular, sequential ignorability plays a key role, but it is untestable. In our application we have adjusted for all important confounders related to the sequential ignorability, according to our substantive biological knowledge, but we still cannot rule out the possibility of unobserved confounders. For example, the loss of a close companion would affect a baboon's social bond and stress afterward, but such data may be not systematically collected. This is a common challenge in causal mediation analysis. Conducting a sensitivity analysis would shed light on the consequences of violating such assumptions (Imai, Keele and Yamamoto (2010)). However, it is a nontrivial task to design a sensitivity analysis in complex settings such as ours, which usually involves more untestable structural and modeling assumptions. This is probably why sensitivity analysis is rarely performed in the causal mediation analysis literature despite its obvious value. Nonetheless, we believe it is important to explicitly acknowledge this limitation in applications and be cautious with interpretation, and, if possible, design and conduct sensitivity analysis. Alternatively, one could consider the framework

developed by Didelez, Dawid and Geneletti (2006), VanderWeele, Vansteelandt and Robins (2014) and relax sequential ignorability to allow for observed treatment-induced mediator-outcome confounding. However, this framework targets a different set of causal estimands from those considered in this paper and thus would have to be modified accordingly.

An important extension of our method is to incorporate time-to-event outcomes, a common practice in longitudinal studies (Lange, Vansteelandt and Bekaert (2012), VanderWeele (2011)). For example, it is of much scientific interest to extend our application to investigate the causal mechanisms among early adversity, social bonds, GC concentrations and length of lifespan. A common complication in the causal mediation analysis with time-to-event outcomes and time-varying mediators is that the mediators are not well defined for the time period in which a unit was not observed (Didelez (2019), Vansteelandt et al. (2019)). Within our framework, which treats the time-varying observations as realizations from a process, we can bypass this problem by imputing the underlying smooth process of the mediators in an identical range for every unit.

Acknowledgments. We thank Surya Tokdar, Fernando Campos, and Georgia Papadogeorgou for helpful discussions.

Funding. The majority of the data represented here was supported by the National Institutes of Health and the National Science Foundation, currently through NSF IOS 1456832 and through NIH R01AG053308, R01AG053330, R01HD088558 and P01AG031719. We also thank Duke University, Princeton University and the University of Notre Dame for financial and logistical support. For assistance and cooperation in Kenya, we are grateful to the Kenya Wildlife Service (KWS), University of Nairobi, Institute of Primate Research (IPR), National Museums of Kenya, National Environment Management Authority, and National Commission for Science, Technology, and Innovation (NACOSTI). We also thank the members of the Amboseli-Longido pastoralist communities and the Enduimet Wildlife Management Area for their cooperation and assistance in the field. Particular thanks go to the Amboseli Baboon Project long-term field team (R.S. Mututua, S. Sayialel, J.K. Warutere, Siodi, I.L.) and to T. Wango and V. Oudu for their untiring assistance in Nairobi. The baboon project database, Babase, is expertly managed by N. Learn and J. Gordon. Database design and programming are provided by K. Pinc. This research was approved by the IACUC at Duke University, University of Notre Dame and Princeton University and adhered to all the laws and guidelines of Kenya. For a complete set of acknowledgments of funding sources, logistical assistance and data collection and management, please visit http://amboselibaboons.nd.edu/acknowledgements/.

SUPPLEMENTARY MATERIAL

Supplement A to "Causal mediation analysis for sparse and irregular longitudinal data" (DOI: 10.1214/20-AOAS1427SUPPA; .pdf). It contains the proof of Theorem 1 (Supplement A.1), details of the Gibbs Sampler (Supplement A.2), examples of the imputed individual process (Supplement A.3), and simulation results with $N = 500, 1000$.

Supplement B to "Causal mediation analysis for sparse and irregular longitudinal data" (DOI: 10.1214/20-AOAS1427SUPPB; .zip). We provide the dataset from the Amboseli Baboon Research Project used in this paper and the programming code, which are also available on https://github.com/zengshx777/MFPCA_Codebase.

REFERENCES

ALBERTS, S. C. and ALTMANN, J. (2012). The Amboseli baboon research project: 40 years of continuity and change. In *Long-Term Field Studies of Primates* 261–287. Springer, Berlin.

ANDERSON, M. and MARMOT, M. (2011). The effects of promotions on heart disease: Evidence from Whitehall. *Econ. J.* **122** 555–589.

BARON, R. M. and KENNY, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psychol.* **51** 1173–1182. https://doi.org/10.1037//0022-3514.51.6.1173

BATESON, P., BARKER, D., CLUTTON-BROCK, T., DEB, D., D'UDINE, B., FOLEY, R. A., GLUCKMAN, P., GODFREY, K., KIRKWOOD, T. et al. (2004). Developmental plasticity and human health. *Nature* **430** 419.

BHATTACHARYA, A. and DUNSON, D. B. (2011). Sparse Bayesian infinite factor models. *Biometrika* **98** 291–306. MR2806429 https://doi.org/10.1093/biomet/asr013

BIND, M.-A. C., VANDERWEELE, T. J., COULL, B. A. and SCHWARTZ, J. D. (2016). Causal mediation analysis for longitudinal data with exogenous exposure. *Biostatistics* **17** 122–134. MR3449855 https://doi.org/10.1093/biostatistics/kxv029

CASE, A. and PAXSON, C. (2011). The long reach of childhood health and circumstance: Evidence from the Whitehall II study. *Econ. J.* **121** F183–F204.

COHEN, S. and WILLS, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychol. Bull.* **98** 310–357.

DANIELS, M. J., ROY, J. A., KIM, C., HOGAN, J. W. and PERRI, M. G. (2012). Bayesian inference for the causal effect of mediation. *Biometrics* **68** 1028–1036. MR3040009 https://doi.org/10.1111/j.1541-0420.2012.01781.x

DIDELEZ, V. (2019). Defining causal mediation with a longitudinal mediator and a survival outcome. *Lifetime Data Anal.* **25** 593–610. MR4015373 https://doi.org/10.1007/s10985-018-9449-0

DIDELEZ, V., DAWID, A. P. and GENELETTI, S. (2006). Direct and indirect effects of sequential treatments. In *Proceedings of the Twenty-Second Conference on Uncertainty in Artificial Intelligence* 138–146.

DURANTE, D. (2017). A note on the multiplicative gamma process. *Statist. Probab. Lett.* **122** 198–204. MR3584158 https://doi.org/10.1016/j.spl.2016.11.014

FORASTIERE, L., MATTEI, A. and DING, P. (2018). Principal ignorability in mediation analysis: Through and beyond sequential ignorability. *Biometrika* **105** 979–986. MR3877878 https://doi.org/10.1093/biomet/asy053

GLUCKMAN, P. D., HANSON, M. A., COOPER, C. and THORNBURG, K. L. (2008). Effect of in utero and early-life conditions on adult health and disease. *N. Engl. J. Med.* **359** 61–73.

GOLDSMITH, J., GREVEN, S. and CRAINICEANU, C. (2013). Corrected confidence bands for functional data using principal components. *Biometrics* **69** 41–51. MR3058050 https://doi.org/10.1111/j.1541-0420.2012.01808.x

HAN, K., HADJIPANTELIS, P. Z., WANG, J.-L., KRAMER, M. S., YANG, S., MARTIN, R. M. and MÜLLER, H.-G. (2018). Functional principal component analysis for identifying multivariate patterns and archetypes of growth, and their association with long-term cognitive development. *PLoS ONE* **13** e0207073.

HOLT-LUNSTAD, J., SMITH, T. B. and LAYTON, J. B. (2010). Social relationships and mortality risk: A meta-analytic review. *PLoS Med.* **7** e1000316. https://doi.org/10.1371/journal.pmed.1000316

IMAI, K., KEELE, L. and TINGLEY, D. (2010). A general approach to causal mediation analysis. *Psychol. Methods* **15** 309–334. https://doi.org/10.1037/a0020761

IMAI, K., KEELE, L. and YAMAMOTO, T. (2010). Identification, inference and sensitivity analysis for causal mediation effects. *Statist. Sci.* **25** 51–71. MR2741814 https://doi.org/10.1214/10-STS321

IMBENS, G. W. and RUBIN, D. B. (2015). *Causal Inference in Statistics, Social, and Biomedical Sciences*. Cambridge Univ. Press, Cambridge.

JIANG, C.-R. and WANG, J.-L. (2010). Covariate adjusted functional principal components analysis for longitudinal data. *Ann. Statist.* **38** 1194–1226. MR2604710 https://doi.org/10.1214/09-AOS742

JIANG, C.-R. and WANG, J.-L. (2011). Functional single index models for longitudinal data. *Ann. Statist.* **39** 362–388. MR2797850 https://doi.org/10.1214/10-AOS845

KIM, C., DANIELS, M. J., MARCUS, B. H. and ROY, J. A. (2017). A framework for Bayesian nonparametric inference for causal effects of mediation. *Biometrics* **73** 401–409. MR3665957 https://doi.org/10.1111/biom.12575

KIM, C., DANIELS, M., LI, Y., MILBURY, K. and COHEN, L. (2018). A Bayesian semiparametric latent variable approach to causal mediation. *Stat. Med.* **37** 1149–1161. MR3777965 https://doi.org/10.1002/sim.7572

KIM, C., DANIELS, M. J., HOGAN, J. W., CHOIRAT, C. and ZIGLER, C. M. (2019). Bayesian methods for multiple mediators: Relating principal stratification and causal mediation in the analysis of power plant emission controls. *Ann. Appl. Stat.* **13** 1927–1956. MR4019162 https://doi.org/10.1214/19-AOAS1260

KOWAL, D. R. and BOURGEOIS, D. C. (2020). Bayesian function-on-scalars regression for high-dimensional data. *J. Comput. Graph. Statist.* **29** 629–638. MR4153187 https://doi.org/10.1080/10618600.2019.1710837

LAIRD, N. M. and WARE, J. H. (1982). Random-effects models for longitudinal data. *Biometrics* 963–974.

LANDERMAN, R., GEORGE, L. K., CAMPBELL, R. T. and BLAZER, D. G. (1989). Alternative models of the stress buffering hypothesis. *Am. J. Community Psychol.* **17** 625–642.

LANGE, T., VANSTEELANDT, S. and BEKAERT, M. (2012). A simple unified approach for estimating natural direct and indirect effects. *Am. J. Epidemiol.* **176** 190–195.

LIANG, K. Y. and ZEGER, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika* **73** 13–22. MR0836430 https://doi.org/10.1093/biomet/73.1.13

LIN, S.-H., YOUNG, J., LOGAN, R., TCHETGEN TCHETGEN, E. J. and VANDERWEELE, T. J. (2017a). Parametric mediational g-formula approach to mediation analysis with time-varying exposures, mediators, and confounders. *Epidemiology* **28** 266.

LIN, S.-H., YOUNG, J. G., LOGAN, R. and VANDERWEELE, T. J. (2017b). Mediation analysis for a survival outcome with time-varying exposures, mediators, and confounders. *Stat. Med.* **36** 4153–4166. MR3713656 https://doi.org/10.1002/sim.7426

LINDQUIST, M. A. (2012). Functional causal mediation analysis with an application to brain connectivity. *J. Amer. Statist. Assoc.* **107** 1297–1309. MR3036396 https://doi.org/10.1080/01621459.2012.695640

LINDQUIST, M. A. and SOBEL, M. E. (2011). Graphical models, potential outcomes and causal inference: Comment on Ramsey, Spirtes and Glymour. *NeuroImage* **57** 334–336.

LINDSTRÖM, J. (1999). Early development and fitness in birds and mammals. *Trends Ecol. Evol.* **14** 343–348.

MACKINNON, D. (2012). *Introduction to Statistical Mediation Analysis*. Routledge, London.

MARMOT, M. G., STANSFELD, S., PATEL, C., NORTH, F., HEAD, J., WHITE, I., BRUNNER, E., FEENEY, A. and SMITH, G. D. (1991). Health inequalities among British civil servants: The Whitehall II study. *Lancet* **337** 1387–1393.

MCEWEN, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Ann. N.Y. Acad. Sci.* **840** 33–44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x

MCEWEN, B. S. (2008). Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. *Eur. J. Clin. Pharmacol.* **583** 174–185.

MILLER, G. E., CHEN, E. and PARKER, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychol. Bull.* **137** 959.

MILLER, G. E., COHEN, S. and RITCHEY, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychology* **21** 531–541. https://doi.org/10.1037//0278-6133.21.6.531

MONTAGNA, S., TOKDAR, S. T., NEELON, B. and DUNSON, D. B. (2012). Bayesian latent factor regression for functional and longitudinal data. *Biometrics* **68** 1064–1073. MR3040013 https://doi.org/10.1111/j.1541-0420.2012.01788.x

NEYMAN, J. (1923). On the application of probability theory to agricultural experiments. Essay on principles. Section 9 (translated). *Statist. Sci.* 465–480.

NGUYEN, T. Q., SCHMID, I. and STUART, E. A. (2020). Clarifying causal mediation analysis for the applied researcher: Defining effects based on what we want to learn. *Psychol. Methods* in press.

PEARL, J. (2001). Direct and indirect effects. In *Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence* 411–420. Morgan Kaufmann, San Mateo.

RAMSAY, J. O. and SILVERMAN, B. W. (2005). *Functional Data Analysis*, 2nd ed. *Springer Series in Statistics*. Springer, New York. MR2168993

ROBINS, J. M. and GREENLAND, S. (1992). Identifiability and exchangeability for direct and indirect effects. *Epidemiology* 143–155.

ROBINS, J. M., HERNAN, M. A. and BRUMBACK, B. (2000). Marginal structural models and causal inference in epidemiology. *Epidemiology* **11**.

ROSENBAUM, S., ZENG, S., CAMPOS, F., GESQUIERE, L., ALTMANN, J., ALBERTS, S., LI, F. and ARCHIE, E. (2020). Social bonds do not mediate the relationship between early adversity and adult glucocorticoids in wild baboons. *Proc. Natl. Acad. Sci. USA* in press.

ROTH, D. L. and MACKINNON, D. P. (2012). Mediation analysis with longitudinal data. In *Longitudinal Data Analysis*: *A Practical Guide for Researchers in Aging*, *Health*, *and Social Sciences* 181–216.

RUBIN, D. B. (1974). Estimating causal effects of treatments in randomized and nonrandomized studies. *J. Educ. Psychol.* **66** 688.

RUBIN, D. B. (1980). Randomization analysis of experimental data: The Fisher randomization test comment. *J. Amer. Statist. Assoc.* **75** 591–593.

SHPITSER, I. and VANDERWEELE, T. J. (2011). A complete graphical criterion for the adjustment formula in mediation analysis. *Int. J. Biostat.* **7** 16. MR2775083 https://doi.org/10.2202/1557-4679.1297

SILK, J. B. (2007). The adaptive value of sociality in mammalian groups. *Philos. Trans. R. Soc. B, Biol. Sci.* **362** 539–559.

SILK, J. B., ALTMANN, J. and ALBERTS, S. C. (2006). Social relationships among adult female baboons (Papio cynocephalus) I. Variation in the strength of social bonds. *Behav. Ecol. Sociobiol.* **61** 183–195.

SOBEL, M. E. (2008). Identification of causal parameters in randomized studies with mediating variables. *J. Educ. Behav. Stat.* **33** 230–251.

TCHETGEN TCHETGEN, E. J. and SHPITSER, I. (2012). Semiparametric theory for causal mediation analysis: Efficiency bounds, multiple robustness and sensitivity analysis. *Ann. Statist.* **40** 1816–1845. MR3015045 https://doi.org/10.1214/12-AOS990

TEN HAVE, T. R. and JOFFE, M. M. (2012). A review of causal estimation of effects in mediation analyses. *Stat. Methods Med. Res.* **21** 77–107. MR2867539 https://doi.org/10.1177/0962280210391076

THORSTEINSSON, E. B. and JAMES, J. E. (1999). A meta-analysis of the effects of experimental manipulations of social support during laboratory stress. *Psychol. Health* **14** 869–886.

TUNG, J., ARCHIE, E. A., ALTMANN, J. and ALBERTS, S. C. (2016). Cumulative early life adversity predicts longevity in wild baboons. *Nat. Commun.* **7** 1–7.

VANDERWEELE, T. J. (2011). Causal mediation analysis with survival data. *Epidemiology* **22** 582.

VANDERWEELE, T. J. (2014). A unification of mediation and interaction: A four-way decomposition. *Epidemiology* **25** 749.

VANDERWEELE, T. (2015). *Explanation in Causal Inference*: *Methods for Mediation and Interaction*. Oxford Univ. Press, London.

VANDERWEELE, T. J. (2016). Mediation analysis: A practitioner's guide. *Annu. Rev. Public Health* **37** 17–32. https://doi.org/10.1146/annurev-publhealth-032315-021402

VANDERWEELE, T. J. and TCHETGEN TCHETGEN, E. J. (2017). Mediation analysis with time varying exposures and mediators. *J. R. Stat. Soc. Ser. B. Stat. Methodol.* **79** 917–938. MR3641414 https://doi.org/10.1111/rssb.12194

VANDERWEELE, T. J., VANSTEELANDT, S. and ROBINS, J. M. (2014). Effect decomposition in the presence of an exposure-induced mediator-outcome confounder. *Epidemiology* **25** 300.

VANSTEELANDT, S., LINDER, M., VANDENBERGHE, S., STEEN, J. and MADSEN, J. (2019). Mediation analysis of time-to-event endpoints accounting for repeatedly measured mediators subject to time-varying confounding. *Stat. Med.* **38** 4828–4840. MR4022831 https://doi.org/10.1002/sim.8336

VAN DER LAAN, M. J. and PETERSEN, M. L. (2008). Direct effect models. *Int. J. Biostat.* **4** 23. MR2456975 https://doi.org/10.2202/1557-4679.1064

YAO, F., MÜLLER, H.-G. and WANG, J.-L. (2005). Functional data analysis for sparse longitudinal data. *J. Amer. Statist. Assoc.* **100** 577–590. MR2160561 https://doi.org/10.1198/016214504000001745

ZENG, S., ROSENBAUM, S., ARCHIE, E., ALBERTS, S. and LI, F. (2021). Supplement to "Causal mediation analysis for sparse and irregular longitudinal data." https://doi.org/10.1214/20-AOAS1427SUPPA, https://doi.org/10.1214/20-AOAS1427SUPPB

ZHAO, Y., LUO, X., LINDQUIST, M. and CAFFO, B. (2018). Functional mediation analysis with an application to functional magnetic resonance imaging data. *Preprint. Available at* arXiv:1805.06923.

ZHENG, W. and VAN DER LAAN, M. (2017). Longitudinal mediation analysis with time-varying mediators and exposures, with application to survival outcomes. *Journal of Causal Inference* **5**.

ZIGLER, C. M., DOMINICI, F. and WANG, Y. (2012). Estimating causal effects of air quality regulations using principal stratification for spatially correlated multivariate intermediate outcomes. *Biostatistics* **13** 289–302.

ZIPPLE, M. N., ARCHIE, E. A., TUNG, J., ALTMANN, J. and ALBERTS, S. C. (2019). Intergenerational effects of early adversity on survival in wild baboons. *eLife* **8** e47433.