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**A Negative Control Outcome Regression Accounting for Unobserved Confounding and
Lagged Causal Effects**

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Abstract

Background: Epidemiologists are increasingly interested in using negative controls to eliminate unobserved confounding. Particularly, difference-in-differences method, which uses pre-exposure outcomes as negative control outcomes, is widely used. However, it obtains biased estimations when pre-exposure outcome has lagged causal effect on post-exposure outcome.

Methods: Taking advantage of pre-exposure outcomes as negative control outcomes, Negative Control Outcome Regression (NCOR) is proposed to eliminate unobserved confounding. The intercept term of NCOR provides an unbiased causal effect estimate of exposure on post-exposure outcome, and the slope minus 1 denotes the lagged causal effect estimation of pre-exposure outcome on post-exposure outcome. We then illustrate the potential of NCOR in a challenging application to estimate the causal association of PM_{2.5} on all-cause mortality rates (AMR) and lagged causal effect of pre AMR on post AMR.

Results: Both theoretical justifications and simulation studies validate that the causal effect of exposure on outcome, along with the lagged causal effect of outcomes are identifiable and can be estimated by proposed NCOR model. The application results demonstrate that the previously estimated association between PM_{2.5} and AMR can be attributed to the unobserved confounding. Furthermore, the NCOR model reveal that pre AMR has no causal association with post AMR.

Conclusion: The proposed NCOR model can obtain unbiased and robust causal effect estimation of exposure on outcome, and the lagged causal effect of outcomes. The proposed NCOR is implemented as an R package, called NCOR, and is freely available on GitHub.

Key words: Negative Control Outcome Regression; Unobserved Confounding; Weighted Linear Regression Model; Lagged Causal Effects

Background

Unobserved confounding is a well-known threat to identify and estimate the causal effects, and it is rarely avoided with certainty in observational studies [1, 2]. The use of negative controls to detect or eliminate unobserved confounding has gained increasing acceptance and popularity [3-5]. In general, a variable that is related to the unobserved confounding factors but not causally affected by the observed exposure is called negative control outcome [6-8]. Similarly, a negative control exposure is associated with the unobserved confounding factors, but it does not causally affect the interested outcome [6-8]. Remarkably, a proper negative control exposure or outcome needs to share common confounding mechanisms with the exposure or outcome variables. Difference-in-differences (DID) is typically quasi-experimental design to estimate the causal effect by comparing the changes in outcomes over time between two different groups [9-12]. As a matter of fact, DID method uses the pre-exposure outcomes as the negative control outcomes [9]. The approach is most commonly used when pre- and post-exposure outcome measurements are available, and one can assume that the association of the unobserved confounder with the outcome is equal in the two exposure groups, and constant over time [10-12]. However, it obtains biased estimations when pre-exposure outcome has lagged causal effect on post-exposure outcome.

Studies that used negative controls to detect potential confounding can be traced back to Rosenbaum who detected the potential confounders using an auxiliary outcome [13]. In epidemiological studies, Lipsitch et al. tested the unmeasured confounding, selection and measurement biases using negative control variables [4]. Recently, the use of negative control methods for correcting the confounding bias has been popularized instead of merely detecting the unmeasured confounding. Tchetgen et al proposed the outcome calibration method that regarded the counterfactual primary outcome as the proxy variable of unmeasured confounders [5]. In addition, Schuemie et al. developed an empirical null distribution of treatment effect via

a collection of negative controls to correct the p-value [14]. Sofer et al. interpreted the DID method as a negative outcome control approach through a monotonicity hypothesis of the unmeasured confounding effects [9]. However, it needs a strict assumption that pre-exposure outcome has no lagged causal effect on post-exposure outcome [9]. Using both negative control exposure and outcome variables under certain completeness conditions, Miao et al. proposed practical inference methods for identifying and inferencing the bridge function and the average causal effect [6]. Moreover, Shi et al. identified the average treatment effect through nonparametric estimation under weaker conditions when the unmeasured confounding and negative control variables were categorical [15]. They also proposed multiply robust and locally efficient estimators when nonparametric estimation may not be feasible [15]. Recently, Shi et al. reviewed the existing negative control methods including the detection, reduction, and correction for confounding bias, and further provided practical guidance on the use of negative control methods in epidemiology [16]. In the time-series studies, Flanders et al. partially corrected the residual confounding by using a future exposure as a negative control exposure [17]. However, future exposure worked as a surrogate for unobserved confounders, hence, it cannot obtain unbiased causal effect estimation [17]. The authors further proposed a bias reduction method for linear and log-linear time-series models through a negative control exposure, but this method required prior knowledge of the association between the confounder and negative control exposure [18]. Using both past and future exposures as multiple negative control exposures, Miao et al. extend Flanders' method to identify and estimate the causal effect in the time-series setting [19]. Recently, Yu et al proposed a negative control exposure based on a time-series study model to effectively eliminate unobserved confounders using post-outcome exposure as a negative control exposure ²⁰.

In this study, following the idea of meta-regression, we propose a negative control outcome regression (NCOR) approach to accurately estimate the causal effect of exposure on the future

outcome using only a pre-exposure outcome. Both theoretical proofs and simulation studies are performed to validate the effectiveness of NCOR. Furthermore, we illustrate the potential of the NCOR to estimate the causal association of PM_{2.5} with the all-cause mortality rates (AMRs). In addition, we also provide an R package that can be used by the research community to implement the NCOR model, which is freely available on GitHub (<https://github.com/yuyy-shandong/NCOR>).

Methods

Difference-in-difference model

DID model is most commonly used when pre- and post-exposure outcome can be observed. The causal effect can be estimated by comparing the changes in outcomes over time between two different groups. Figure 1(a) illustrates a visual representation of DID model. The outcome $Y(t)$ is measured at 2 occasions, $t = 0, 1$ with $Y(0)$ and $Y(1)$ pre- and post-exposure outcome, respectively. X represents the exposure. In addition, we assume that confounders (represented by a single variable U) are unknown.

Assumption 1(a). (Linear additive structural model)

$$E\{Y(1)|U, X\} = \alpha_0 + c_0X + c_3U ;$$

Assumption 2(a). (No reverse causality)

$$Y(0) \perp X | U ;$$

Assumption 3(a). (Parallel trend assumption)

$$c_1 = c_3 ,$$

where c_1 is the effect of unobserved confounder (U) on pre-exposure outcome ($Y(0)$) and c_3 is the effect of unobserved confounder (U) on post-exposure outcome ($Y(1)$).

For Assumption 1(a), a simple causal model supposes that $Y(t)$ follows the simple linear model, which is depend on exposure (X) and unmeasured confounders (U). Assumption 2(a)

represents that $Y(0)$ does not affect future exposure X , and the future exposure X does not affect pre-exposure outcome $Y(0)$, reflected by the absence of arrow between $Y(0)$ and X . For assumption 3(a), the association of the unobserved confounder with the outcome is assumed equal across exposure groups and constant over time.

Under the assumption as above[9, 11], the formula $\frac{\partial E(Y(1)|X)}{\partial X} - \frac{\partial E(Y(0)|X)}{\partial X}$ can be used to estimate the causal effect of exposure on post-exposure outcomes.

However, the biased causal effect estimation can be obtained when the pre-exposure outcome has effect on the post-exposure outcome. In order to account for unobserved confounding and lagged causal effects, we proposed a novel method, NCOR, which can accurately estimate the causal effect of exposure on the future outcome, and the lagged causal effect of pre-exposure outcome on the post-exposure outcome.

Negative Control Outcome Regression Model

Figure 1(b) illustrates a visual representation of the NCOR model. Let $Y(0)$ and $Y(1)$ denote observed pre- and post- exposure outcome at time $t=0$ and $t=1$, respectively. X is an exposure and U denotes a set of confounders that considers all confounding effects between Y and X . Let $U(0), U(1/2), U(1)$ denote the unmeasured confounding factors at times $t = 0, 1/2, 1$, respectively. We are interested in estimating the causal effect of X on $Y(1)$ and the lagged causal effect of $Y(0)$ on $Y(1)$. Using the $do(x)$ operator of Pearl and linear additive structural model [21-24], the causal effect of X on $Y(1)$ can be expressed as c_0 and the lagged causal effect of $Y(0)$ on $Y(1)$ can be expressed as δ .

We consider that J independent studies from different areas of spatial or research centers. For each participant i in the j -th ($j=1, L, J$) study, a pre-exposure outcome $Y(0)_{i,j}$, an exposure ($X_{i,j}$), and a post-exposure outcome ($Y(1)_{i,j}$) can be observed.

Model Assumptions

Assumption 1(b). (Linear additive structural model),

For each study j , $E\{Y(1)_j | U(1)_j, X_j, Y(0)_j\} = \alpha_{0,j} + c_0 X_j + c_{3,j} U(1)_j + \delta Y(0)_j$;

Assumption 2(b). (No reverse causality assumption)

For each study j , $Y(0)_j \perp X_j | U(0)_j$;

Assumption 3(b). (Parallel trend assumption)

For each study j , $c_{1,j} = c_{3,j}$ and

$U(0)_j, U(1/2)_j, U(1)_j$ satisfy the stationary time series with fixed variance;

Assumption 4. (Fixed causal effect assumption)

For multiple studies, the causal effect (c_0) of X on $Y(1)$ and the lagged causal effect (δ) of $Y(0)$ on $Y(1)$ are fixed;

Assumption 5. (Random effect assumption)

For each study j , $c_{1,j} \xrightarrow{\text{i.i.d.}} F_1(c_1), r_{1,j} \xrightarrow{\text{i.i.d.}} F_2(r_1), c_{2,j} \xrightarrow{\text{i.i.d.}} F_3(c_2)$.

Comparing with Assumption 1(a), Assumption 1(b) allows for the lagged causal effect of $Y(0)$ on $Y(1)$. Similarly with Assumption 2(a), Assumption 2(b) means that $Y(0)_j$ does not affect future exposure X_j , and the future exposure X_j does not affect pre-exposure outcome $Y(0)_j$ for each study j . Assumption 3(b) implies that the effects of confounders U on the outcome Y do not change over time for each study j . For example, it is understandable that the effect of socioeconomic status on the mortality in 2014 is same as that in 2015. The unmeasured confounding factors in DID model are single variables and do not change over time, Assumption 3(b) assumes that the unmeasured confounders (U) is a stationary autoregressive process with a fixed auto-correlation coefficient (i.e. the effect of $U(0)_j$ on $U(1/2)_j$ is the same as the effect of $U(1/2)_j$ on $U(1)_j$, $r_{1,j} = r_{2,j}$) and fixed variance

($\sigma_{U(0)}^2 = \sigma_{U(1/2)}^2 = \sigma_{U(1)}^2$) for each study j . In order to satisfy assumptions 3(b), we prefer that the time points of $Y(0)$ and $Y(1)$ are symmetrical with respect to those of X .

Theorem. Under Assumptions 1(b)-3(b), 4, 5, the causal effect of X on $Y(1)$ and the lagged causal effect of $Y(0)$ on $Y(1)$ can be identified and estimated by the following weighted regression based on J independent studies.

$$\beta_1 = \kappa_0 + \kappa_1 \beta_0 + \varepsilon \quad \varepsilon \sim N(0, \Sigma)$$

$$\Sigma = \text{diag}(se(\beta_{1,1})^2, se(\beta_{1,2})^2, \dots, se(\beta_{1,J})^2)$$

where $\beta_1 = (\beta_{1,1}, \beta_{1,2}, \dots, \beta_{1,J})^T$, $\beta_0 = (\beta_{0,1}, \beta_{0,2}, \dots, \beta_{0,J})^T$. For each study j , $\beta_{1,j}$ can be estimated by the linear regression $\mathbf{Y}(\mathbf{1})_j = \alpha_{1,j} + \beta_{1,j} \mathbf{X}_j + \varepsilon_{1,j}$, $\varepsilon_{1,j} \sim N(0, \sigma_{1,j}^2)$. And $\beta_{0,j}$ can be estimated by the linear regression $\mathbf{Y}(\mathbf{0})_j = \alpha_{0,j} + \beta_{0,j} \mathbf{X}_j + \varepsilon_{2,j}$, $\varepsilon_{2,j} \sim N(0, \sigma_{2,j}^2)$. This model performs NCOR, a special case of the general method of meta-regression [25, 26]. Then, the causal effect of X on $Y(1)$ can be identified and estimated by the intercept term $\hat{\kappa}_0$. The lagged causal effect from $Y(0)$ to $Y(1)$ can be estimated by $\hat{\kappa}_1 - 1$.

Based on a weighted linear regression model with the residual term following a normal distribution Σ [27-30], the estimator for κ_0 is

$$\hat{\kappa}_0 = \frac{\left\{ \mathbf{I}_J - \beta_0 (\beta_0^T \Sigma^{-1} \beta_0)^{-1} (\beta_0^T \Sigma^{-1} \mathbf{I}_J) \right\}^T \Sigma^{-1} \beta_1}{\left\{ \mathbf{I}_J - \beta_0 (\beta_0^T \Sigma^{-1} \beta_0)^{-1} (\beta_0^T \Sigma^{-1} \mathbf{I}_J) \right\}^T \Sigma^{-1} \mathbf{I}_J},$$

and the estimator for κ_1 is

$$\hat{\kappa}_1 = \frac{\left\{ \beta_0 - \mathbf{I}_J (\mathbf{I}_J^T \Sigma^{-1} \mathbf{I}_J)^{-1} \mathbf{I}_J^T \Sigma^{-1} \beta_0 \right\}^T \Sigma^{-1} \beta_1}{\left\{ \beta_0 - \mathbf{I}_J (\mathbf{I}_J^T \Sigma^{-1} \mathbf{I}_J)^{-1} \mathbf{I}_J^T \Sigma^{-1} \beta_0 \right\}^T \Sigma^{-1} \beta_0}.$$

The proof for NCOR is shown in Web Appendix 1 in Supplementary Material. More details

about the sensitivity analysis for Assumptions violated are provided in Web Appendix 2 in Supplementary Material.

Sample size calculation

To implement the NCOR method, we provide a formula to calculate the number of studies (J) and sample size of each study (n_j). The number of studies (J) required for level α and power

π is $J = \max(n_{\kappa_0}, n_{\kappa_1})$, where $n_{\kappa_0} = \frac{[\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(\pi)]^2 \sigma(\kappa_0)^2}{\kappa_0^2} + 1$ and

$n_{\kappa_1} = \frac{[\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(\pi)]^2 \sigma(\kappa_1)^2}{(\kappa_1 - 1)^2} + 1$. The sample size of each study (n_j) required for level

α and power π is $n_j = \max(n_{1,j}, n_{2,j})$, where $n_{1,j} = \frac{[\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(\pi)]^2 \sigma(\beta_{1,j})^2}{\beta_{1,j}^2} + 1$

and $n_{2,j} = \frac{[\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(\pi)]^2 \sigma(\beta_{0,j})^2}{\beta_{0,j}^2} + 1$. More details about the sample size calculation

are provided in Web Appendix 3 in Supplementary Material.

Simulation

To further investigate the statistical potential of the NCOR model, we perform a series of simulation studies with the artificial data of J studies under realistic conditions. For each study, the simulated data is generated as follows.

$$U(0, 1/2, 1) \sim N \left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{bmatrix} 1 & r & r^2 \\ r & 1 & r \\ r^2 & r & 1 \end{bmatrix} \right);$$

$$Y(0) = c_1 U(0) + \varepsilon_1, \quad \varepsilon_1 \sim N(0, \sigma_{\varepsilon_1}^2);$$

$$X = c_2 U(1/2) + \varepsilon_2, \quad \varepsilon_2 \sim N(0, \sigma_{\varepsilon_2}^2);$$

$$Y(1) = c_0 X + c_3 U(1) + \delta Y(0) + \varepsilon_3, \quad \varepsilon_3 \sim N(0, \sigma_{\varepsilon_3}^2);$$

$$c_2 \sim N(p_2, \sigma_{c_2}^2); \quad c_1 = c_3 \sim N(p_1, \sigma_{c_1}^2).$$

To evaluate the performances of NCOR model, five methods including the linear regression model conditional on the surrogate of unmeasured confounders (i.e., the pre-exposure outcome) (LR-SU model), fixed-effect meta-analysis based on the LR-SU model (LR-SU-Meta model), DID model, fixed-effect meta-analysis based on the DID model (DID-Meta model) and NCOR model are used to estimate the causal effect of X on $Y(1)$. The details of these models are as follows:

- i) LR-SU model: $\mathbf{y}(\mathbf{1}) = \lambda_0 + \lambda_1 \mathbf{x} + \lambda_2 \mathbf{y}(\mathbf{0}) + \varepsilon_\lambda$ for all data, where λ_1 stands for the association between X and $Y(1)$ after partial correction for unmeasured confounders;
- ii) LR-SU-Meta model: For each study j , we have $\mathbf{y}(\mathbf{1})_j = \lambda_{0,j} + \lambda_{1,j} \mathbf{x}_j + \lambda_{2,j} \mathbf{y}(\mathbf{0})_j + \varepsilon_{\lambda,j}$. A fixed-effect meta-analysis is used to estimate the association between X and $Y(1)$;
- iii) DID model: $\mathbf{y}(\mathbf{1}) - \mathbf{y}(\mathbf{0}) = \eta_0 + \eta_1 \mathbf{x} + \varepsilon_\eta$ for all data, where η_1 is the causal effect estimation of X on $Y(1)$;
- iv) DID-Meta model: For each study j , we have $\mathbf{y}(\mathbf{1})_j - \mathbf{y}(\mathbf{0})_j = \eta_{0,j} + \eta_{1,j} \mathbf{x}_j + \varepsilon_{\eta,j}$. A fixed effect meta-analysis is used to estimate the causal effect of X on $Y(1)$;

$$\text{v) NCOR model: } \hat{\kappa}_0 = \frac{\left\{ \mathbf{I}_J - \beta_0 \left(\beta_0^T \Sigma^{-1} \beta_0 \right)^{-1} \left(\beta_0^T \Sigma^{-1} \mathbf{I}_J \right) \right\}^T \Sigma^{-1} \beta_1}{\left\{ \mathbf{I}_J - \beta_0 \left(\beta_0^T \Sigma^{-1} \beta_0 \right)^{-1} \left(\beta_0^T \Sigma^{-1} \mathbf{I}_J \right) \right\}^T \Sigma^{-1} \mathbf{I}_J},$$

where $\beta_1 = (\beta_{1,1}, \beta_{1,2}, \dots, \beta_{1,J})^T$, $\beta_0 = (\beta_{0,1}, \beta_{0,2}, \dots, \beta_{0,J})^T$.

In addition, a linear regression model after adjusting for the observed confounders (LR-AC model), fixed effect meta-analysis based on the LR-AC model (Meta-LR-AC model), NCOR model are used to estimate the lagged causal effect of $Y(0)$ on $Y(1)$.

- i) LR-AC model: $\mathbf{y}(\mathbf{1}) = \lambda_0 + \lambda_1 \mathbf{x} + \lambda_2 \mathbf{y}(\mathbf{0}) + \varepsilon_\lambda$ for all data, where λ_2 stands for the association after adjusting for the observed confounders;
- ii) Meta-LR-AC model: For any study or time series fragment j , we have

$\mathbf{y}(\mathbf{1})_j = \lambda_{0,j} + \lambda_{1,j}\mathbf{x}_j + \lambda_{2,j}\mathbf{y}(\mathbf{0})_j + \varepsilon_{\lambda,j}$. Then, the fixed-effect model is used to estimate the effects of $Y(0)$ on $Y(1)$;

$$\text{iii) NCOR model: } \hat{\kappa}_1 - 1 = \frac{\left\{ \beta_0 - I_J \left(I_J^T \Sigma^{-1} I_J \right)^{-1} I_J^T \Sigma^{-1} \beta_0 \right\}^T \Sigma^{-1} \beta_1}{\left\{ \beta_0 - I_J \left(I_J^T \Sigma^{-1} I_J \right)^{-1} I_J^T \Sigma^{-1} \beta_0 \right\}^T \Sigma^{-1} \beta_0} - 1.$$

In the first simulation study, we compare the biases, standard errors (SEs) and mean square errors (MSEs) of these models under different sample sizes, effect parameters and number of studies with 1000 simulation repetitions. In the second simulation study, the type I error rates and statistical power are used to evaluate the stability and power of the NCOR model when varying across the number of studies. The type I error rate occurs when the test rejects a null hypothesis that is actually true. The statistical power is defined as the probability that the test correctly rejects the null hypothesis when the alternative hypothesis is true. In the third simulation, we evaluate the sensitivity of the NCOR estimator by relaxing Assumption 2(b) and 3(b), respectively. For relaxed Assumption 2(b) (Web Figure 1 in Supplementary Material), we compare biases, SEs and MSEs of these models when varying across the effect of $Y(0)$ on X with other parameters fixed. For Assumption 3(b), we do three sensitivity analyses. i) we change the size of $\omega = c_3 - c_1$ from 0 to 1 to observe the biases, SEs, and MSEs of these models. ii) we consider another model structures for the unmeasured confounder to observe the performance of the NCOR model (Web Figure 2 in Supplementary Material).

$$U(1/2) = \gamma_1 U(0) + \varepsilon_{u2} \quad \varepsilon_{u2} \sim N(0, \sigma_u^2 - \gamma_1^2)$$

$$U(1) = \gamma_2 U(1/2) + \gamma_3 U(0) + \varepsilon_{u2} \quad \varepsilon_{u2} \sim N(0, \sigma_u^2 - \text{var}(\gamma_2 U(1/2) + \gamma_3 U(0)))$$

iii) we change the size of $\eta = r_2 - r_1$ to observe the difference of η on the causal effect estimation of X on $Y(1)$ and the lagged causal effect estimation of $Y(0)$ on $Y(1)$ via the proposed NCOR model. The R language is used to conduct the statistical simulations.

Application

To illustrate the NCOR model in epidemiology studies, we assess the potential causal effect of fine particulate matter (PM_{2.5}) on the AMR and the lagged causal effect of AMR. Data for county-level PM_{2.5} are derived from the Health Effects Institute 2019, State of Global Air 2019 (<https://www.stateofglobalair.org/data/air/table>). PM_{2.5} is defined as fine particles with an aerodynamic diameter of less than or equal to 2.5µm. The adult mortality rate (probability of dying between 15 and 60 years per 1000 population) for each country is extracted from World Health Organization (<https://www.who.int/data/gho>).

Evidence from cohort studies indicate an association between increased AMR and long-term exposure to fine PM_{2.5} pollution at reasonably low concentrations (<30 µg/m³) [31-33]. However, ruling out confounding factors remains a great challenge. Web Figure 3 in Supplementary Material shows the realistic causal diagram of PM_{2.5} and AMR. PM_{2.5} represents the exposure in *year* (from 2010 to 2015). AMR_{pre} and AMR_{post} are all-cause adult mortality rates in *year* - 1 and *year* + 1, respectively. $U(0), U(1/2), U(1)$ represent unmeasured or unobserved confounders. Potential confounders in time series studies are time-varying variables such as complex climatological, atmospheric processes, volatile organic compounds, baseline and NOx emissions are known to vary spatially and have strong associations with PM_{2.5} and AMR, however, they are often unmeasured [34-36]. We divide 183 countries into six studies according to the continent. To demonstrate the potential of the NCOR model, LR-SU, LR-SU-Meta, DID, DID-Meta and NCOR model are used to study the causal effect of PM_{2.5} on AMR in the population worldwide. LR-AC, LR-AC-Meta and NCOR model are used to estimate the lagged causal effect of AMR_{pre} on AMR_{post}.

Results

Simulation results

As for the causal effect of X on $Y(1)$, our simulation results (Figure 2 and Web Figure 4-8 in Supplementary Material) demonstrate that in comparison to the LR-SU, LR-SU-Meta, DID

and DID-Meta model, which show substantial biases, the NCOR model can get almost unbiased causal effect estimates. Furthermore, the SEs and MSEs of NCOR model are generally smaller than those of other models. Figure 2a illustrates that NCOR model can obtain unbiased causal effect estimations of X on $Y(1)$ as the number of studies increases. Furthermore, among the four models (LR-SU, LR-SU-Meta, DID and DID-Meta) that show significant biases, DID and DID-Meta methods have less biases than LR-SU and LR-SU-Meta models. Figure 2b illustrates that the NCOR model achieve the highest precision among all models, followed by DID, LR-SU, DID-Meta, and LR-SU-Meta model. In addition, the MSEs of the proposed NCOR model perform better than the other models (Figure 2c). Robust performances of the NCOR model are also observed when varying across the effect of U on X , $U(0)$ on $Y(0)$, X on $Y(1)$ and sample size, respectively (Web Figure 4-7 in Supplementary Material, respectively). Specifically, when varying across the effect of $Y(0)$ on $Y(1)$ (δ) with other parameters fixed (Web Figure 8 in Supplementary Material), the classical DID model and DID-Meta model could obtain unbiased causal effect estimations in the case of $\delta = 0$, that is, there is no lag effect of the pre-exposure outcome on the future outcome. Moreover, the biases monotonically increase with δ increasing.

Figure 3 indicates the type I error rates and statistical power of the NCOR model with the increasing number of studies. The rejection rates of the causal null hypothesis are controlled at a nominal 5% level for the NCOR models. In addition, the statistic power monotonically increases with the number of studies increasing.

Sensitivity analysis which relaxes Assumptions 2(b), 3(b) is performed to examine the robustness of NCOR model. When Assumption 2(b) is not satisfied ($Y(0)$ has effect on X), the SEs of NCOR model increase with the effect of $Y(0)$ on X increasing, however, biases and MSEs are lower than those of other models (Web Figure 9 in Supplementary Material). When Assumption 3(b) is violated, Web Figure 10-12 in Supplementary Material shows that the SEs

and MSEs of the NCOR model are lower than those of other models with accepted biases.

For the lagged causal effect of $Y(0)$ on $Y(1)$, the simulation results (Web Figure 13-18 in Supplementary Material) indicate that NCOR model show unbiased causal effect estimations, whereas the LR-AC and LR-AC-Meta models show conspicuous biased estimations. The SEs and MSEs of the NCOR model are generally smaller than those of the other three models. Web Figure 19 in Supplementary Material reveals that type I error rates for NCOR model remain nominal ($\alpha = 0.05$). Furthermore, the power of the NCOR model monotonically increases with increasing numbers of studies. When Assumption 2(b) is not satisfied, the biased estimation of $Y(0)$ on $Y(1)$ can be observed when it varies across the effect of $Y(0)$ on X (Web Figure 20 in Supplementary Material). When Assumption 3(b) is violated, the biases of NCOR model are lower than those of other models with acceptance SEs and MSEs (Web Figure 21-23 in Supplementary Material).

Application results

Previous studies showed that the number of deaths is positively associated with high levels of $PM_{2.5}$ [37-41]. Table 1 shows the causal effect estimations and the 95%CI of $PM_{2.5}$ on AMR through LR-SU, LR-SU-Meta, DID, DID-Meta, and NCOR models. LR model shows that the higher $PM_{2.5}$ leads to higher mortality with statistical significances in 2010 and 2011. However, there was no association between $PM_{2.5}$ and AMR in other years. When the fixed effect meta-analysis was used to estimate the causal association between $PM_{2.5}$ and AMR, AMR is not associated with $PM_{2.5}$. Finally, the other three models (DID, DID-Meta, NCOR models) reveal $PM_{2.5}$ has no causal association with AMR. The estimated associations in association analysis are most likely caused by unobserved confounders.

Table 2 shows the lagged causal effect estimations and the 95%CI of AMR_{Year-1} on AMR_{Year+1} via the LR-AC, LR-AC-Meta, and NCOR models. LR and Meta-LR-AC show positive association with statistical significances between AMR_{Year-1} on AMR_{Year+1} .

Nevertheless, the NCOR model reveal that AMR_{Year-l} has no causal association with AMR_{Year+l} . The results indicate that the association between AMR_{Year-l} and AMR_{Year+l} is most likely caused by spurious associations due to unobserved confounders.

DISCUSSION

A significant challenge in observational studies is to control the potential confounders between exposure and outcome [1, 2]. The negative control analysis aims to identify the presence of residual confounders and further correct the unmeasured confounders [7, 19]. The DID method can be regarded as a negative outcome control approach through a monotonicity hypothesis of unmeasured confounding effects[9]. Theoretically, the formula $\frac{\partial E(Y(1)|X)}{\partial X} - \frac{\partial E(Y(0)|X)}{\partial X}$ can be used to estimate the causal effect of exposure on post-exposure outcomes. The causal effect estimation is $c_0 + c_1 r_1 c_2 \delta$ and the bias is $c_1 r_1 c_2 \delta$ because of the existence of a lagged causal effect of pre-exposure outcome on post-exposure outcome. The proof for the bias formula of the DID model is shown in Web Appendix 4 in Supplementary Material.

In this paper, we develop a new framework for the identification and inference of causal effects of exposure on outcome using a pre-exposure outcome as a negative control outcome. For multiple studies, the intercept term of the NCOR model is the causal effect estimation of exposure on outcome. Then, the slope coefficient of the NCOR model minus 1 is the lagged causal effect estimation of pre-exposure outcome on post-exposure outcome. Under feasible assumptions, unbiased causal effect estimation of the exposure on the outcome in the NCOR model can be obtained. Furthermore, a robust estimation can still be obtained when relaxed assumptions. Simulations suggest that the NCOR model could eliminate approximately all unmeasured confounders and obtain unbiased and robust causal effect estimations. In contrast, other models, such as the LR-SU, LR-SU-Meta, LR-AC and Meta-LR-AC, DID, DID-meta models can't remove residual confounding.

In the context of severe episodes of poor air quality in the 20th century, such as the London Fog of 1952, researchers originally recognized the correlation between particulate pollution and all-cause mortality [42]. These episodes clearly indicate that the increase in deaths is association with high levels of particulate matter. Time-series studies can be confounded by time-varying factors such as influenza epidemics and temperature; however, statistical methods have been developed to reduce such unmeasured confounding [37-41]. In this paper, linear regression model, fixed effect meta-analysis, DID, DID-Meta and NCOR models are used to estimate the causal effect of PM_{2.5} on all-cause mortality rates and the lagged causal effect of all-cause mortality rates. The results of the proposed model indicated that there was no causal effect of pre-exposure AMR on post-exposure AMR. Therefore, both the proposed and DID models could obtain an unbiased causal effect of PM_{2.5} on AMR. As expected, DID, DID-Meta and NCOR models reveal PM_{2.5} has no causal association with AMR, whereas the LR model showed an inconsistent conclusion. Therefore, the estimated associations in association analysis are most likely caused by unobserved confounders. In conclusion, our method can remove approximately all confounders using a pre-exposure outcome as a negative control outcome.

Conclusions

The proposed NCOR model can obtain unbiased and robust causal effect estimation of the exposure on the outcome, along with the lagged causal effect of outcomes. The application results demonstrate that the previously estimated association between PM_{2.5} and all-cause mortality rates can be attributed to the unobserved confounding factors. Furthermore, the NCOR model reveal that pre all-cause mortality rates has no causal association with post all-cause mortality rates.

Abbreviations List

AMR, All-cause Mortality Rate; MSE, Mean Square Error; NCOR, Negative Control Outcome

375 Regression; NCOR, Negative Control Outcome Regression; SE, Standard Error

376

377 **Declarations**

378 **Ethics approval and materials**

379 Not applicable

380 **Consent for publication**

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384 **Competing interests**

385 The authors declare that they have no competing interests.

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392 **Authors' contributions**

393 FX, YY and HL jointly conceived the main idea behind the article and designed the study. YY
394 helped conduct the literature review, performed the simulation and prepared the first draft of
395 the manuscript. LH, XS, XL, FY, YY and QW participated in the design of the study. FX

advised on critical revision of the manuscript for important intellectual content. All authors revising it critically for important intellectual content, read and approved the final manuscript.

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Figure legend

Figure 1. Causal diagram for Difference in Difference (DID) model (a). X is the exposure and $Y(0)$ and $Y(1)$ are the pre- and post-exposure outcome, respectively. U represents the unobserved confounders. Causal diagram for Negative Control Outcome Regression (NCOR) (b). $U(0)$, $U(1/2)$, $U(1)$ denote the unobserved confounding factors at times $t=0, 1/2, 1$

respectively. X represents the exposure. $Y(0)$ and $Y(1)$ represents the outcome at time $t=0, 1$, respectively. $\{c_0, c_1, c_2, c_3, \gamma_1, \gamma_2\}$ are the relevant effect parameters.

Figure 2 Simulation results of the bias (a), Standard Error, SE (b) and Mean Square Error, MSE (c) for causal effect of X on $Y(1)$ when the number of studies change from 5 to 200. LR-SU represents linear regression model conditional on the surrogate of unmeasured confounders, the pre-exposure outcome. LR-SU-Meta denotes the fixed effect meta-analysis based on LR-SU model. DID model is Difference in Difference model and DID-Meta model is the fixed effect meta-analysis based on DID model. NCOR is Negative Control Outcome Regression model.

Figure 3 Type I error (a) and statistic power (b) of NCOR model for causal effect estimation of X on $Y(1)$ with the number of studies increasing.

Table 1. The causal effect estimations and its 95%CI of PM_{2.5} on AMR

Year	LR-SU	LR-SU-Meta	DID	DID-Meta	NCOR
2010	0.137(0.043, 0.231)	0.107(-0.184, 0.397)	0.025(-0.096, 0.146)	0.052(-0.246, 0.350)	0.084(-0.137, 0.304)
2011	0.349(0.082, 0.616)	0.095(-0.150, 0.340)	0.138(-0.170, 0.446)	0.014(-0.234, 0.262)	-0.011(-0.682, 0.661)
2012	0.131(-0.024, 0.285)	0.019(-0.208, 0.246)	0.046(-0.110, 0.202)	-0.011(-0.233, 0.212)	-0.007(-0.285, 0.272)
2013	0.053(-0.070, 0.177)	-0.015(-0.221, 0.191)	0.015(-0.106, 0.136)	-0.043(-0.249, 0.164)	-0.049(-0.126, 0.027)
2014	0.064(-0.009, 0.137)	0.016(-0.194, 0.226)	-0.013(-0.093, 0.066)	-0.014(-0.226, 0.197)	0.028(-0.057, 0.113)
2015	0.062(-0.008, 0.133)	0.003(-0.192, 0.197)	-0.050(-0.134, 0.033)	-0.037(-0.234, 0.161)	0.044(-0.141, 0.229)

LR-SU represents linear regression model conditional on the surrogate of unmeasured confounders, the pre-exposure outcome. LR-SU-Meta denotes the fixed effect meta-analysis based on LR-SU model. DID represents Difference in difference model and DID-Meta denotes the fixed effect meta-analysis based on DID model. NCOR is Negative Control Outcome Regression model.

Table 2. The lagged causal effect estimations and its 95%CI of AMR_{Year-1} on AMR_{Year+1}

Year	LR-AC	Meta-LR-AC	NCOR
2010	0.910(0.895, 0.926)	0.940(0.811, 1.068)	-0.018(-0.210, 0.175)
2011	0.820(0.777, 0.863)	0.870(0.708, 1.033)	0.168(-0.545, 0.881)
2012	0.940(0.912, 0.969)	0.968(0.853, 1.084)	0.008(-0.223, 0.238)
2013	0.972(0.950, 0.995)	0.973(0.867, 1.079)	0.005(-0.057, 0.068)
2014	0.952(0.938, 0.965)	0.963(0.860, 1.066)	-0.031(-0.101, 0.039)
2015	0.925(0.910, 0.939)	0.952(0.852, 1.052)	-0.060(-0.222, 0.103)

LR-SU represents linear regression model conditional on the surrogate of unmeasured confounders, the pre-exposure outcome. Meta-LR-SU denotes the fixed effect meta-analysis based on LR-SU model. NCOR is Negative Control Outcome Regression model.

Figures

Figure 1

Causal diagram for Difference in Difference (DID) model (a). X is the exposure and $Y(0)$ and $Y(1)$ are the pre- and post-exposure outcome, respectively. U represents the unobserved confounders. Causal diagram for Negative Control Outcome Regression (NCOR) (b). $U(0)$, $U(1/2)$, $U(1)$ denote the unobserved confounding factors at times $t=0, 1/2, 1$ respectively. X represents the exposure. $Y(0)$ and $Y(1)$ represents the outcome at time $t=0, 1$, respectively. $\{c_0, c_1, c_2, c_3, \gamma_1, \gamma_2\}$ are the relevant effect parameters.

Figure 2

Simulation results of the bias (a), Standard Error, SE (b) and Mean Square Error, MSE (c) for causal effect of X on $Y(1)$ when the number of studies change from 5 to 200. LR-SU represents linear regression model conditional on the surrogate of unmeasured confounders, the pre-exposure outcome. LR-SU-Meta denotes the fixed effect meta-analysis based on LR-SU model. DID model is Difference in Difference model and DID-Meta model is the fixed effect meta-analysis based on DID model. NCOR is Negative Control Outcome Regression model.

Figure 3

Type I error (a) and statistic power (b) of NCOR model for causal effect estimation of X on Y(1) with the number of studies increasing.

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