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Causal measures using generalized difference-in-difference approach with nonlinear models

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To assess the impact of interventions on observational studies, several approaches have been proposed for identification of causal effects. They include propensity score matching, regression discontinuity, instrumental variables and causal graphs. In this paper, we focus on the Differences-in-Differences. We review the subject, discuss its scope and limitations, and extend it to a class of nonlinear models, inducing more appropriate causal measures in relation to the type of response variable and the corresponding statistical model. More specifically, we extend the usual causal effect identification procedure for more general setups, particularly Generalized Linear Models, presenting the necessary assumptions. We call such methodology Generalized Difference-in-Difference method. To illustrate, we analyze novel data from three relevant health issues in Brazil: the demographic impact of the Zika virus outbreak on birth rates, and the impact of two distinct interventions in primary health care, namely the Family Health Program and the More Doctors Program, on hospitalizations rate. Such analyzes, besides original and referring to important topics, complement and extend previous studies. Finally, we argue, in the methodological and application sections, that the use of the Generalized Difference-in-Difference will help us to avoid errors and fallacies arising from the misapplication of the usual Difference-in-Difference method at different scales.

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1. INTRODUCTION

Although controversial, the notion of causality permeates science in the sense that every researcher seeks through his/her research to establish a connection between empirical facts. The question of what would be the effect of some specific action, such as the attribution of a treatment or a socioeconomic intervention on a population of interest, is therefore legitimate. Such a question lies outside the scope of traditional statistics because it refers to what would happen to that population if it were manipulated in a sense. A major challenge for estimating causal effects, known as the fundamental problem of causal inference [31], is given by the self-evident fact that an individual cannot be simultaneously observed in both intervention/treatment or control/placebo groups. On the other hand, the use of natural or quasi-experimental studies, instead of randomized ones, to evaluate treatment effects is very popular in economics, social and health sciences [38, 39] and brings in an additional difficulty because the individuals are not randomly assigned to treatment and control groups. Hence analysts often face the problem of adequately controlling confounding variables and identifying comparison groups capable of providing good estimates for causal effect.

The research in Epidemiology focus mainly on the natural history, frequency, patterns of occurrence, risk factors and potential causes of diseases or health events in specific populations, but it is constrained by ethical issues regarding the manipulation of human groups for scientific purposes, which inhibits the wide use of experimental studies. In this way, the complex structure of health-disease-care processes motivates the development of designs for observational studies and hence the improvement of analytical techniques to reduce the effect of systematic errors and biases produced by confounding variables [49]. The econometric literature, in its turn, presents several different approaches for dealing with the identification of causal effects given observational data. Some examples would include propensity scores [8, 25], regression discontinuity [32, 16], instrumental variables [5, 28], and, more recently, causal graphs [27, 50]. In this article, however, we focus on the difference-in-difference (*diff-in-diff*) strategy for causal identification. Many quasi-experiment studies are induced by policy changes with given eligibility criteria which define who will, or will not, receive the benefit after a certain moment in time. In such cases, the comparison of pre- and post-treatment outcomes can be a

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powerful tool to identify causal effects, which is exactly the essence of the *diff-in-diff* approach. In its simplest applications, for each unit, the observations in two distinct instants (before & after intervention) are used to compare the two groups of interest (treatment/control). It is usually assumed that none of the units is exposed to treatment in the first period, though those in the treatment group are exposed in the second period. Under suitable assumptions, the effect of the treatment on the treated can be identified by the average difference between the changes in the outcome in the treated/exposed ($G = 1$) and control/unexposed ($G = 0$) groups, *i.e.* $E[Y(1) - Y(0)|G = 1] - E[Y(1) - Y(0)|G = 0]$, where $Y(T)$ is the outcome of interest. Here, $T = 0, 1$ denotes pre- and post-intervention periods (though it is also possible to consider longer panels with more complex temporal dynamics, before or after the intervention). Indeed, as detailed later, this double difference identifies the causal effect by removing any biases resulting from differences between groups, as well as biases related to temporal trends not associated to the treatment.

All these basic ideas evolved to identify causal effects directly from usual statistical models and they have been adopted by many studies. Most usually, *diff-in-diff* is used to analyze continuous data, usually through linear models. However, in many situations, one must consider different kinds of data (*e.g.* counts, binary, rates, positive asymmetric etc.). For example, Poisson and logistic regression models have been used to estimate effects associated to counts/rates and binary outcomes [29, 19]. The impact of insurance expansion on the use of knee and hip replacement procedures in the United States is estimated by Hanchate et al. [29], while Deb and Norton [19] estimated the effect of the young adult health insurance coverage expansion in the Patient Protection and Affordable Care Act (ACA) on health care expenditures and use in US, focusing on the interpretation of the results from the two-part or hurdle models for count data. In Brazil, specifically, some social programs, such as the More Doctors Program (MDP) and the Family Health Program (FHP) — in Portuguese, the More Doctors Program is referred to as *'Programa Mais Médicos'* and the Family Health Program is referred to as *'Programa Saúde da Família'* — have been recently evaluated using *diff-in-diff* methods [46, 24]. These studies estimated, respectively, the impact of the MDP on the number of hospitalizations for ambulatory care sensitive conditions and the impact of the FHP on mortality rates, child labor and schooling, among other outcomes. Both studies considered repeated observations of the outcomes over time (in years) and adopted fixed effects linear models as the statistical approach for estimation of causal effects. Fontes et al [24] also considered the *diff-in-diff* approach weighted by propensity scores to reduce both selection bias by unobservable characteristics and other potential biases caused by the distribution of observed characteristics and the lack of common support.

In this article, we study the *diff-in-diff* approach in a more general framework and how to identify its causal effects, particularly for Generalized Linear Models (GLMs). More specifically, we present the necessary assumptions for the its appropriate use as well as its interpretation considering applications in public health. To illustrate the proposed methodology, we analyze data from three relevant health issues in Brazil. One application is an analysis of the demographic impacts of the Zika virus (ZIKV) outbreak (an arbovirus) in 2015, comparing two Brazilian states, one that was strongly affected by the epidemic and another that was not. The other analyses are related to the evaluation of two interventions in primary health care, namely the Family Health Program (FHP) and the More Doctors Program (MDP), and the estimation of their impact on the occurrence of avoidable hospitalizations. We believe that the theoretical and conceptual ponderations as well as the evidence of our applications contribute to reduce the risk of fallacious interpretations due to the noncompliance with the assumptions required for the use of this methodology.

2. DIFFERENCES-IN-DIFFERENCES

To assess the impact of interventions or treatment assignments on an outcome Y, let Y^1 and Y^0 be the potential outcomes when a sample unit, respectively, receives and does not receive treatment [47, 48]. We are trying to conceive the value that would be assigned to Y for an individual in the treatment group when he has not received treatment, and vice versa. The use of counterfactual responses allows us to assess the actual effect of a treatment. The idea, therefore, is to compare the necessarily non-coexistent variables Y^0 and Y^1 for the sole purpose of evaluating such an effect. In the hypothetical case where both Y^0 and Y^1 were observed concomitantly, the causal effect associated to a unit could be defined as the difference $\tau = Y^1 - Y^0$. Unfortunately, however, only one of them is effectively observed and the other one must be a counterfactual. To circumvent this problem, one of the most popular approaches is to randomly assign treatment to individuals in order to unbiasedly estimate the causal effect. This could be done, for instance, by taking averages of Y on each group (treated/non treated), so that $\hat{\tau} = \bar{Y}^{(1)} - \bar{Y}^{(0)}$, where $\bar{Y}^{(g)}$ is the empirical average of Y in group $G = g$ [47, 48]. This approach, though suitable for experimental studies, fails for observational studies where treatment assignment is usually not random. Indeed, naive estimators for the causal effect not controlling for confounding are usually biased. For this reason, a number of approaches has been developed to get good estimates of the causal effect in observational studies. Particularly, in this paper we focus in the *diff-in-diff* method, which, for the sake of completeness, will be reviewed here. Additional details are included in Appendix A. For a more comprehensive account on this, see Lechner [34].

Differences-in-differences are based on the comparison of two groups, treated and untreated, in two distinct instants of time $T \in \{0,1\}$. Denote the observed and potential responses at T by $Y(T)$, $Y^0(T)$ and $Y^1(T)$, so that $I = G \times T$ indicates the effective treatment indicator. Under this framework, we need assumptions [A1]–[A5] (Appendix A) to identify the causal effect of interest. As a consequence of SUTVA (Assumption [A1]), Y^0 or Y^1 should coincide with Y depending on the treatment status of the unit. Assumption [A2] states that covariates are not influenced by the treatment assignment mechanism, while Assumption [A3] allows us to compare treatment and control groups, since the noncompliance would imply the absence of controls in certain strata. Assumption [A4] is typical of the *diff-in-diff* method and it rules out the possibility of a unit behaving differently in the pre-treatment period due to the anticipation of a possible treatment. From assumption [A5] we know that the expected dynamics of $Y(T)$ from $T = 0$ to $T = 1$ is invariant with respect to group allocation, *i.e.* $\mathrm{E}[Y^0(1)|G = 1, \boldsymbol{X}] - \mathrm{E}[Y^0(1)|G = 0, \boldsymbol{X}] = \mathrm{E}[Y^0(0)|G = 1, \boldsymbol{X}] - \mathrm{E}[Y^0(0)|G = 0, \boldsymbol{X}]$. In particular, this relation justifies the parallelism condition typical of the *diff-in-diff* method (Figure 1a). Thus, the average treatment effect on the treated (ATT) given $\boldsymbol{X} = \boldsymbol{x}$ is defined by

$$\tau(\boldsymbol{x}) = \mathrm{E}[Y^1(1) - Y^0(1)|G = 1, \boldsymbol{x}]. \tag{1}$$

The overall effect $\mathrm{E}[Y^1(1) - Y^0(1)|\boldsymbol{x}]$, obtained by disregarding the restriction $G = 1$, unfortunately requires additional and inconvenient assumptions, since it would demand an available subpopulation of treated individuals at $T = 0$. Identification of (1) easily follows from [A1]–[A5] and is also presented in Appendix A. From that, we have that if $Y(T) = \alpha + \varphi T + \gamma G + \tau_o I + \theta(\boldsymbol{X}) + \varepsilon$, where $\varepsilon \sim N(0, \sigma^2)$, then τ_o stands for treatment effect and it can be estimated by regressing Y_i on the associated covariates [33].

If the assumptions for the previous model do not hold, nonlinear models, such as the logit, probit, log-linear or even semiparametric [2] models, should be fitted, but the interaction parameter and the causal parameter do not match anymore [3]. Indeed, contrary to the present case, where the treatment effect is completely identified through τ_o, in nonlinear cases the treatment effect will now explicitly depend on G, T and $\boldsymbol{X}$ [43]. For example, if $\mathrm{E}[Y^0(T)|G, \boldsymbol{X}] = \Phi(\alpha + \beta T + \gamma G + \theta(\boldsymbol{X}))$ and $\mathrm{E}[Y^1(T)|G, \boldsymbol{X}] = \Phi(\alpha + \beta T + \gamma G + \tau_o + \theta(\boldsymbol{X}))$ under the probit model, then

$$\begin{aligned}\tilde{\tau}(\boldsymbol{X}) &= \mathrm{E}[Y^1(1)|G = 1, \boldsymbol{X}] - \mathrm{E}[Y^0(1)|G = 1, \boldsymbol{X}] \\ &= \Phi(\alpha + \beta + \gamma + \tau_o + \theta(\boldsymbol{X})) - \Phi(\alpha + \beta + \gamma + \theta(\boldsymbol{X})),\end{aligned}$$

clearly indicating that effect and interaction parameters do not coincide, *i.e.* $ATT = \tau_o$ only for the linear model with the identity link function. Moreover, not even the sign of the treatment effect must be the same as that of τ_o. Of course, it could be argued that (*i*) in the particular case where Φ is strictly monotone, $\tilde{\tau}(\boldsymbol{X}) = 0$ if, and only if, $\tau_o = 0$ and (*ii*) additionally if Φ is strictly increasing (decreasing), then the sign of $\tilde{\tau}(\boldsymbol{X})$ is the same as (opposite of) the sign of τ_o, reinforcing the idea of τ_o as a proxy of the treatment effect. Nevertheless, it still remains not possible to strictly identify both τ_o and the causal effect in a nonlinear setup. Actually, identification for nonlinear models requires more than a cross difference as in (9) in Appendix A [43].

The main purpose of this paper is to reconcile the linear and nonlinear cases in the particular settings to be detailed in the next section, and express the causal effect in distinct metrics depending on the response type. In this way, we seek to make explicit the proper use of the *diff-in-diff* framework for different causal risk measures in epidemiology.

3. CAUSAL TREATMENT EFFECTS IN NONLINEAR MODELS

When the response is otherwise bounded (*e.g.* binomial data) or skewed (*e.g.* count or interval data), linear models can be unsuitable, and then both the causal effect (1) and its identification formula (Appendix A) should be rewritten. The aim is to generalize the results described in the previous section by defining and identifying other causal "ATT"s tailored for different types of data. It should be noticed that such definitions were dealt by Lechner [34] and, in a slightly different context, by Athey and Imbens [7]. Let $h : \mathbb{R} \to \mathbb{R}$ be a monotone (link) function such that $\eta = h(\mathrm{E}[Y(T)|G, \boldsymbol{X}])$ is in the interval (difference) scale. For the Exponential family, for example, this link coincides with the canonical link $h = (b')^{-1}$ (assuming densities in the Exponential Family to be given as $f(y|\theta, \phi) = \phi^{-1}(y\theta - b(\theta)) + c(y, \phi)$, so that $\mathrm{E}[Y|\theta, \phi] = b'(\theta) = \mu$). Let $\tau = \tau(\boldsymbol{x})$ be

$$\tau = h\left(\mathrm{E}[Y^1(1)|G = 1, \boldsymbol{X}]\right) - h\left(\mathrm{E}[Y^0(1)|G = 1, \boldsymbol{X}]\right) \tag{2}$$

and define the *generalized average treatment (effect) on treated* (GATT) as a function of τ, say $g(\tau)$, suitably chosen according to the function h and the response distribution. The function g is chosen to improve interpretability. The dependence of the effect on X occurs in the general case, but it is removed when using a linear predictor η. In this case, the effect τ is invariant with respect to X. Moreover, it is worth noting that the link function h is not a purely statistical choice and its determination should be dictated by the underlying causal mechanism. For instance, in the classic *diff-in-diff*, h is the identity function. However, if the true relationship is not linear, the estimated causal effect will be biased. Besides that, the treatment effect (1) is just a particular case of (2) where h and g are equal to the identity function. To identify τ for different link functions, we assume the following variant of [A5]:

[A5'] *(Common Trend Condition)* The variation in the transformed expected potential outcomes from $T = 0$

Table 1. Assessment of the causal effect under [A5'] and under its violation through Monte-Carlo simulations

Model	Sample size	Assumption [A5'] True Bias	True MSE	False Bias	False MSE
Linear ($\tau = 3$)	50	−0.0030	16.38	2.4970	639.89
	200	−0.0029	1.03	2.4971	156.92
	500	0.0016	0.16	2.5016	62.74
Poisson ($\tau = 0.3$)	50	0.0013	2.84	−0.3513	15.32
	200	0.0015	0.18	−0.3509	3.26
	500	−0.0013	0.03	−0.3504	1.26

to $T = 1$ is invariant with respect to group allocation, *i.e.*

$$h\left(\mathrm{E}[Y^0(1)|G=1,\boldsymbol{X}]\right) - h\left(\mathrm{E}[Y^0(0)|G=1,\boldsymbol{X}]\right) = h\left(\mathrm{E}[Y^0(1)|G=0,\boldsymbol{X}]\right) - h\left(\mathrm{E}[Y^0(0)|G=0,\boldsymbol{X}]\right).$$

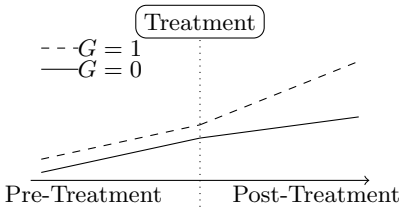
Identification of GATT follows the same steps from the linear model and is presented in details in Appendix B. From those developments, it follows that

$$\tau_o = \{h\left(\mathrm{E}[Y(1)|G=1,\boldsymbol{X}]\right) - h\left(\mathrm{E}[Y(0)|G=1,\boldsymbol{X}]\right)\} - \{h\left(\mathrm{E}[Y(1)|G=0,\boldsymbol{X}]\right) - h\left(\mathrm{E}[Y(0)|G=0,\boldsymbol{X}]\right)\}. \quad (3)$$

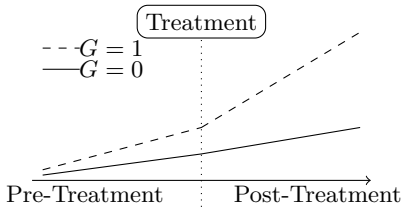
In other words, if $h\left(\mathrm{E}[Y(T)|G,\boldsymbol{X}]\right) = \alpha + \varphi T + \gamma G + \tau_o I + \theta(\boldsymbol{X})$, then $\tau = \tau_o$ is the causal effect. Notice that it is not demanded that η be linear with respect to $\boldsymbol{X}$. This is true, however, only if φ (the time effect) is invariant with respect to the treatment group. Indeed, if $h\left(\mathrm{E}[Y(T)|G,\boldsymbol{X}]\right)$ is linear with respect to T, G and I, then each side of the identity in [A5'] is equal to the parameter associated to T at each group, so that equality follows only if they are the same. More precisely, if φ_0 is the parameter associated to T for $G = 0$ and $\varphi_1 = \varphi_0 + \kappa$ for $G = 1$, then [A5'] holds only if $\kappa = 0$. To illustrate, Table 1 presents what happens for the linear and Poisson models with different sample sizes in two different scenarios ($\varphi_0 = \varphi_1$ and $\varphi_0 \neq \varphi_1$). For the case in which [A5'] fails, we took $\varphi_0 = 3$ and $\varphi_1 = 5.5$ ($\kappa = 2.5$) under the linear model and $\varphi_0 = 0.20$ and $\varphi_1 = -0.15$ ($\kappa = -0.35$) under the Poisson model. In order to assess the impact on the estimated causal effect, we evaluated the biases and mean squared errors (MSE) assuming $\varphi_1 = \varphi_2 = \varphi$ in both scenarios. As one can see, when [A5'] fails, the biases concerning the causal effect are nearly constant and very close to κ regardless the sample size. In fact, that such bias is equal to τ is actually a general result, see Appendix C.

The graphical evaluation of parallel curves used in practice, which is based on assumption [A5], must be reinterpreted in the light of the chosen link function h. The graphs of $\mathrm{E}[Y(T)|G,\boldsymbol{X}]$ along time, for the treated and untreated groups, should be parallel (before treatment) only if h is the identity function. Otherwise, they might behave differently. For example, Fig. 1 highlights the cases $h = \mathrm{id}$ and $h = \log$. In Fig. 1(a) (identity case), the graphs should be, as expected, parallel before effective treatment takes place. Differently, if $h = \log$, then the $\mathrm{E}[Y(T)|G = 1,\boldsymbol{X}]/\,\mathrm{E}[Y(T)|G = 0,\boldsymbol{X}]$ should be constant over time (before treatment) as in Fig. 1(b) (see discussion on count data in Section 3.1). Clearly, if such a ratio is approximatelly one, parallelism would be apparent in both graphical representions. This does not invalidate the fact that a given model is more appropriate than another because of the nature of the outcome. In any case, strict parallelism (before treatment) is valid when we look at $h(\mathrm{E}[Y(T)|G = 0,\boldsymbol{X}])$ and $h(\mathrm{E}[Y(T)|G = 1,\boldsymbol{X}])$, instead of $\mathrm{E}[Y(T)|G = 0,\boldsymbol{X}]$ and $\mathrm{E}[Y(T)|G = 1,\boldsymbol{X}]$. So, in order to assess the validity of the *diff-in-diff* method for different models and data structures, care must be taken when analyzing the graphs of $\mathrm{E}[Y(T)|G,\boldsymbol{X}]$ along time. Although the assumption [A5'] is not testable, from an empirical point of view, we can assess this assumption through the graph of the inverse of the link function calculated at the empirical average of Y per treatment group over time.

It is worth noting that another approach called Changes-in-Changes (CiC) to generalize the *diff-in-diff* method was proposed by Athey and Imbens [7]. Although similar in certain aspects, they differ on fundamental points. Unlike the method discussed in this article, which is based on a change in the original scale of Y (and its counterfactual counterparts) in terms of a link function applied to its expected value conditioned in G and X, the CiC method is based on a function of (U,T), where U represents all the variables other than T, so that $Y^0 = h(U,T)$. Athey and Imbens [7] discuss their method for continuous and discrete cases, but in the discrete case, they only allow finite support (which does not include, for example, count data as considered here). In addition, both approaches differ in the definition and interpretation of the causal effect. In this work, we understand that the way in which the causal effect can be expressed is naturally induced by the type of data and underlying model, so that (1) is not always the most appropriate measure. Regarding Lechner [34], although he makes use of link functions, the context in which such functions arise is different when compared to our article. Indeed, in Lechner [34], ATT is defined in terms of a latent variable, which is used as a proxy for the outcome, whereas we do not need this device. In our view, this makes our approach simpler in practice. Moreover, we discuss the *diff-in-diff* methodology in a context that includes nonlinear statistical models such as those in the GLM class, while such a relationship is not explicit in Lechner [34]. We also generalize the notion of ATT in order to make it sufficiently flexible for different applications. Particularly, this point is illustrated when we explicitly present the expressions of causal metrics in widely used probabilistic models and their relationship with risk measures frequently used in epidemiology (relative risk and odds ratio) in Section 3.1. Furthermore, we briefly mention the possibility of expanding the approach to semiparametric models, such as



(a) Identity link: $h = \text{id}$.



(b) Log link: $h = \log$.

Figure 1: Relative behavior of $\mathrm{E}[Y(T)|G, \boldsymbol{X}]$ over time for different link functions.

GAM, and also discuss issues about inference and sensitivity analysis in Section 4. Finally, we illustrate our method with applications to real data in Sections 5 and 6.

3.1 Causal measures in epidemiology

The definition of causal measures involving counterfactual contrasts might encompass a number of traditionally used association measures between outcome and exposure [23]. In Epidemiology, a first group of measures is defined as differences, such as differences in prevalences for categorical responses, attributable risk or differences of incidence for counts, and differences of means (such as in (1)) for continuous outcomes. A second group of measures is based on ratios, including relative risk, prevalence ratio and odds ratio for categorical or count outcomes; and correlation coefficient for continuous variables. Among the most important and main criteria for causality attribution in observational studies are the relative risk (RR) and incidence ratio for cohort studies. When the study design is cross-sectional or case-control, the RR is, respectively, replaced by the prevalence ratio (PR) and by the odds ratio (OR). In particular, the OR approximates the RR under specific conditions, such as the rarity of the disease [26]. As usual, the estimation of these measures in observational studies must take into account other study variables acting as confounders, mediators or effect modifiers [37]. Depending on the type of the response (*e.g.* continuous, categorical or counts), different regression models are adopted (linear, logistic or Poisson/Negative Binomial). Interestingly, these models induce commonly used association measures such as risk differences in linear models, risk ratios using Poisson or Negative Binomial models, prevalence ratios or odds ratios using logistic regression, and hazard ratios for time-to-event outcomes, in survival models [52, 23, 49]. In the next subsections we define a causal rate ratio and a causal odds ratio as particular cases of the GATT using Poisson and logistic regression models. Other particular cases encompassing probit, Gamma and Normal Inverse models are presented in Appendix D.

3.1.1 Causal risk ratio for count data

Let $Y \geq 0$ be the number of observed events and consider $P(Y = 0) < 1$. Let $\mathrm{E}[Y(T)|G, \boldsymbol{X}] = \mu$ and take the logarithmic (canonical) link function, so that the predictor is determined by $h(\mu) = \log \mu$. Hence, from (2), the treatment effect in terms of counterfactuals can be expressed as

$$\begin{aligned} \text{GATT} = e^{\tau} &= \frac{\mathrm{E}[Y^1(1)|G = 1, \boldsymbol{X}]}{\mathrm{E}[Y^0(1)|G = 1, \boldsymbol{X}]} \\ &= \mathrm{RR}\left([Y^1(1)|G = 1, \boldsymbol{X}]; [Y^0(1)|G = 1, \boldsymbol{X}]\right), \end{aligned} \tag{4}$$

where $\mathrm{RR}\left([Y^i(T)|G, \boldsymbol{X}]; [Y^j(T)|G', \boldsymbol{X}]\right)$ stands for the risk ratio between $Y^i(T)$ (in group G) and $Y^j(T)$ (in group G') with covariates $\boldsymbol{X}$. In this case, assumption [A5'] states that *the risk ratio variation associated to the potential outcomes is invariant with respect to variations in treatment groups, i.e.*

$$\frac{\mathrm{E}[Y^0(1)|G = 1, \boldsymbol{X}]/\,\mathrm{E}[Y^0(0)|G = 1, \boldsymbol{X}]}{\mathrm{E}[Y^0(1)|G = 0, \boldsymbol{X}]/\,\mathrm{E}[Y^0(0)|G = 0, \boldsymbol{X}]} = 1.$$

Moreover, from (10) in Appendix B, the effect is identified, in terms of observed outcomes, by $\text{GATT} = \{\mathrm{E}[Y(1)|G = 1, \boldsymbol{x}]/\,\mathrm{E}[Y(0)|G = 1, \boldsymbol{X}]\}/\{\mathrm{E}[Y(1)|G = 0, \boldsymbol{x}]/\,\mathrm{E}[Y(0)|G = 0, \boldsymbol{X}]\}$, referred to as a multiplicative interaction measure [51]. In particular, considering the log-linear model

$$\log \mathrm{E}[Y(T)|G, \boldsymbol{X}] = \alpha + \varphi T + \gamma G + \tau I + \theta(\boldsymbol{X}),$$

the treatment effect is identified by τ. For instance, if $Y(T)|G, \boldsymbol{X}$ is Poisson or Negative Binomial, standard tools from Generalized Linear Models (GLM) can be used to estimate the effect $\hat{\tau} = \log \widehat{RR}$ or, directly as in (4), the $\widehat{\text{GATT}} = e^{\hat{\tau}}$, an estimated risk ratio.

3.1.2 Causal odds ratio for binary data

Let Y be a binary variable and take the logit (canonical) link function, so that $h(\mu) = \operatorname{logit} \mu = \log(\mu/(1-\mu))$, $0 < \mu < 1$. In this case, from (2) we have

$$\begin{aligned} \tau &= \operatorname{logit}(\mathrm{E}[Y^1(1)|G = 1, \boldsymbol{X}]) - \operatorname{logit}(\mathrm{E}[Y^0(1)|G = 1, \boldsymbol{X}]) \\ &= \log \mathrm{OR}\left([Y^1(1)|G = 1, \boldsymbol{X}]; [Y^0(1)|G = 1, \boldsymbol{X}]\right), \end{aligned}$$

where $\mathrm{OR}\left([Y^i(T)|G, \boldsymbol{X}]; [Y^j(T)|G', \boldsymbol{X}]\right)$ stands for the odds ratio between $Y^i(T)$ (in group G) and $Y^j(T)$ (in group G') with covariates $\boldsymbol{X}$. Put differently, it is reasonable to let

the generalized effect on the treated for binary data be

$$\begin{aligned}\text{GATT} &= e^{\tau} \\ &= \text{OR}\left([Y^1(1)|G=1,\boldsymbol{X}];[Y^0(1)|G=1,\boldsymbol{X}]\right)\end{aligned} \tag{5}$$

i.e., GATT expresses the OR defined by the comparison of the odds of the event using potential outcomes. Assumption [A5'] now states that *the odds ratio variation associated to the potential outcomes is invariant with respect to group allocation, i.e.*

$$\begin{aligned}&\text{OR}([Y^0(1)|G=1,\boldsymbol{X}];[Y^0(1)|G=0,\boldsymbol{X}]) \\ &\quad = \text{OR}([Y^0(0)|G=1,\boldsymbol{X}];[Y^0(0)|G=0,\boldsymbol{X}]).\end{aligned}$$

From (10) in Appendix B, the identification formula, in terms of observed outcomes, is given by $\text{GATT} = \frac{\text{OR}([Y(1)|G=1,\boldsymbol{X}];[Y(0)|G=1,\boldsymbol{X}])}{\text{OR}([Y(1)|G=0,\boldsymbol{X}];[Y(0)|G=0,\boldsymbol{X}])}$, and if

$$\text{logit}\,\text{E}[Y(T)|G,\boldsymbol{X}] = \alpha + \varphi T + \gamma G + \tau I + \theta(\boldsymbol{X}),$$

the treatment effect is identified by τ. Particularly, if $Y(T)|G,\boldsymbol{X}$ is Bernoulli or Binomial, then standard tools from GLM can be used to get the estimate $\widehat{\text{GATT}} = e^{\hat{\tau}} = \widehat{OR}$.

4. SOME NOTES ON EXTENSIONS, INFERENCE AND SENSITIVITY ANALYSIS

If $\theta(\boldsymbol{x}) = \boldsymbol{\theta}^{\top}\boldsymbol{x}$, then one can test whether the effect τ is null through the likelihood ratio test by comparing models with and without interaction. If L_o denotes the likelihoods with $\tau_o = 0$ and L the full likelihood, then $-2\log(L_o/L) \overset{a}{\sim} \chi^2_1$ is the test statistic. Alternatively, one could rely on the Wald statistic $W = \widehat{\tau}^2/\text{Var}_{\infty}(\widehat{\tau})$, where $\text{Var}_{\infty}(\widehat{\tau})$ is the asymptotic variance of $\widehat{\tau}$ extracted from the inverse of Fisher's information matrix. Particularly, one can use the fact that $\widehat{\tau} \overset{a}{\sim} \mathcal{N}(\tau, \text{Var}_{\infty}(\widehat{\tau}))$ to construct a confidence interval for the causal effect. On the other hand, if the GATT is a transformation of τ, say $\psi(\tau)$, such as in (4) or (5), we can apply the delta method to obtain its asymptotic distribution $\widehat{\tau} = \psi(\widehat{\tau}) \overset{a}{\sim} \mathcal{N}(\psi(\tau), \psi'(\tau)^2\,\text{Var}_{\infty}(\widehat{\tau}))$. For instance, for count and binary data, the asymptotic distribution of the causal risk ratio is determined by considering $\psi(\tau) = e^{\tau}$, so that the asymptotic variance is given by $e^{2\tau}\,\text{Var}_{\infty}(\widehat{\tau})$. Another issue that deserves attention is the assumption of independence of the observations. Here we considered the use of fixed effects models to appropriately estimate the covariance matrix. Another common approach could be applied by including a random effect in the model, which can lead us directly to the class of mixed generalized linear models (GLMM). More specifically, if $h\left(\text{E}[Y(T)|G,\boldsymbol{X},\boldsymbol{U}]\right) = \alpha + \varphi T + \gamma G + \tau_o I + \theta(\boldsymbol{X}) + \boldsymbol{U}$, where $\boldsymbol{U}$ refers to the random effect, then the same type of argument used at the end of Appendix B, but now conditioning the expectation of Y also on the random effect factor, leads us to the same conclusion as before. That is, τ_o correctly identifies the causal effect GATT) when using GLMM's. In the particular case where $\theta(\boldsymbol{x}) = \boldsymbol{\theta}^{\top}\boldsymbol{x}$ and $\boldsymbol{U} = \boldsymbol{\xi}^{\top}\boldsymbol{Z}$ (i.e. $\boldsymbol{\xi}$ is the random effect and $\boldsymbol{Z}$ some design matrix), we can again use Wald's statistic W (with asymptotic variance adjusted by virtue of the random effect) to test $H_o : \tau_o = 0$ as well as to construct the corresponding confidence interval. Finally, the influence of the covariates $\boldsymbol{X}$ on Y doesn't need to be linear, as indicated in Appendix B. The fact that θ is unknown, in turn, does not render the analysis unfeasible. For example, if each covariate contributes additively to Y, i.e. if $\theta(\boldsymbol{X}) = \theta_1(X_1) + \cdots + \theta_p(X_p)$, one could use a semiparametric generalized additive model (GAM) with a partially linear predictor. In this case, the parameters and functions of interest can be estimated by using the Backfitting algorithm as described in [30].

Next, we briefly discuss sensitivity analysis, *i.e.* how sensitive are the causal estimates to the corresponding assumptions, in our case [A1] – [A5']. We focus particularly on [A5'] because the estimation of the causal effect as defined by (2) differs from that obtained by the classic *diff-in-diff* method essentially through [A5']. Therefore, the relevant question is to know what happens when such assumption fails. To do so, assume that

$$\begin{aligned}&h(\text{E}[Y^0(1)|G=1,\boldsymbol{X}]) - h(\text{E}[Y^0(0)|G=1,\boldsymbol{X}]) \\ &= h(\text{E}[Y^0(1)|G=0,\boldsymbol{X}]) - h(\text{E}[Y^0(0)|G=0,\boldsymbol{X}]) + h(\rho(\boldsymbol{X})).\end{aligned}$$

for some $\rho(\boldsymbol{X})$ in the same scale as $\text{E}[Y^j(T)|G,\boldsymbol{X}]$. In this case, by following the sames steps as in Appendix B, if $\tau(\boldsymbol{X})$ is the estimated effect then the true causal effect is related to τ by $\tau^*(\boldsymbol{X}) = \tau(\boldsymbol{X}) - h(\rho(\boldsymbol{X}))$, so that $h(\rho(\boldsymbol{X}))$ represents the causal effect bias by wrongly assuming [A5']. On the other hand, if [$A5'$] is true, then clearly $h(\rho(\boldsymbol{X})) = 0$ and $\tau^*(\boldsymbol{X}) = \tau(\boldsymbol{X})$. We illustrate this by considering the Poisson and Binomial distributions. In the Poisson case, $\rho(\boldsymbol{X})$ would act multiplicatively on the counterfactual risk ratios, so that

$$\frac{\text{E}[Y^0(1)|G=1,\boldsymbol{X}]}{\text{E}[Y^0(0)|G=1,\boldsymbol{X}]} = \frac{\text{E}[Y^0(1)|G=0,\boldsymbol{X}]}{\text{E}[Y^0(0)|G=0,\boldsymbol{X}]} \times \rho(\boldsymbol{X}).$$

The true and estimated generalized average treatment effect are then related according to the expression $\text{GATT}(\boldsymbol{X}) = \text{GATT}^*(\boldsymbol{X}) \times \rho(\boldsymbol{X})$, so that the estimated effect will underestimate (or overestimate) the actual effect if $\rho(\boldsymbol{X}) < 1$ (or $\rho(\boldsymbol{X}) > 1$). In the Binomial case, on the other hand,

$$\frac{\text{OR}(\text{E}[Y^0(1)|G=1,\boldsymbol{X}];\text{E}[Y^0(0)|G=1,\boldsymbol{X}])}{\text{OR}(\text{E}[Y^0(1)|G=0,\boldsymbol{X}];\text{E}[Y^0(0)|G=0,\boldsymbol{X}])} = \frac{\rho(\boldsymbol{X})}{1-\rho(\boldsymbol{X})},$$

so that [A5'] is satisfied only if $\rho(\boldsymbol{X}) = 1/2$. The relation between the true and estimated generalized average treatment effect is given by $\text{GATT}(\boldsymbol{X}) = \text{GATT}^*(\boldsymbol{X}) \times \frac{\rho(\boldsymbol{X})}{1-\rho(\boldsymbol{X})}$, so that the estimated effect will underestimate (or overestimate) the actual effect if $\rho(\boldsymbol{X}) < 1/2$ (or $\rho(\boldsymbol{X}) > 1/2$). Since ρ is not identifiable through the data only, it cannot

be estimated. However, this factor can still be used in practice to contrast the estimated causal effect with the possible effects that would be obtained for different values of ρ in a pre-specified range.

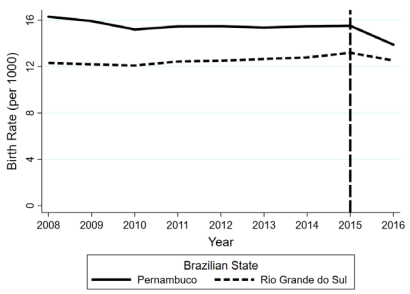
5. ZIKA EPIDEMIC AND BIRTH RATES

In this first application we analyze the demographic impacts of Zika virus (ZIKV) (an arbovirus) outbreak in Brazil, reported in early 2015. We could think of the ZIKV outbreak as a natural experiment, an event which affected some areas and did not affect others. Although it does not constitute a classical intervention, it is quite localized in time and the corresponding variation in exposure can be used to evaluate the impact on health or other outcomes of interest by using proper methodological approaches.

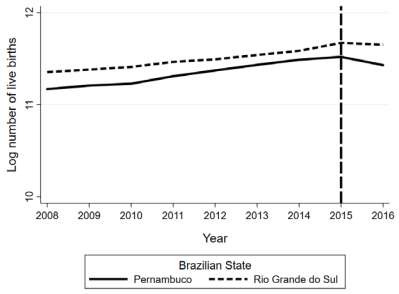
It is known that a change in microcephaly pattern was detected in Brazil in 2015. Among all cases that occurred before November of that year, 65% of them were detected in the state of Pernambuco (PE), located in the northeastern region of Brazil. At the same time, no cases were reported in some other states, among them, the Brazilian southernmost state Rio Grande do Sul (RS). The presence of the Zika virus (ZIKV) genome in the amniotic fluid of pregnant women was confirmed in 18 different states in 2015. Even without the establishment of a causal relationship between ZIKV infection and the occurrence of microcephaly, the Brazilian Ministry of Health declared a state of health emergency in November 2015 and defined several actions to combat the disease vector (*Aedes aegypti*), such as the development of disease surveillance protocols and attention to pregnant women and children, as well as the promotion of research and development of strategies against Zika virus and its associated syndromes. In February 2016, the World Health Organization declared Zika epidemic to be a Public Health Emergency of International Concern [55]. Accordingly, several studies have been conducted since then and many evidences have been accumulated regarding the causal link between ZIKV and complications at birth, termed as congenital zika syndrome (CZS), including microcephaly [11, 22, 41]. As a consequence, it was reported a decline in births due to the postponement of pregnancy and an increase of abortions due to ZIKV outbreak in many Brazilian states [20, 13].

In order to further provide evidence for the impact of ZIKV epidemic on the number of live births in Brazil, we analyzed time series of annual births extracted from administrative databases regarding 682 municipalities during the period from 2008 to 2016 in two Brazilian states: PE (Northeast, $n = 185$ municipalities), where the epidemic was more severe, as the treatment group; and RS (South, $n = 497$ municipalities), as control group. RS was virtually unharmed by Zika and is also spatially very distant from PE, avoiding spillover effects. It is important to note that clear national guidelines have been adopted for suspected cases, for which laboratory tests (serology and RT-PCR) should be performed in addition to specific guidelines for clinical and imaging tests (ultrasound) for pregnant women in prenatal care and for the newborn. Therefore, RS seems to be a valid control since it is located in one of the richest regions of the country and there is no evidence of unidentified suspected cases or low quality in prenatal care. Moreover, several surveillance actions were carried out in the state in compliance with the national surveillance plan. The birth rates varied between 16.3, 15.5 and 13.9 (per 1,000 total population), respectively, in 2008, 2014 and 2016 in PE, while these figures were 12.3, 12.8 and 12.5 (per 1,000) in RS (Figure 2a). The number of live births in PE from mothers with at least 8 years of schooling was 97,607 in 2014 and 92,052 in 2016. In RS, the corresponding numbers, in the original scale, were 107,518 and 114,929 (Figure 2b). It is worth noting that highly educated (high school at least) people in PE and RS correspond, respectively, to 46% and 55% of the population in 2000, according to national census data. Moreover, the number of births and the birth rate in both states evolved similarly until 2015, the year in which the apparent causal connection between Zika's epidemic and microcephaly was noticed. However, in the next year, the number and rate of births declined more sharply in PE than in RS. Particularly, these figures support the common trend assumption [A5']. Clearly, it could be argued that pregnancy decisions could be contaminated by other people's decisions. However, the choice of states (RS and PE) really far from each other, not only geographically but also culturally, and very differently affected in intensity by ZIKV, tends to alleviate the effect of any eventual contamination. Thus, it is reasonable to assume valid SUTVA [A1]. It is reasonable to assume that the occurrence of ZIKV in a distant region (Northeast) would not influence the population of RS so much, which would be feeling more protected from the epidemic, since it had not yet reached the south region. Additionally, even though the epidemic was markedly observed in one of the regions, all municipalities were clearly susceptible to ZIKV outbreak, strengthening assumption [A3]. It should be noticed that, although we did not control for covariates, exogeneity assumption [A2] and no pre-treatment effect assumption [A4] are reasonable since there is no clear indication of any relevance of socioeconomic variables to the relationship between the ZIKV epidemic and the live births counts/rates [13, 20]. As far as the population was not completely aware of the consequences associated to ZIKV outbreak before November 2015, it is also reasonable to assume that no decision concerning pregnancy was related to ZIKV before the outbreak.

To evaluate the impact of ZIKV epidemic on birth rates and number of births from mothers with higher schooling, we used data from one year before (2014) and one year after (2016) the ZIKV outbreak in 2015. The focus was on applying the generalized *diff-in-diff* strategy for estimating causal



(a) Birth rates



(b) Live births among women with higher schooling

Figure 2: Observed birth rates and logarithm of the number of live births among women with at least 8 years of schooling in Pernambuco (solid line) and Rio Grande do Sul (dashed line) in Brazil. 2008–2016 (*Source: SINASC; IBGE*).

Table 2. Zika effect on birth rates and number of births in PE and RS using fixed effect models. Brazil. 2014–2016

Parameter	Birth Rates				Number of births$^{(\star)}$	
	Linear ($h = id$)		Poisson ($h = \log$)		Negative Binomial ($h = \log$)	
	Estimate	95%CI	*Estimate*	95%CI	*Estimate*	95%CI
Interaction parameter ($\hat{\tau}$)	−1.21	(−1.559; −0.855)	−0.09	(−0.097; −0.076)	−0.13	(−0.149; −0.113)
Treatment Effect (GATT)	−1.21	(−1.559; −0.855)	0.92	(0.908; 0.927)	0.88	(0.861; 0.893)

$^{(\star)}$ for mothers with at least 8 years of schooling.

effects related to ZIKV outbreak. We fitted a fixed effects linear model for the birth rates and a fixed effects Poisson model for the number of overall live births considering the total population of each municipality as offset. For the number of live births from mothers with higher schooling, we fitted a fixed effects Negative Binomial (NB) model due to overdispersion. Because the size of the population with at least 8 years of schooling by municipality was not available, we used total population as offset, which could have underestimated the birth rates in the target population. On the other hand, this underestimation should be larger in PE than in RS since schooling rates are higher in RS. Thus, it is reasonable to expect that the actual effect could be even larger than the one reported here.

The results in Table 2 provide further evidence of a major impact of the ZIKV epidemic on birth rates, regardless of the outcome and statistical model. We estimated a reduction of 1.21 (95% ATT: −1.56; −0.85) on the birth rates in the municipalities of the state of PE compared to RS between 2014 and 2016 using the linear model, which is in line of an estimated reduction of about 8% on the rate of births according to the Poisson model (95% RR_{GATT}: 0.91; 0.93). According to residual analysis, both linear and Poisson models fit the birth rates data well, which is exquisite. A slightly higher reduction on the number of births in the municipalities were estimated among mothers with higher schooling (12%) using the NB model (95% RR_{GATT}: 0.86; 0.89), as expected. For the sake of illustration and comparison, we applied the CiC method [7] to this data set. Under the continuous and discrete CiC models, the estimated effects were, respectively, −1.45 (95% CI: −2.31; −0.59) and −1.30 (95% CI: −2.16; −0.44). Bootstrap standard errors were obtained using 1,000 replications. It should be noted that these results compare only to the effect associated to the linear case with the identity link in Table 2. Comparisons with the other scales (Poisson and Binomial Negative) do not apply for the reasons presented in Section 3.

As highlighted in the methodological sections, the conditions for identificability in linear models allow us to interpret the interaction parameter τ as the treatment (ZIKV) effect (ATT), which in turn is the difference of birth rates between municipalities affected and not affected by the outbreak. On the other hand, this interpretation is not true for nonlinear models, such as the Poisson and NB models considered here. In these cases, instead of the "linear" *diff-in-diff* assessment of the intervention effect, τ expresses the difference of the logarithm of the birth rates (4). As seen in Table 2, by wrongly considering the interaction parameter estimate (−0.09) in the Poisson model as the difference of potential responses results in a considerable underestimation of the "linear" effect (−1.21). This last figure, however, is in line with the generalized effect given by relative risk associated to the potential outcomes $\widehat{\text{GATT}} = \widehat{RR} = 0.92$, see Eq. (4). It is interesting that both estimates point to the same direction and also indicate (in their own way) compatible reductions in birth rates in the municipalities between 2014 and 2016. Particularly, it illustrates how the chosen statistical model should drive the choice of the causal effect measure to be used, so that τ can be correctly interpreted as the causal effect.

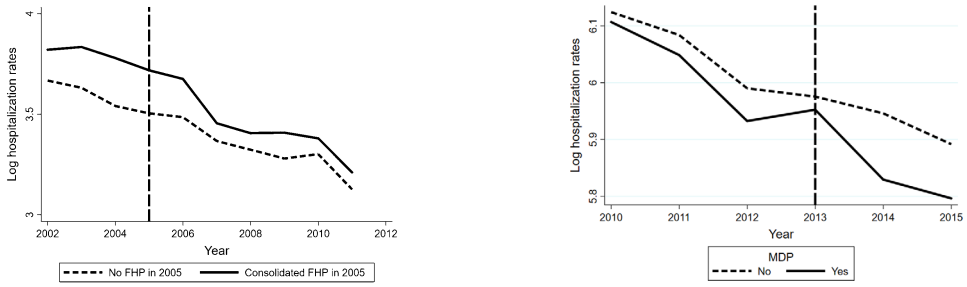
6. PRIMARY HEALTH CARE AND AVOIDABLE HOSPITALIZATIONS

Our aim now is to assess the impact of two interventions in primary health care (PHC) in Brazil, the Family Health Program (FHP) and More Doctors Program (MDP), on the occurrence of avoidable hospitalizations. Since 1994, the reorganization of PHC in Brazil has been carried out through the FHP, a federal policy consisting of several mechanisms including financial incentives for municipalities. Since then, a number of other initiatives has been implemented to foster the improvement of the qualification of professionals connected to FHP teams and the health facilities conditions. In particular, we highlight the creation of the MDP in 2013, by then the largest initiative to combat the shortage of doctors in the country.

It has been argued that, under specific health conditions, many hospitalizations could be avoided due to PHC, which means more prevention, diagnosis and timely treatment. They would reduce the occurrence of diseases, mitigate severity and avoid complications [14]. Hence hospitalizations would occur mainly in rarer and more severe cases beyond the scope of PHC [4]. A list of admissions due to conditions sensitive to primary care (CSPC) based on nineteen diagnostic groups was designed and validated for use in 2008. The dataset used here was from the Hospital Information System of the Unified Health System (SIH-SUS), which uses Hospitalization Authorization (AIH) as records of all government (SUS) funded hospitalizations. In both cases, it is reasonable to state that the CSPC hospitalization in a given municipality does not depend on the implementation of FHP and MDC in another municipality, so that assumption SUTVA [A1] is adequate. Moreover, assumptions [A2] and [A4] are reasonable since we do not expect an interference of those interventions on the observed covariates at baseline as well as any antecipation of the benefit. The covariates for both applications were selected among factors that are associated with the risk of hospitalizations for preventable causes [21, 35, 36]. The socio-demographic and economic conditions of the population are related to the incidence or prevalence of diseases and their complications that can determine the need for hospitalization, while the provision of hospital health services in the municipalities allows to adjust for the difference in access to these services. If these covariates are not controlled for, the analyses might lead to biased estimates.

We start with the impact evaluation of the FHP on hospitalizations due to CSPC among children under 5 years old in 1,427 municipalities. The FHP is based on the principles of integrality, equality and universality of health care, and it relies on the work of multiprofessional teams (physician, nurses, community health workers and dentists). Each team is responsible for the permanent and systematic monitoring of a given number of families in a restricted area by organizing actions of health promotion, prevention and attention to diseases and injuries. Over the last two decades, the FHP has been expanded to become a large-scale policy reaching almost 100% of Brazilian municipalities. Due to this universality, we considered the consolidation of 2005 to assess the impact of the FHP. Municipalities that implemented the FHP before 2000 and maintained high coverage ($\geq$ 70%) until 2005 were defined as members of the intervention group (n = 982), and municipalities that did not implement the FHP until 2005 as the control group (n = 445). We notice that all municipalities were eligible to be included in FHP, as required by assumption [A3]. We compared the hospitalizations of children under 5 years between 2003 (prior to intervention) and 2007 (after intervention) due to conditions sensitive to primary care (Figure 3a). The rate of CSPC hospitalizations varied from 37.8 to 28.9 (per 1,000 children under 5 years) between 2003 and 2007 in municipalities without FHP implementation up to 2005, and from 46.3 to 31.7 in municipalities under the FHP by 2005. We fitted a fixed effects Negative Binomial model for the rate of CSPC hospitalizations among children under 5 years old. The analysis was adjusted by life expectancy at birth, adult illiteracy rate (population aged 15 years and over), proportion of the population below the poverty line, per capita income, Human Development Index (HDI) and hospital beds rate. Data sources were the Brazilian Demographic Census (for all variables, but last) and the register of health establishments of the Ministry of Health. For comparison, we also fitted a Binomial model (logistic regression for aggregated data). Under the Negative Binomial model, it was found a statistically significant reduction of 12% (95% CI $\text{RR}_{\text{GATT}} = 0.81; 0.95$) on the CSPC hospitalization rates between 2003 and 2007 (Table 3). Similar reduction was observed using the logistic fixed effects model ($\widehat{\text{OR}}_{\text{GATT}} = 0.85$, 95% CI $\text{OR}_{\text{GATT}} = 0.83; 0.87$). In this case, the causal OR_{GATT} approximates well the causal RR_{GATT} due to the rarity of the events (around 40 per 1.000) and because we are modeling the proportion of hospitalizations for children under 5 years using the binomial model for aggregated data. Nevertheless, we were able to illustrate the estimation of causal OR_{GATT} using this data.

Finally, we have also assessed the impact of MDP on hospitalizations due to CSPC in elderly population (60–74-year-olds) in Brazilian northeast. The MDP was based on three strategic axes: 1) training for SUS, with investments in the creation of more medical training courses; 2) expansion and improvement of the infrastructure of the health basic units (UBS); and 3) emergency relief with Brazilian and foreign physicians. One of the main goals of MDP is the attraction and fixation of physicians to FHP teams in remote or vulnerable areas, helping to expand access to PHC, so that the priority areas for MDP were those less likely to attract qualified professionals. Eligibility criteria were essentially: high percentage of the population living in extreme poverty; low human development or very poor regions; semi-arid and Amazon region; areas with indige-



(a) < 5 years old in Brazil (b) $60 - 74$ years old in the Northeastern Region of Brazil

Figure 3: Hospitalization rates (in log scale) due to CSPC in younger than 5-year-olds and in 60–74-year-olds. (*Source: SIH/SUS*).

Table 3. Primary health care intervention effects on hospitalizations due to CSPC in Brazil

Parameter	FHP Effect in < 5-year-olds (2003–2007)		MDP Effect in $60 - 74$-year-olds (2011–2015)	
	Negative Binomial ($h = \log$) Estimate (95%CI)	Binomial ($h = \text{logit}$) Estimate (95%CI)	Poisson ($h = \log$) Estimate (95%CI)	Negative Binomial ($h = \log$) Estimate (95%CI)
Interaction parameter ($\hat{\tau}$)	-0.13 (-0.209; -0.053)	-0.16 (-0.189; -0.142)	-0.03 (-0.068; 0.008)	-0.05 (-0.138; 0.046)
Treatment Effect (GATT)	0.88 (0.811; 0.949)	0.85 (0.827; 0.867)	0.97 (0.934; 1.008)	0.96 (0.871; 1.047)

nous and quilombola populations [10]. To assess the impact of the MDP, we defined the intervention group as municipalities with a proportion of MDP physicians in primary care services greater than 30% during the whole period analyzed (semiannual data from June 2014 to December 2016) and the control group as municipalities with no professionals attached to MDP in the same period (Figure 3b). Since any municipality was able to apply for participation on the MDP, we may consider the assumption [A3] valid. We compared the hospitalizations in 2011 (prior to intervention) to those in 2015 (after intervention) among elderly population living in the 20% poorest municipalities (MDP classification) in Brazilian northeast ($n = 721$ municipalities, being 483 and 238 with and without, respectively, implementation of MDP). The overall number of CSPC hospitalizations was 36,863 and 31,671, respectively, in 2011 and 2015 among 60–74-year-olds. According to the arguments in Section 3 and Figures 3a and 3b, assumption [A5'] for identification of causal effect holds. We fitted fixed effects Poisson and Negative Binomial models for the rate of CSPC hospitalizations among 60–74-year-olds. The covariates in the models were life expectancy at birth, illiteracy rate in older than 15 years, Gini index, average per capita income, percentage of population living in households with running water and sewage, and rate of urbanization from the Brazilian 2010 census. Both models pointed out for a reduction (3%–4%) on the hospitalization rates from CSPC, although not statistically significant. However, overdispersion was detected in the data. Hence results from the Negative Binomial model should be preferred ($\widehat{\text{RR}}_{\text{GATT}} = 0.96$; 95% CI $\text{RR}_{\text{GATT}} = 0.87; 1.05$).

7. DISCUSSION

Social interventions, such as those promoted by governments and international multilateral agencies, usually connected to health, education and social protection, are critical in many societies and are commonly associated with very large investments. Since it is noticeable a rising trend in their implementation, especially in developing countries, in recent decades, the enormous need to assess their impact is clear. But when it comes to large-scale social policies, there are a number of ethical, feasibility and economic issues that prevent the use of experimental designs [38, 39]. On the other hand, many advances have been made in the construction of robust quasi-experimental methodologies that seek to meet the premises of a rigorous impact assessment, or causal effect, of certain interventions. In addition, it is worth noting that quasi-experimental studies have a high level of external validity, are useful in evaluating long-term interventions or which have a long causal chain effect, can be performed using retrospective data, and finally they can be faster and less expensive than actual experiments [9, 12, 31, 33, 42]. The methods described here can also be useful to assess the adverse effects of epidemics, such as ZIKV, which cannot be studied through experimental studies.

However, careful consideration should be given to the nature of the data, the sample design and the statistical model in defining the reported causal effect. The cost of negligence at this point is the underestimation or overestimation of crucial measures in the decision-making process by maintaining, extinguishing, extending or reducing a given intervention. In this paper, we present an extension of the

diff-in-diff method, as also described in [7, 34], and define adequate measures to assess the causal effect (impact) of an intervention in situations where data deviate from the classical structure. We show how the usual conditions associated with the traditional version of the method should be modified to ensure the identifiability of causal effects, which are described in terms of the generalized ATT, or GATT. In addition, we proposed and discussed how the GATT should be defined and interpreted when associated to certain special situations commonly encountered in practice (*e.g.* binary, counting and asymmetric data) and to specific models (logistic, Poisson, Binomial Negative).

To illustrate the proposed methodology, we analyzed data associated with three very relevant health issues in Brazil. That is, we considered the demographic impacts of the 2015 Zika virus outbreak on birth rate and the impact of two interventions on primary health care, namely the Family Health Program and the More Doctors Program, on preventable hospitalizations. In all of them, it is worth mentioning that the sample unit considered is the municipality. Extrapolating the results obtained to the individual level would therefore consist of an ecological fallacy. The results showed that, by using a *diff-in-diff* generalized approach, we were able to adequately evaluate policies (FHP and MDP) and estimate causal impact of events that were not the result of intentional actions (ZIKV outbreak), and are not naturally represented in the interval scale. The results corroborated findings in the literature that described birth trends in Brazil and conjectured about its relationship to ZIKV outbreak [26, 20], but did not directly estimate causal effects. Regarding the FHP, nationwide studies in Brazil have shown its impact on infant and under-five mortality [6], especially on mortality from diarrhea and pneumonia [44] and on the reduction of hospitalizations for causes sensitive to primary care [21]. Even though the previous assessments did not use *diff-in-diff* approach, our analysis confirms the importance of this intervention for various health outcomes in this population, concluding for a significant reduction (12%) of avoidable hospitalizations in children under 5 years-old. The implementation of MDP, on the other hand, had been previous investigated using *diff-in-diff* approach and Propensity Score Matching, alone or in combination [15, 24]. The studies have been shown that MDP is strongly associated with an increase in the number of physicians, the number of medical appointments in all age groups, and prenatal consultations performed by physicians, with reductions on overall hospitalizations and, specifically, due to CSPC, infectious, parasitic and respiratory diseases [24]. However, no evidence was found of its impact on child health as measured by infant mortality (including various causes of death), low birth weight and prematurity [15]. In our study, we did not find evidence of MDP impact on hospitalizations due to conditions sensitive to primary care in a elderly population from the Northeast region of Brazil. Similarly, other study found no evidence of its impact on cause-specific hospitalizations under 1 year and 5 years (diarrhea, respiratory infections, and nutritional problems), nor on the incidence of low birth weight or prenatal care coverage.

We believe that the theoretical framework described here and the evidences of our applications contribute to avoid fallacious interpretations following the noncompliance with assumptions required by the usual *diff-in-diff* approach [2, 34] (as well as the generalized *diff-in-diff*), which has been widely used in quasi-experimental studies for evaluation of public policies [19, 29, 33]. Indeed, as highlighted in the ZIKV application, the use of the same causal metric in models with different specifications can lead to the (under) overestimation of effects. Even worse, it can reverse the direction of the causal relationship. Moreover, thinking in terms of generalized causal effects allows us to consider and attach causal meaning to measures that are well known to practitioners, such as risk differences, relative risks or odds ratios. As a consequence, it can lead to improved interpretations of important relationships [26, 23]. Another (practical) issue that should be highlighted here is the fact that the interaction coefficient in a statistical model can only be interpreted as a causal effect if the causal assumptions of the *diff-in-diff* approach are satisfied. Hence, even though such assumptions can not be always testable, they are fundamental to the identificability of the causal effects, here represented by the ATT or the GATT. In this respect, each of the applications considered here proved, to the best of our knowledge, compatible with the generalized *diff-in-diff* method hypotheses. The reliability of the conclusions, and so the identificability of the causal effects and their interpretation, depends hardly on the validy of the (generalized) *diff-in-diff* assumptions. Unfortunately, such caution is not always observed. For example, even thought Poisson and Negative Binomial models were used to assess the impact of Affordable Care Act (ACA) on the health care expenditures and other measures of interest by means of the *diff-in-diff* approach [19], the causal assumptions were not well established, blurring the causal meaning of the estimated coefficients. Other authors applied Poisson regression in a quasi-experimental *diff-in-diff* study, but interpreted the estimates of the interaction parameter as the difference of the expected potential responses and, again, did not argued for the validity of the *diff-in-diff* assumptions [29].

We have also limited our discussions about GATT to the cases where the potential outcomes refer to only two points in time. However, the usual *diff-in-diff* approach can be extended for more than two time points (panel data). For example, under multilevel or fixed effects modeling, a set of time-period dummies could be added to the model [33, 34]. However, most applications concerning panel data consider the fixed effects linear model [54]. Moreover, in most studies, the intervention is applied in a certain point of time, but time dynamics may play an important role in the process. For instance, it is possible that an intervention changes over time [1]. This data feature can be explicitly defined using the structural nested model [45] and marginal structural

models, which have been extended to a range of outcomes (i.e., dichotomous, survival time, etc). Mediation analysis in a counterfactual causal perspective has also been addressed into impact assessments, allowing complex situations involving nonlinearity, interactions between exposures and mediators, and multiple mediators [51, 18].

In addition the extensions discussed in Section 4, other features for GLM's might be considered for future research in the *diff-in-diff* framework, including zero-inflated and truncated models for counting data, and overdispersion for binomial outcomes. A recent discussion about the use of regression and matching-based estimators in the context of linear models under the *diff-in-diff* framework [53] could be extended in the context of nonlinear models. Moreover, Machine Learning techniques as used in [40] could be extended to assess nonlinear effects under the *diff-in-diff* approach with high-dimensional data.

Although a wide range of methodologies for causal inference are currently available to tackle the complexities of data sampling, and to overcome the intervention dynamics and underlying sophisticated causal mechanisms, the *diff-in-diff* approach is still relevant when estimating ATT, so that a variety of studies can benefit from its generalization, the GATT, presented here. By making use of a causally identifiable and interpretable estimator/metric, researchers can adequately support their findings regarding impact assessment associated to key interventions in different fields.

APPENDIX A

The assumptions [A1]–[A5] below are necessary conditions to identify the effect of interest under the *diff-in-diff* framework.

(A1) *(Stable Unit Treatment Value Assumption – SUTVA)* $Y(T) = IY^1(T) + (1-I)Y^0(T)$.

(A2) *(Exogeneity)* The covariates $\boldsymbol{X}$ are observable and exogoneous, *i.e.* they are not influenced by the treatment assignment mechanism: $\boldsymbol{X}^0 = \boldsymbol{X}^1 = \boldsymbol{X}$.

(A3) *(Treated/Untreated Common Support)* All individuals are eligible for treatment, and, for any $\boldsymbol{X}$, there is a positive probability of remaining untreated (Assumption 3.2. in Abadie [2]): $P(G=1) > 0$ and $P(G=1|\boldsymbol{X}) < 1$.

(A4) *(No Pre-Treatment Effect)* In the treated group and for each stratum defined by $\boldsymbol{X}$, the expected difference of potential responses in the pre-treatment period ($T=0$) is zero, *i.e.*, $\mathrm{E}[Y^1(0) - Y^0(0)|G=1,\boldsymbol{X}] = 0$.

(A5) *(Common Trend Condition)* The expected difference of potential outcomes in a group due to the transition from $T=0$ to $T=1$ is invariant with respect to G (Assumption 3.1. in Abadie [2]): $\mathrm{E}[Y^0(1) - Y^0(0)|G=1,\boldsymbol{X}] - \mathrm{E}[Y^0(1) - Y^0(0)|G=0,\boldsymbol{X}] = 0$.

SUTVA is a classic assumption in the causal literature and refer us to [17]: *"the observation on one unit should be unaffected by the particular assignment of treatments to the other units"*, *i.e.* the responses of other units should not interfere on the response of a given unit to treatment. It also states that *"there are no versions of treatments"* [48].

We also present some important results for the identification of (1), following [A1]–[A5], (see [34], Section 3.2.2.) so that

$$\begin{aligned}\tau(\boldsymbol{x}) = &\big\{\mathrm{E}[Y(1)|G=1,\boldsymbol{x}] - \mathrm{E}[Y(0)|G=1,\boldsymbol{x}]\big\} \\ &- \big\{\mathrm{E}[Y(1)|G=0,\boldsymbol{x}] - \mathrm{E}[Y(0)|G=0,\boldsymbol{x}]\big\}.\end{aligned} \tag{6}$$

In particular, if

$$Y^0(T) = \alpha + \varphi T + \gamma G + \theta(\boldsymbol{X}) + \varepsilon, \tag{7}$$

where ε stands for an exogenous error with $\mathrm{E}[\varepsilon|\boldsymbol{X}] = 0$ and there is a constant τ_o such that $Y^1(T) - Y^0(T) \equiv \tau_o$, then

$$Y^1(T) = Y^0(T) + \tau_o = \alpha + \varphi T + \gamma G + \tau_o + \theta(\boldsymbol{X}) + \varepsilon.$$

It is worth noting that, since T and G are binary, the right side in (7) is equivalent to the semiparametric formulation $\alpha + \varphi(T) + \gamma(G) + \theta(\boldsymbol{X}) + \varepsilon$, where φ and γ are (unknown) functions. Since an individual is effectively exposed to treatment only if $I=1$ (*i.e.* if $T=G=1$), then

$$\begin{aligned}Y(T) &= Y^0(T) + I(Y^1(T) - Y^0(T)) \\ &= \alpha + \varphi T + \gamma G + \tau_o I + \theta(\boldsymbol{X}) + \varepsilon.\end{aligned} \tag{8}$$

Assuming $\varepsilon \perp\!\!\!\perp T, G|\boldsymbol{X}$, we have

$$\begin{aligned}
\mathrm{E}[Y(1)|G=1,\boldsymbol{X}] &= \alpha + \varphi \times 1 + \gamma \times 1 + \tau_o + \theta(\boldsymbol{X}), \\
\mathrm{E}[Y(0)|G=1,\boldsymbol{X}] &= \alpha + \varphi \times 0 + \gamma \times 1 + \quad + \theta(\boldsymbol{X}), \\
\mathrm{E}[Y(1)|G=0,\boldsymbol{X}] &= \alpha + \varphi \times 1 + \gamma \times 0 + \quad + \theta(\boldsymbol{X}), \\
\mathrm{E}[Y(0)|G=0,\boldsymbol{X}] &= \alpha + \varphi \times 0 + \gamma \times 0 + \quad + \theta(\boldsymbol{X}),
\end{aligned}$$

so that

$$\begin{aligned}\tau_o = &\mathrm{E}[Y(1) - Y(0)|G=1,\boldsymbol{X}] \\ &- \mathrm{E}[Y(1) - Y(0)|G=0,\boldsymbol{X}].\end{aligned} \tag{9}$$

We are using here the notation $\mathrm{E}[Y(t)|G=g,\boldsymbol{X}] = \mathrm{E}[Y(T)|T=t,G=g,\boldsymbol{X}]$. In other words, if (8) holds, then τ_o stands for treatment effect and it can be estimated by regressing Y_i on the associated covariates [33].

If (8) does not hold, nonlinear models such as the logit, probit, log-linear or even semiparametric [2] ones should be taken into account, affecting the potential expectations $\mathrm{E}[Y^g(T)|G,\boldsymbol{X}]$, $g \in \{0,1\}$.

APPENDIX B

Here we present some results for the identicability of $\tau = \tau(\boldsymbol{X})$ for nonlinear models under assumption [A5']. Using

SUTVA, $\mathrm{E}[Y^g(1)|G=g,\boldsymbol{X}]=\mathrm{E}[Y(1)|G=g,\boldsymbol{X}]$, we get

$$\begin{aligned}\tau &= h\left(\mathrm{E}[Y^1(1)|G=1,\boldsymbol{X}]\right)-h\left(\mathrm{E}[Y^0(1)|G=1,\boldsymbol{X}]\right)\\ &= h\left(\mathrm{E}[Y(1)|G=1,\boldsymbol{X}]\right)-h\left(\mathrm{E}[Y^0(0)|G=1,\boldsymbol{X}]\right)\\ &\quad -h\left(\mathrm{E}[Y^0(1)|G=0,\boldsymbol{X}]\right)+h\left(\mathrm{E}[Y^0(0)|G=0,\boldsymbol{X}]\right)\\ &= h\left(\mathrm{E}[Y(1)|G=1,\boldsymbol{X}]\right)-h\left(\mathrm{E}[Y^0(0)|G=1,\boldsymbol{X}]\right)\\ &\quad -h\left(\mathrm{E}[Y(1)|G=0,\boldsymbol{X}]\right)+h\left(\mathrm{E}[Y(0)|G=0,\boldsymbol{X}]\right).\end{aligned}$$

Hence, from [A4] we get the generalized identification formula in terms of the transformed expectations

$$\begin{aligned}\tau &= \{h\left(\mathrm{E}[Y(1)|G=1,\boldsymbol{X}]\right)-h\left(\mathrm{E}[Y(0)|G=1,\boldsymbol{X}]\right)\}\\ &\quad -\{h\left(\mathrm{E}[Y(1)|G=0,\boldsymbol{X}]\right)-h\left(\mathrm{E}[Y(0)|G=0,\boldsymbol{X}]\right)\}.\end{aligned}\tag{10}$$

Clearly, (6) and (10) agree when h is the identity link function.

Now, if $h\left(\mathrm{E}[Y^1(T)|G,\boldsymbol{X}]\right)-h\left(\mathrm{E}[Y^0(T)|G,\boldsymbol{X}]\right)\equiv\tau_o$ is the same for all individuals, then from (2) and

$$h\left(\mathrm{E}[Y^0(T)|G,\boldsymbol{X}]\right)=\alpha+\varphi T+\gamma G+\theta(\boldsymbol{X}),$$

it follows that

$$h\left(\mathrm{E}[Y^1(T)|G,\boldsymbol{X}]\right)=\alpha+\varphi T+\tau_o+\gamma G+\theta(\boldsymbol{X}).$$

From SUTVA again,

$$\begin{aligned}h\left(\mathrm{E}[Y(T)|G,\boldsymbol{X}]\right) &= (1-I)h\left(\mathrm{E}[Y^0(T)|G,\boldsymbol{X}]\right)\\ &\quad +Ih\left(\mathrm{E}[Y^1(T)|G,\boldsymbol{X}]\right),\end{aligned}$$

so that

$$h\left(\mathrm{E}[Y(T)|G,\boldsymbol{X}]\right)=\alpha+\varphi T+\tau_o I+\gamma G+\theta(\boldsymbol{X}),$$

and

$$\begin{aligned}h\left(\mathrm{E}[Y(1)|G=1,\boldsymbol{X}]\right)&=\alpha+\varphi+\gamma+\tau_o+\theta(\boldsymbol{X}),\\ h\left(\mathrm{E}[Y(0)|G=1,\boldsymbol{X}]\right)&=\alpha+0+\gamma+\quad+\theta(\boldsymbol{X}),\\ h\left(\mathrm{E}[Y(1)|G=0,\boldsymbol{X}]\right)&=\alpha+\varphi+0+\quad+\theta(\boldsymbol{X}),\\ h\left(\mathrm{E}[Y(0)|G=0,\boldsymbol{X}]\right)&=\alpha+0+0+\quad+\theta(\boldsymbol{X}).\end{aligned}$$

Hence,

$$\begin{aligned}\tau_o &= \{h\left(\mathrm{E}[Y(1)|G=1,\boldsymbol{X}]\right)-h\left(\mathrm{E}[Y(0)|G=1,\boldsymbol{X}]\right)\}\\ &\quad -\{h\left(\mathrm{E}[Y(1)|G=0,\boldsymbol{X}]\right)-h\left(\mathrm{E}[Y(0)|G=0,\boldsymbol{X}]\right)\},\end{aligned}$$

As noted in the argument above, there is no impediment to consider time-varying $\boldsymbol{X}$. In these cases, the expression for the causal effect is simply given by

$$\begin{aligned}\tau_o &= \{h\left(\mathrm{E}[Y(1)|G=1,\boldsymbol{X}(1)]\right)-h\left(\mathrm{E}[Y(0)|G=1,\boldsymbol{X}(0)]\right)\}\\ &\quad -\{h\left(\mathrm{E}[Y(1)|G=0,\boldsymbol{X}(1)]\right)-h\left(\mathrm{E}[Y(0)|G=0,\boldsymbol{X}(0)]\right)\}.\end{aligned}$$

APPENDIX C

If (i) $h\left(\mathrm{E}[Y(T)|G,\boldsymbol{X}]\right)$ is linear with respect to T, G and I and (ii) we wrongly treat φ as group invariant (when it is actually equal to φ_0 for $G=0$ and to $\varphi_1=\varphi_0+\kappa$ for $G=1$), then the estimated causal effect is biased by κ. Indeed, the estimated τ is actually an estimate of

$$\begin{aligned}&\{h\left(\mathrm{E}[Y(1)|G=1,\boldsymbol{X}(1)]\right)-h\left(\mathrm{E}[Y(0)|G=1,\boldsymbol{X}(0)]\right)\}\\ &\quad -\{h\left(\mathrm{E}[Y(1)|G=0,\boldsymbol{X}(1)]\right)-h\left(\mathrm{E}[Y(0)|G=0,\boldsymbol{X}(0)]\right)\}.\end{aligned}$$

Hence, using the fact that $\varphi_1=\varphi_0+\kappa$ when $G=1$, we can easily see that such a difference is equal $\tau_o+\kappa$.

APPENDIX D

A common link function in the econometric literature associated to binary data is connected to probit models. It is particularly compelling if there are reasons to accept that the response is such that $Y=\mathbf{1}(\tilde{Y}>0)$, where $\tilde{Y}$ is a latent variable satisfying $\tilde{Y}=\alpha+\varphi T+\tau I+\gamma G+\theta^\top\boldsymbol{x}+\varepsilon$ and $\varepsilon\sim\mathcal{N}(0,\sigma^2)$. If this is true then Y is a binary response with $h=\Phi^{-1}(\mu)$. From (2), the treatment effect τ is such that

$$\tau(\boldsymbol{x})=\Phi^{-1}\left(\mathrm{E}[Y^1(1)|G=1,\boldsymbol{x}]\right)-\Phi^{-1}\left(\mathrm{E}[Y^0(1)|G=1,\boldsymbol{x}]\right).$$

Including the linear predictor, we have

$$\Phi^{-1}\left(\mu[T;\boldsymbol{X},G]\right)=\alpha+\varphi T+\tau_o I+\gamma G+\theta^\top\boldsymbol{x},$$

and the effect is simply identified by τ_o. These expressions suggest that it might be more suitable to consider $\zeta=\Phi(\tau)$ as a proxy for the treatment effect. ζ is a standardized value between 0 and 1, so that the closer it is to 1, the stronger is the treatment effect in relation to the control. Conversely, the closer it is to 0, the stronger is the effect of no treatment/control on the response. ζ close to 0.5, indicates no effect. Actually, this behavior is typical for bijective links $h:[0,1]\to\mathbb{R}$ (except for the value 0.5).

On the other hand, if Y is a positive random variable following, for example, a Gamma or Inverse Gaussian distribution, one could choose (though not necessarily) a link function different from the identity. In this case, we must review the interpretation of the interaction parameter. If considering the Gamma distribution, the usual choices for the link function are the logarithmic and reciprocal. In the first (and more usual) case, we can use e^τ, interpreted as the risk ratio (4), to measure the causal effect. If considering the reciprocal link, $h=\mu^{-1}$, then

$$\tau(\boldsymbol{x})=\frac{1}{\mathrm{E}[Y^1(1)|G=1,\boldsymbol{x}]}-\frac{1}{\mathrm{E}[Y^0(1)|G=1,\boldsymbol{x}]}.$$

It is interesting to notice that a negative (positive) τ means an increase (decrease) in the treatment effect on Y. Hence, in this case, it could be more appropriate to use $\mathrm{GATT}=-\tau$ as a measure of the treatment effect on the response. Again,

the treatment effect can be infered by using standard GLM tools.

Similarly, it is also usual to model asymetric responses by using the Inverse Gaussian distribution, particularly using the logarithm link function. However, the canonical link in this case is the squared reciprocal, $h(\mu) = \mu^{-2}$, so that

$$\tau(\boldsymbol{x}) = \frac{1}{\mathrm{E}[Y^1(1)|G=1,\boldsymbol{x}]^2} - \frac{1}{\mathrm{E}[Y^0(1)|G=1,\boldsymbol{x}]^2}.$$

Similar to the Gamma distribution with reciprocal link function, a negative (positive) τ means an increase (decrease) in the treatment effect on Y, so that, again, we could use GATT $= -\tau$ as a measure of the treatment effect.

DATA AVAILABILITY STATEMENT

Data sharing is applicable to this article. Software syntax for the analyses is also provided. Supplementary data to this article can be found online at https://dataverse.harvard.edu/dataverse/Causal.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES

[1] Aalen, O., Roysland, K. and Gran, J. (2012). Causality, mediation and time: a dynamic viewpoint. *Journal of the Royal Statistical Society* **175** 831–861. MR2993496

[2] Abadie, A. (2005). Semiparametric Difference-in-Difference estimators. *The Review of Economic Studies* **72** 1–19. MR2116973

[3] Ai, C. and Norton, E. (2003) Interaction terms in logit and probit models. *Economic Letters* **80** 123–129.

[4] Alfradique, M., Bonolo, P. and Dourado, I. et al. (2009). Internações por condições sensíveis à atenção primária: a construção da lista brasileira como ferramenta para medir o desempenho do sistema de saúde (Projeto ICSAP – Brasil). *Cadernos de Saúde Pública* **25** 1337–1349.

[5] Angrist, J., Imbens, G. and Rubin, D. (1996). Identification of causal effects using instrumental variables. *Journal of the American Statistical Association* **91** 444–455.

[6] Aquino, R., Oliveira, N. and Barreto, M. (2008). Impact of the Family Health Program on Infant Mortality in Brazilian Municipalities. *American Journal of Public Health.* **99** 87–93.

[7] Athey, S. and Imbens G. (2006). Identification and inference in nonlinear difference-in-difference models. *Econometrica* **74** 431–497. MR2207397

[8] Austin, P. (2011) An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behavioral Research* **46** 399–424.

[9] Barreto M. Invited Commentary on Quasi-Experiments: Going Beyond the Observational and Experimental Dichotomy in Epidemiological Study Design. *Current Epidemiology Reports* 2016 (3):259–261.

[10] Brasil (2015). Programa mais médicos – dois anos: mais saúde para os brasileiros. *Ministério da Saúde, Secretaria de Gestão do Trabalho e da Educação na Saúde.* Available from: http://maismedicos.gov.br/images/PDF/Livro_2_Anos_Mais_Medicos_Ministerio_da_Saude_2015.pdf.

[11] Brito, C. (2015) Zika virus: A new chapter in the history of medicine. *Acta Medica Portugues.* **28** 679–680.

[12] Cameron, D., Mishra, A. and Brown, A. (2016). The growth of impact evaluation for international development: how much have we learned?. *Journal of Development Effectiveness* **8** 1–21. doi: https://doi.org/10.1080/19439342.2015.1034156.

[13] Castro, M., Han, Q., Carvalho, L., Victora, C. and França, G. (2018). Implications of Zika virus and congenital Zika syndrome for the number of live births in Brazil. *Proceedings of the National Academy of Sciences of the United States of America* **115** 6177–6182.

[14] Caminal-Homar, J. and Casanova-Matutano, C. (2003) La evaluación de la atención primaria y las hospitalizaciones por ambulatory care sensitive conditions. Marco conceptual. *Aten Primaria* **31** 61–65.

[15] Carrillo, B. and Feres, J. (2017). More doctors, better health? Evidence from a physician distribution policy. *University of York, Health, Econometrics and Data Group, WP 17/29.* Available at http://www.york.ac.uk/economics/postgrad/herc/hedg/wps/.

[16] Chen, H., Li, Q., Kaufman, J., Wang, J., Copes, R., Su, Y. and Benmarhnia, T. (2018) Effect of air quality alerts on human health: a regression discontinuity analysis in Toronto, Canada. *Lancet Planet Health* **2** e19–e26.

[17] Cox, D. (1958). *Planning of Experiments.* New York: John Wiley & Sons. MR0095561

[18] Daniel, R., De Stavola, B., Cousens S. and Vansteelandt S. (2015). Causal mediation analysis with multiple mediators. *Biometric* **71** 1–14. MR3335344

[19] Deb, P. and Norton, E. (2018). Modeling Health Care Expenditures and Use. *Annual Review of Public Health* **39** 489–505.

[20] Diaz-Quijano, F., Pelissani, D. and Chiavegatto Filho, A. (2018). Zika-associated microcephaly epidemic and birth rate reductions in Brazilian cities. *American Journal of Public Health* **108** 514–516.

[21] Dourado, I., Veneza, B. and Oliveira, M. *et al* (2011). Trends in Primary Health Care-sensitive Conditions in Brazil. The Role of the Family Health Program (Project ICSAP-Brazil). *Medical Care* **49** 577–584.

[22] Faria, N., Azevedo, R. and Kramer, M. *et al* (2016). Zika virus in the Americas: Early epidemiological and genetic findings. *Science* **352** 345–349.

[23] Flanders, W. and Klein M. (2015). A General, Multivariate Definition of Causal Effects in Epidemiology. *Epidemiology* **26** 481–489.

[24] Fontes, L., Conceição, O. and Jacinto, P. (2018). Evaluating the impact of physicians' provision on primary healthcare: evidence from Brazil's More Doctors Program. *Health Economics* **27** 1284–1299.

[25] Gray, E., Marti, J., Brewster, D., Wyatt, J., Piaget-Rossel, R. and Hall P. (2019). Real-world evidence was feasible for estimating effectiveness of chemotherapy in breast cancer: a cohort study. *Journal of Clinical Epidemiology* **109** 125–132.

[26] Greenland, S. (1987). Interpretation and choice of effect measures in epidemiologic analyses. *American Journal of Epidemiology* **125** 761–768.

[27] Greenland, S., Pearl, J. and Robins, J. (1999). Causal diagrams for epidemiologic research. *Epidemiology* **1** 37–48.

[28] Hamad, R., Nguyen, T., Bhattacharya, J., Glymour, M. and Rehkopf, D. (2019). Educational attainment and cardiovascular disease in the United States: A quasi-experimental instrumental variables analysis. *PLoS Medicine* **16** e1002834.
[29] Hanchate, A., Kapoor, A., Katz, J. *et al.* (2015). Massachusetts health reform and disparities in joint replacement use: difference in differences study. *BMJ* **350:h440** 1–10.
[30] Hastie, T., Tibshirani, R. and Friedman, J. (2009). *The Elements of Statistical Learning: Data Mining, Inference and Prediction.* New York: Springer. MR2722294
[31] Holland, P. (1999). Statistics and causal inference. *Journal of the American Statistical Association* **81** 945–960. MR0867618
[32] Imbens, G. and Lemieux, T. (2008). Regression discontinuity designs: a guide to practice. *Journal of Econometrics* **142** 615–635. MR2416821
[33] Imbens, G. and Wooldridge, J. (2009). Recent developments in the econometrics of program evaluation. *Journal of Economic Literature* **47** 5–86.
[34] Lechner, M. (2010). The estimation of causal effects by Difference-in-Difference methods. *Foundations and Trends® in Econometrics* **4** 165–224.
[35] Lumme, S., Manderbacka, K., Arffman, M., Karvonen, S. and Keskimaki, I. (2020). Cumulative social disadvantage and hospitalisations due to ambulatory care-sensitive conditions in Finland in 2011–2013: a register study. *BMJ Open* **10(8)** e038338.
[36] Macinko, J., Dourado, I., Bonolo, P., Aquino, R., Lima-Costa, M., Medina, M., Mota, E., Oliveira, B. and Turci, M. (2010). Major expansion of primary care in Brazil linked to decline in unnecessary hospitalization. *Health Affairs* **29** 2149–2160.
[37] MacKinnon, D. (2008). *Introduction to Mediation Analysis.* New York, NY: Erlbaum.
[38] Meyer, B. (1995). Natural and quasi-experiments in economics. *Journal of Business and Economic Statistics* **13** 151–161.
[39] Morgan, S. and Winship, C. (2007). *Counterfactuals and Causal Inference: Methods and Principles for Social Research.* New York, NY: Cambridge University Press.
[40] Ning, Y., Peng, S. and Tao, J. (2020). Doubly robust semiparametric difference-in-difference estimators with high-dimensional data. In: https://github.com/psdsam/HDdiffindiff.
[41] de Oliveira, C. and da Costa Vasconcelos P. (2016). Microcephaly and Zika virus. *Journal of Pediatric* **92** 103–105.
[42] Pearl, J. (2009). *Causality: models, reasoning, and inference.* New York, NY: Cambridge University Press, 2nd edition. MR2548166
[43] Puhani, P. (2012). The treatment effect, the cross difference, and the interaction term in nonlinear "difference-in-difference" models. *Economic Letters* **115** 85–87. MR2878767
[44] Rasella, D., Aquino, R. and Barreto, M. (2010). Reducing childhood mortality from diarrhea and lower respiratory tract infections in Brazil. *Pediatrics* **126** e534.
[45] Robins, J. and Rotnitzky, A. (2004). Estimation of treatment effects in randomized trials with non-compliance and a dichotomous outcome using structured mean models. *Biometrika* **91** 763–783. MR2126032
[46] Rocha, R. and Soares, R. (2010). Evaluating the impact of community-based health interventions: evidence from Brazil's Family Health Program. *Health Economics* **19** 126–158.
[47] Rubin, D. (1974). Estimating causal effects of treatments in randomized and nonrandomized studies. *Journal of Educational Psychology* **66** 688–701.
[48] Rubin, D. (1980). Randomization analysis of experimental data: the fisher randomization test: comment. *Journal of the American Statistical Association* **75** 591–593.
[49] Sjolander, A. (2018). Estimation of causal effect measures with the R-package stdReg. *European Journal of Epidemiology* **33** 847–858.
[50] Staplin, N., Herrington, W., Judge, P. et al. (2017). Use of causal diagrams to inform the design and interpretation of observational studies: an example from the study of heart and renal protection (SHARP). *Clin J Am Soc Nephrol* **12** 546–552.
[51] VanderWeele, T. (2015). *Explanation in Causal Inference: Methods for Mediation and Interaction.* New York: Oxford University Press.
[52] Xu, Y., Cheung, Y., Lam, K., Tan, S. and Milligan, P. (2010). Simple approach to the estimation of incidence rate difference. *American Journal of Epidemiology* **172** 334–343.
[53] Zeldow, B. and Hatfield, L. (2021). Confounding and regression adjustment in difference-in-differences studies. *Health Serv Res.* 1–10. doi: https://doi.org/10.1111/1475-6773.13666.
[54] Zhou, H., Taber, C., Arcone, S. and Li, Y. (2016). Difference-in-difference method in comparative effectiveness research: utility with unbalanced groups. *Applied Health Economic and Health Policy* **14** 419–429.
[55] WHO (2016). An R&D blueprint for action to prevent epidemics. Plan of Action Geneva.

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