Supplementary Note 1: Sites in the PEDSnet Database

In our study, participating institutions in the PEDSnet database included Cincinnati Children's Hospital Medical Center, Children's Hospital of Philadelphia, Children's Hospital of Colorado, Ann & Robert H. Lurie Children's Hospital of Chicago, Nationwide Children's Hospital, Nemours Children's Health System (in Delaware and Florida), Seattle Children's Hospital, and Stanford Children's Health.

Supplementary Note 2: PASC Symptoms and Conditions

This study included 24 PASC symptoms and conditions: abdominal pain, abnormal liver enzyme, acute kidney injury, acute respiratory distress syndrome, arrhythmias, cardiovascular signs and symptoms, changes in taste and smell, chest pain, cognitive functions, fatigue and malaise, fever and chills, fluid and electrolyte, generalized pain, hair loss, headache, heart disease, mental health disorders, musculoskeletal pain, myocarditis, myositis, Postural Orthostatic Tachycardia Syndrome (POTS) or dysautonomia, respiratory signs and symptoms, skin symptoms, and thrombophlebitis and thromboembolism.
The ICD and SNOMED diagnosis codes are available in Razzaghi et al.'s work.[1]
The classification of symptoms and conditions into systematic and syndromic groups are listed as follows:

- Systemic (diagnosed health conditions): acute kidney injury, acute respiratory distress syndrome, arrhythmias, fluid and electrolyte, heart disease, myocarditis, myositis, POTS or dysautonomia, and thrombophlebitis and thromboembolism
- Syndromic (symptoms, signs, non-specific laboratory abnormalities): abdominal pain, abnormal liver enzyme, cardiovascular signs and symptoms, changes in taste and smell, chest pain, cognitive functions, fatigue and malaise, fever and chills, generalized pain, hair loss, headache, mental health disorders, musculoskeletal pain, respiratory signs and symptoms, skin symptoms

Supplementary Note 3: Sensitivity Analysis of Different Sets of NCOs

The proposed method's robustness is affected by the selection of NCOs. **Supplementary Table 1** showed the 62 NCOs that were manually reviewed by the clinicians. Originally, we selected 30 NCOs as the sensitivity analysis, which included acne, closed fracture of distal end of radius, closed injury of head, concussion, contact dermatitis, diaper rash, displacements - bone, falls, foreign body in ear, impetigo, inguinal hernia, injury of finger, injury of free lower limb, injury of head, injury of left leg, injury of right foot, injury of right hand, injury of right leg, injury of upper extremity, insect bite, plagiocephaly, scoliosis, snoring or obstructive sleep apnea, speech delay,

speech dysfunction, sprain of ankle, tinea capitis, tinea corporis, tongue tie, umbilical hernia, and wax in ear or impacted cerumen.

NCO name
Acanthosis nigricans
Acne
Alkalosis
Anemia neoplastic disease
Biliary calculus
Bronchiectasis
Burping
Cannabis abuse
Chalazion
Closed fracture of distal end of radius
Closed injury of head
Concussion
Contact dermatitis
Curvature spine
Cystic fibrosis
Diaper rash
Displacements - bone
Epilepsy
Esotropia
Falls
Foreign body in ear
Hashimoto thyroiditis
Hemochromatosis
Hyperlipidemia
Hypoparathyroidism
Impetigo
Inguinal hernia
Injury of finger
Injury of free lower limb
Injury of head
Injury of left leg
Injury of right foot
Injury of right hand
Injury of right leg
Injury of upper extremity
Insect bite
Jaundice

Leukemia
Low back pain
Lump right breast
Myopia
Nystagmus
Opioid dependence
Osteodystrophy
Perforation of tympanic membrane
Plagiocephaly
Postural kyphosis
Raynauds disease
Scoliosis
Secondary malignant neoplasm large intestine
Snoring or obstructive sleep apnea
Solitary nodule of lung
Speech delay
Speech dysfunction
Sprain of ankle
Tinea capitis
Tinea corporis
Tinea pedis
Tongue tie
Umbilical hernia
Vitamin d deficiency
Wax in ear or impacted cerumen

Supplementary Table 1. The full list of 62 NCOs. The NCO list has been manually reviewed by medical clinicians.

Supplementary Table 2 showed the systematic bias by using full list of NCOs or partial list of NCOs. From this sensitivity analysis the estimation from the systematic bias does not change.

Minority Group	Systematic bias estimated from full NCO list	Systematic bias estimated from partial NCO list
AAPI	0.75	0.74
Hispanic	1.02	1.01
NHB	0.88	0.88

Supplementary Table 2. Sensitivity analysis for estimated systematic bias from the partial NCO list from 30 NCOs versus the full list from 62 NCOs.

Supplementary Note 4: Simulation Setup And Performance in MSE

While our approach is a general method that could be used for both binary and Poisson outcomes, simulation studies are performed with scenarios generating relative risk as examples. Assume that there are n patients in total. For the i-th patient, the observed confounding variables are denoted as X_i, which is of p-dimension. For X_i, the categorical variables were generated by a uniform distribution and cut into different categories with cutoff values. The binomial variables were generated with different probabilities of success. The unmeasured confounders are denoted as U_i, which is of q-dimension. For U_i, the binomial variables were generated with different probabilities of success, and variables with a normal distribution were generated with mean zero and standard deviation of 2. An intercept term was included automatically in both X_i and U_i. We set $p = 7$ and $q = 3$. The average treatment effect τ was set to -1. $M = 40$ NCOs are generated.

To evaluate type I error rates, we generated the systematic error of the m-th NCO via the normal distribution $N(b, \sigma^2)$, where b was set to 0 and σ was set to 0.20. The function $\beta(A_i, X_i)$ of measured confounders to the potential outcomes for the intervention and control groups was set to $\beta(0, X_i) = X_i^T(-1, 0.5, 0.3, 0.6, 0.5, -0.1, -0.5, 0.1, 0.5)$,
$\beta(1, X_i) = X_i^T(-2, 1, 0.6, 1.2, 0.8, -0.6, -1, 0.4, 1)$, respectively. The function $\gamma_t(U_i)$ of the time-varying effect of unmeasured confounders on the potential outcomes was set to $\gamma_0(U_i) = \gamma_1(U_i) = U_i^T(-2, 0.5, 0.3, -1)$. We ranged sample sizes as 1000, 2000, and 3000.

To evaluate statistical power, $b_0 \sim N(b, \sigma^2)$ was ranged as 0.05, 0.10, and 0.15. $\gamma_1(U_i) = U_i^T(-2, 0.5, 0.3, -1) + b_0$. The other parameters were generated the same as in the previous paragraph.

To show the estimated bias and coverage probabilities for the proposed calibration method compared to the DiD method, we set b as 0.5 and $\tau(X_i)$ as -1. The other parameters were generated the same as in the previous paragraph.

Supplementary Table 3 showed the mean square error for comparison of the proposed method with the baseline method before the calibration.

Method	N=1000	N=2000	N=3000
Before calibration	0.425	0.352	0.331
After calibration	0.149	0.065	0.039

Supplementary Table 3. The mean square error (MSE) across different sample sizes. The MSE is defined as the average of squared differences between the estimated treatment effects and the true treatment effect across simulation replicates.

Supplementary Note 5: Theoretical Investigation for NC-DiD

A traditional difference-in-differences (DiD) model can be applied to estimate the target estimand. It requires the parallel trends assumption. On the logarithm scale, which is appropriate for the chosen risk ratio estimand, the parallel trends assumption can be stated as

$$\log\left(\frac{E(Y_1(0)|A=1)}{E(Y_1(0)|A=0)}\right) - \log\left(\frac{E(Y_0(0)|A=1)}{E(Y_0(0)|A\ =0)}\right) = 0.$$

With this assumption, the following equation holds:

$$E(Y_1(0) \mid A=1) = \frac{E(Y_0 \mid A=1)}{E(Y_0 \mid A=0)} \times E(Y_1 \mid A=0).$$

Assumption 1. (Consistency)

$$Y|(T=t) = Z_t\, Y_t(1) + (1-Z_t)Y_t(0).$$

By Assumption 1, the conditional treatment effect in the risk ratio on the treated group τ can be identified by

$$\tau = \frac{E(Y_1 \mid A=1)}{E(Y_1 \mid A=0)} \times \frac{E(Y_0 \mid A=0)}{E(Y_0 \mid A=1)}.$$

We denote by $\tau^\star$ the right-hand side of the equation, which is the

$$\tau^\star = \exp(\beta_3).$$

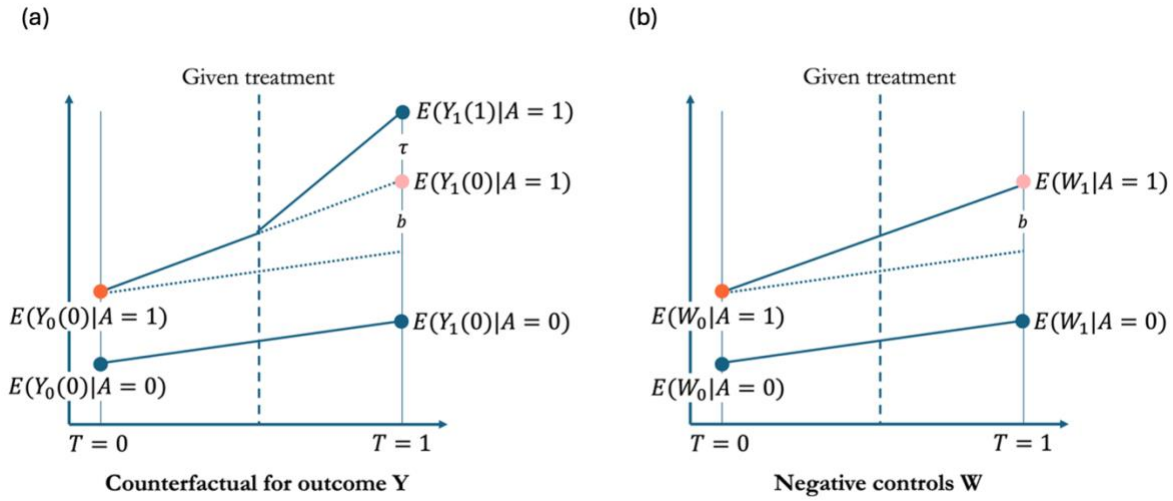
The τ^* is always identifiable from the data but may not be equal to τ if the parallel trends assumption does not hold. The effect of the unmeasured confounders can be quantified by

$$b_0 = \log\left(\frac{E(Y_1(0)|A=1)}{E(Y_1(0)|A=0)}\right) - \log\left(\frac{E(Y_0(0)|A=1)}{E(Y_0(0)|A\ =0)}\right) = \log(\tau) - \log(\tau^*).$$

We refer to b_0 as the unmeasured confounder bias for the outcome of interest. The mean of the control counterfactual for the treated group is not generally identifiable for b_0. Hence the target estimand τ is not identifiable, either.

A negative control outcome (NCO) is a random variable that is not causally affected by the treatment but is influenced by unmeasured confounding variables related to the main outcome of interest. In other words, a statistical association between M NCOs and the treatment assignment would exist only if there were unmeasured confounders affecting both. In the absence of unmeasured confounding, it follows from the definition of the mth NCO that the systematic bias for the NCO $b_m = 0$ ($m = 1, \ldots, M$). In other words, a nonzero b_m is a signal of the violation of the unmeasured confounding. Note that b_m is identifiable from observed data, which is the foundation of our proposed hypothesis testing method.

Supplementary Figure 1 shows the illustration for the proposed calibration method NC-DiD. b_0 corrects for the biased conditional treatment effect among the treated subjects, or $\log(\tau) = \beta_3 - b_0$. If we can identify the bias b_0, then the target estimand can also be identified.



Supplementary Figure 1. **Illustration of systematic bias**. The panel (a) showed the notation for the counterfactual outcome Y changes over time. It illustrates that the systematic bias exists for the outcome of interest. The panel (b) demonstrated the notation for the negative control outcome W. The negative control outcome helps to identify the systematic bias.

We consider the following problems:

- How can we perform hypothesis testing of the parallel trends assumption?
- How can we calibrate $\tau^\star$ by estimating the systematic bias b so that we can identify the target estimand τ?

We can solve the problems with the help of NCOs at time $T = 0$ and $T = 1$. Suppose we have access to M NCOs. We denote the mth NCO at times 0 and 1 as W_{m0} and W_{m1} $(m = 1, \dots, M)$. We define the NCO-revealed confounding bias for the mth NCO as

$$b_m = \log\left(\frac{E(W_{m1}|A=1)}{E(W_{m1}|A=0)}\right) - \log\left(\frac{\mathrm{E}(W_{m0}|A=1)}{E(W_{m0}|A=0)}\right).$$

As discussed in above, nonzero NCO-revealed confounding bias is a signal of the presence of unmeasured confounding with time-varying effects. Note that unmeasured confounding for an NCO does not necessarily violate the parallel trends assumption for the outcome of interest. In

other words, the unmeasured confounder U_t $(t = 0,1)$ can cause heterogeneous effects on the association between treatment and NCOs and the outcome of interest. To adjust for the heterogeneity and to identify $\tau^\star$, we posit the Assumption 2 and Assumption 3 in the Supplement.

Assumption 2. (NCO and systematic bias) The NCO-revealed confounding biases are independent copies of a random variable θ with $\theta \sim N(b, \sigma^2)$, where b represents the systematic bias with the variance term σ^2. The systematic bias from the outcome of interest also comes from θ.

Assumption 2 is formulated as a distributional assumption, implying that the systematic bias affecting the outcome of interest follows a similar distributional pattern as the systematic bias observed in the negative control outcomes (NCOs). In this way, we are able to identify the value of b_0 from NCOs.

The parameter $b = 0$ can be interpreted as that the parallel trend assumption holds essentially, and nonzero b_js occur by some random error. In addition, we state Assumption 3 under which $\tau^\star$ is estimable.

Assumption 3. (Outcome regression model) The following underlying semi-parametric models hold:

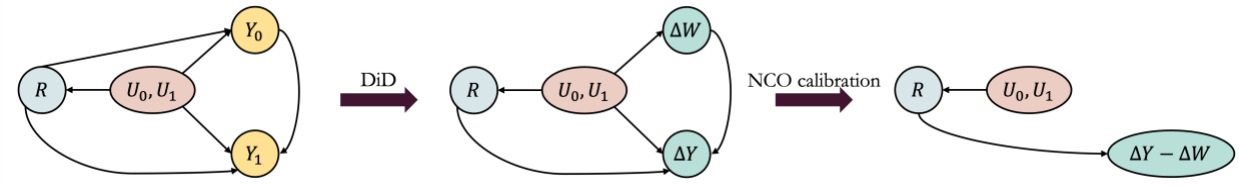
$$\log E\left(Y_T \mid A, X, U_T\right) = \alpha_{0,0} + \alpha_{1,0}A + \alpha_{2,0}T + \alpha_{3,0}T \times A + \gamma_0(X) + \eta(U_T)$$
$$\log E\left(W_{m,T} \mid A, X, U_T\right) = \alpha_{0,m} + \alpha_{1,m}A + \alpha_{2,m}T + \alpha_{3,m}T \times A + \gamma_m(X) + \eta_m(U_T)$$

for some square integrable functions $\gamma_m(X)$ and constants $\alpha_{i,m}$, $m = 0, \ldots, M$, $i = 0,1,2,3$. With the definition of NCO, $\alpha_{3,m} = 0$ and $\alpha_{3,0} = \log(\tau)$.

Recall in the main manuscript, we have the following equations for the working model on the matched cohort,

$$\log E\left(Y_T \mid A, X\right) = \beta_0 + \beta_1 A + \beta_2 T + \beta_3 T \times A$$
$$\log E\left(W_{m,T} \mid A, X\right) = \beta_{0,m} + \beta_{1,m} A + \beta_{2,m} T + \beta_{3,m} T \times A$$

It is worthwhile noting that by Assumption 3 we have $b_m = \beta_{3,m}$. In addition, we illustrated the directed acyclic diagram (DAG) in **Supplementary Figure 2** to explain the rationale of the proposed method.



Supplementary Figure 2. **Directed acyclic diagram (DAG) of the proposed method**. Each node denotes the variables and arrows denote the causal relationship between variables.

With the help of Assumption 1, Assumption 2, and Assumption 3, we can estimate the target estimand. The first step is to conduct propensity-score matching on X. We fit a logistic regression model on the measured confounders and then, we match treated with control individuals based on the propensity score. The second step is to estimate the treatment effect in the matched cohort. We denote by $\hat{\beta}_3$ the estimator for $\tau^\star$ and by $\hat{\sigma}^2_{\beta_3}$ its estimated asymptotic variance. To calibrate the estimate of $\tau^\star$, we further fit the mth NCO ($m = 1,..,M$). The estimate of $\beta_{3,m} = b_m$ is denoted by $\hat{b}_m$, and its asymptotic variance is denoted by $\hat{\sigma}^2_m$. From Assumption 2, we have $\hat{b}_m | b_m \sim N(b_m, \hat{\sigma}^2_m)$, and $b_m, b_0 \sim N(b, \sigma^2)$.

We then estimate b and σ^2 by maximizing the likelihood after integrating b_m out. As a byproduct of estimating b, we can perform a hypothesis test for the parallel trends assumption using the null hypothesis $H_0: b = 0$. The test statistic is $S = \frac{|\hat{b}|}{\sqrt{V}}$, where $V = \left(\sum_{m=1}^{M} \frac{1}{\hat{\sigma}^2_m + \hat{\sigma}^2}\right)^{-1}$. The two-sided p-value of the hypothesis can be founded by p-value$= 2 \times \{1 - \Phi(|S|)\}$.

Finally, we obtain an estimate $\hat{\tau}$ using the fact that, asymptotically, $\hat{\beta}_3 \sim N(\tau + \hat{b}, \hat{\sigma}^2_{\beta_3} + \hat{\sigma}^2)$. The calibrated estimator thus is $\hat{\tau} = \exp(\hat{\beta}_3 - \hat{b})$. The 95% confidence interval of τ is $\left(\exp\left(\hat{\beta} - \hat{b} - 1.96\sqrt{\hat{\sigma}_{\beta_3}{}^2 + \hat{\sigma}^2}\right), \exp\left(\hat{\beta} - \hat{b} + 1.96\sqrt{\hat{\sigma}_{\beta_3}{}^2 + \hat{\sigma}^2}\right)\right)$.

We provide the theoretical guarantees of our proposed method as follows. Proposition 1 considers the validity for the hypothesis testing with respect to the parallel trends assumption. Proposition 2 characterizes the asymptotic behavior for the calibrated estimator. This is used to construct a valid confidence interval for τ.

Proposition 1. (Asymptotic Normality for Bias Estimation.) *Suppose that estimators b_m are independent, and $n \to \infty$ while M is fixed. Then $\hat{b}$ and $\hat{\sigma}^2$ converge in probability to the true values $b^\star$ and $\sigma^{\star 2}$, respectively, that is, $\hat{b} \to_p b^\star$ and $\hat{\sigma}^2 \to_p \sigma^{\star 2}$. Moreover, we further have*

$$\sqrt{MV}\left(\hat{b} - b^\star\right) \to_d N(0,1).$$

Standard asymptotic theory yields that the maximum likelihood estimate from the model shown in Equation (2) satisfies

$$\Omega^{1/2}\left(\hat{\beta} - \beta^*\right) \to_d N(0, I_4),$$

where I_4 denotes the 4-dimensional identity matrix, and

$$\Omega = \left(\frac{1}{n}\sum_{i=1}^{n}\nabla^2 f(\hat{\beta}; Y_i, Z_i)\right)\left[\frac{1}{n}\sum_{i=1}^{n}\nabla f(\hat{\beta}; \mathrm{Y_i}, \mathrm{Z_i})\{\nabla f(\hat{\beta}; Y_i, Z_i)\}^{\mathrm{T}}\right]^{-1}\left(\frac{1}{n}\sum_{i=1}^{n}\nabla^2 f(\hat{\beta}; Y_i, Z_i)\right),$$

where f is the loss function of the working model. Let $\kappa = (\Omega^{-1})_{4,4}$ be the fourth diagonal entry of Ω^{-1}. Based on the asymptotic normality for β, we state our main theorem.

Proposition 2. (Asymptotic Normality for NC-DiD estimator.) *Under Assumptions imposed in Lemma 1 and some regularity conditions, we have*

$$\sqrt{1/\kappa}(\hat{\tau} - \tau) \rightarrow_d N(0,1).$$

Supplementary Reference

1. Razzaghi H, Forrest CB, Hirabayashi K, et al. Vaccine effectiveness against long COVID in children. *Pediatrics* 2024; 153: e2023064446.