Mitigating unobserved spatial confounding bias with mixed models

Patrick Schnell\(^1\)* and Georgia Papadogeorgou\(^2\)

\(^1\)Division of Biostatistics, College of Public Health, The Ohio State University, Columbus, OH, USA
\(^2\)Department of Statistical Science, Duke University, Durham NC, USA

*schnell.31@osu.edu

Abstract

Confounding by unmeasured spatial variables has received some attention in the spatial statistics and causal inference literatures, but concepts and approaches have remained largely separated. In this paper, we aim to bridge these distinct strands of statistics by considering unmeasured spatial confounding within a formal causal inference framework, and estimating effects using modifications of outcome regression tools popular within the spatial literature. First, we show that using spatially correlated random effects in the outcome model, an approach common among spatial statisticians, does not mitigate bias due to spatial confounding. Motivated by the bias term of commonly-used estimators, we propose an affine estimator which addresses this deficiency. We discuss how unbiased estimation of causal parameters in the presence of unmeasured spatial confounding can only be achieved under an untestable set of assumptions which will often be application-specific. We provide one set of assumptions that is sufficient for identification of the causal effect based on the observed data. These assumptions describe how the exposure and outcome of interest relate to the unmeasured variables. Estimation of the model components necessary for unbiased estimation of the causal effect proceeds using tools common in the spatial statistics literature, and specifically via a regularized restricted maximum likelihood approach employing weakly informative priors to avoid degenerate estimates. This work is motivated by and used to estimate the causal effect of county-level (a) exposure to emissions from coal-powered electricity generating units, and (b) relative humidity on particulate matter across the New England area in the United States, and to investigate the potential threat from unmeasured spatial confounders in this context.

Keywords: Air pollution; Causal inference; Markov random field; Particulate matter; Power plants; Spatial confounding; Unmeasured confounding

1 Introduction

Causal inference with spatially referenced data is attracting increasing attention. When the effect of an exposure on an outcome is of primary interest and available data are both spatial and observational, it is important to combine the spatial statistics tools and causal inference methodology within a common framework. Even though some attention has been given to causal inference topics in the spatial statistics literature (Paciorek [2010], Hodges and Reich [2010], Hughes and Haran [2013], Hanks et al. [2015]), and to spatial topics in the causal inference literature (Verbitsky-Savitz and Raudenbush [2012], Keele et al. [2015], Papadogeorgou et al. [2018]), there is a substantial gap in the intersection of the two fields.

Fitting regression models to spatially referenced data sets often results in spatially correlated residuals. In classical spatial statistics, regression models are augmented to include spatially correlated random effects in order to “account” or “adjust” for the spatial dependence in the outcome model residuals. However, there is substantial confusion about what exactly these spatial models are capable of accounting for (Hanks...
et al., 2015). In some settings, spatial mixed models are employed to estimate the relationship between an exposure and outcome of interest without conditioning on spatial information. In this context, Hodges and Reich (2010) and Hughes and Haran (2013) proposed including a spatial random effect (and therefore spatial basis functions) that is orthogonal to the exposure of interest. Other times, it is asserted that spatial models adjust for unobserved covariates which have a spatial dependence structure (Congdon, 2013; Lee and Sarran, 2015). Nevertheless, the usual spatial models do not in general eliminate bias due to unobserved confounders, even when the residual variance components are known (Paciorek, 2010).

From a different perspective, causal inference methodology with spatial data and in the presence of unmeasured spatial confounding has been quite limited, and, to our knowledge, it has been restricted to classic causal inference tools. Within a regression discontinuity framework, Keele et al. (2015) match treated to control units separated by a boundary minimizing geographical distance of matched pairs and balancing observed covariates. Relatedly, Papadogeorgou et al. (2018) proposed matching treated to control units on a criterion incorporating both propensity scores and geographical distance. Although these approaches can, in some cases, address the problem of interest to spatial statisticians, they are not immediately compatible with models commonly used in spatial data analysis which are most often grounded in outcome regression. An exception is found in Thaden and Kneib (2018) where the authors propose a structural equation modeling approach treating the spatial variable as a confounder in a geoadditive model in order to eliminate bias from the unmeasured spatial variable.

In this paper, we seek to bolster the bridge between spatial data analysis and causal inference. In order to do so, we consider unmeasured confounding within a formal causal inference framework and examine estimation approaches grounded on models and tools often employed by spatial statisticians. In order to provide a representation clear to as many readers as possible, we provide information that might be obvious to the experts of each field. Studying the bias of commonly-used estimators, we propose a model-based approach to estimate the effect of a change in the exposure on an outcome of interest. Our approach is designed to easily incorporate popular tools in spatial statistics such as hierarchical and linear mixed models. We explain that identification and estimation of the causal parameter in the presence of unmeasured confounding requires untestable assumptions regarding the unmeasured confounders and their relationship with the exposure and outcome of interest. For that reason, these assumptions have to be application-specific, and identification of the causal parameter needs to be evaluated separately for each set of assumptions. For continuous treatments (referred to as exposures), we provide one set of assumptions that is sufficient for identification of the causal exposure-response curve, and one that is not. The proposed estimator can be straightforwardly adapted to alternative identifying assumptions. This approach is shown to mitigate unmeasured spatial confounding bias by exploiting the spatial structure in the exposure and outcome model residuals. While our development is in the context of areal data, refinements in the context of point-referenced data are possible and are discussed where applicable.

Our work is motivated by the evaluation of the causal effects of coal-powered power plant emissions on ambient pollution concentrations, and particularly ambient particulate matter with diameter of less than 2.5 micrometers (PM$_{2.5}$). PM$_{2.5}$ is a key pollutant in air pollution regulations across the world due to its well-established links with multiple negative health outcomes, even at low levels (see Pinault et al. (2016); Di et al. (2017); Makar et al. (2018); Lim et al. (2018) among many others, and Papadogeorgou et al. (2019) for a review). U.S. policies aiming at the reduction of ambient PM$_{2.5}$ have explicitly targeted source-specific emissions, including emissions from power plants. In this study, we evaluate the causal effect of HyADS
exposure (HYSPLIT average dispersion; Henneman et al. (2019a)) on particulate matter across counties in the New England region of the U.S. accounting for the threat from unmeasured spatial confounders. HyADS provides a unit-less measure of zip-code level exposure to emissions from coal-powered electricity generating units (EGUs). Higher HyADS exposure (and therefore, higher emissions from coal-fired EGUs) is estimated to increase ambient PM$_{2.5}$ concentrations. Moreover, effect estimates remain unchanged when unmeasured spatial confounding is accommodated for or not. In order to illustrate the potential of our methodology in mitigating bias from unmeasured spatial confounding, we also evaluate the effect of relative humidity on PM$_{2.5}$ concentrations. Relative humidity is chosen as the environmental variable with the highest small scale variability across New England. At the annual level, relative humidity is estimated to not have an effect on ambient PM$_{2.5}$. When other environmental variables are not adjusted for, the affine estimator returns effect estimates closer to the results from a regression model that adjusts for these variables explicitly.

In Section 2 we define the causal estimand and discuss commonly invoked identifiability assumptions when the observed covariates include a sufficient confounding adjustment set. In Section 3 and in the presence of unmeasured spatial confounding, we show that commonly-used spatial regression models do not recover the estimands of interest. In Section 4 we provide a set of assumptions relating the exposure and outcome to the unmeasured variables based on which the causal parameter is identifiable from observed data. Based on these assumptions, we propose an estimator of the causal estimand, which is compared to the currently-used estimators under various generative mechanisms via simulation in Section 5. In Section 6 we estimate the effect of HyADS exposure and relative humidity on PM$_{2.5}$, and illustrate the potential of the affine estimator in mitigating bias from unmeasured spatial confounders. We conclude with a discussion in Section 7.

2 Causal Inference Estimands and Spatial Models

Broadly speaking, the causal inference literature places substantial emphasis on defining target quantities of interest, referred to as estimands, and determining sufficient assumptions under which such estimands (which include unobservable quantities) are identifiable based on the observed data. In contrast, the spatial statistics literature emphasizes analytical models aiming to imitate and adequately reflect the generative model, based on which conclusions regarding the “effect” of a variable on the outcome are drawn.

We follow the causal framework formalized by Rubin (1974) and extended to continuous exposures by Hirano and Imbens (2004). A necessary condition for an exposure $Z$ to have an effect on an outcome $Y$ is that $Z$ is temporally precedent. We make the stable unit treatment value assumption (SUTVA, Rubin (1980)) which states that there is a single version of each treatment level and there is no interference between units. Based on SUTVA, we can use $Y_i(z)$ to represent the value that would have been observed at location $i$ had it received exposure $z \in Z$, where $Z$ includes all possible values of the continuous $Z$, and $i = 1, 2, \ldots, n$. Then, $Y_i(z)$ is the potential outcome for location $i$ at exposure level $z$. Note that for every unit at most one potential outcome is observed. The causal assumption of consistency specifies that for every unit $i$ the observed outcome $Y_i$ is exactly the potential outcome for the observed level of the treatment $Z_i$, $Y_i = Y_i(Z_i)$.

The most common estimands for continuous treatments are the population average exposure-response curve $\mu(z) = \text{E}[Y_i(z)], z \in Z$, and the expected rate of change in the outcome for an infinitesimal change in the exposure around $z$, $\mu'(z)$. Since $\mu(z)$ is the expected value of the population assuming everyone experienced exposure $z$ it is clear that $\mu(z)$ includes unobserved quantities, and assumptions need to be
Figure 1: Assumed causal diagram for the generative model. The vector $C$ may represent a collection of multiple confounders.

made to ensure that it is identifiable. Identifiability of an estimand means that, even though it is defined in terms of potential outcomes many of which are not observed, it can be expressed as a function of only the observed data. The positivity and no unmeasured confounding assumptions (referred to together as the ignorability assumption) form a sufficient set of assumptions for identifiability of $\mu(z)$. Positivity states that all units can experience any $z \in Z$, and the no unmeasured confounding assumption states that there exist measured covariates $C$ which satisfy that, conditional on $C$, the observed exposure $Z$ is independent of the potential outcomes $Y(z)$, denoted as $Z \perp Y(z) | C, z \in Z$. (See Appendix A for a discussion on identifiability of $\mu(z)$ based on these assumptions.)

Confounders $C$ are temporally precedent to the exposure $Z$ and are often thought of as common predictors of $Z$ and $Y$, as shown in Figure 1. Since temporal order of variables matters in drawing causal conclusions, observed data are conceived as if generated in the following order: $(C), (Z|C)$ and $(Y|Z, C)$. If the identifiability conditions of positivity, and no unmeasured confounding are met, estimation can proceed by imitating the data generating mechanism for the exposure $Z|C$ known as the propensity score [Rosenbaum and Rubin 1983b], the data generating mechanism for the outcome $Y|Z, C$, or both. In order to adhere to common approaches of spatial statistics, our primary focus is on modeling the outcome generative mechanism $Y|Z, C$.

Even though confounding adjustment is necessary to draw causal conclusions, $C$ might include components that are not measured, hence violating the no unmeasured confounding assumption. Denote $C = (C^m, C^u)$ representing the measured and unmeasured components, respectively. At this point, we assume that at least some of the variables in $C^u$ are spatial and refer to Section 4.9 for a further discussion on this requirement. We refer to a variable as “spatial” if the correlation of the variable for two observations depends on their relative geographic location. For areal data like the ones in our study, the relative location could refer to adjacency of neighborhoods. For point referenced data, relative geographic location could refer to the geographical distance of two points. We assume that potential outcomes arise in the following manner:

$$Y_i(z) = \eta(z, C^m_i) + g(C^u_i) + \varepsilon_i,$$

for some function $\eta$, and $\varepsilon_i$ a mean zero random variable and independent of $C$. Therefore, $C^u$ is assumed to not interact with $Z$ and $C^m$. We denote $U = g(C^u)$, representing the cumulative contribution of all unobserved covariates. Since at least some components of $C^u$ are spatial, $U$ also has a spatial correlation structure. Note that, based on our approach detailed later, $E[g(C^u)] = 0$ will be required for identifying $\mu(z)$. Alternatively, we shift our attention from estimating $\mu(z)$ to estimating the exposure-response curve’s derivative, $\mu'(z) = \lim_{h \to 0} h^{-1}[\mu(z+h) - \mu(z)]$.

For simplicity of presentation, we first assume that $C^m = \emptyset$ and that the average exposure-response curve is linear, in which case $\eta(z) = \mu(z) = \beta_0 + \beta_1 z$, and $\mu'(z) = \beta_1$, corresponding to the usual linear regression coefficient targeted in the spatial statistics literature. The linearity assumption will be relaxed in Section 4.8. Section 6 includes $C^m$ in the outcome model, and in Appendix I we show how $C^m$ may also be
incorporated in the exposure model.

Using vector notation let \( Y = (Y_1, Y_2, \ldots, Y_n)^\top \) and \( Z, U, \varepsilon \) defined analogously. Then, if all of \( Y, Z, U \) were observed, a model

\[
Y = 1\beta_0 + Z\beta_1 + U + \varepsilon, \tag{2}
\]

would lead to unbiased estimation of \( \beta_1 \). Here, \( Z \) and \( U \) are correlated, but \( \varepsilon \) is independent of \((Z, U)\). Thus \( U \) and \( \varepsilon \) is a partition of the variability in \( Y \) not due to \( Z \) into one component \((\varepsilon)\) which is independent of \( Z \) and one \((U)\) which is not.

3 Omitted Variable Bias of Least Squares Estimators

Omitted variable bias is widely known in the literature. If \( U \) is correlated with \( Z \) and is omitted from the outcome regression, the ordinary least squares (OLS) estimator of \( \beta, \hat{\beta} \), will be biased. This is evident by examining the conditional expectation of \( \hat{\beta} \). Writing \( X = (1, Z) \),

\[
E(\hat{\beta}|Z) = E\big[ (X^\top X)^{-1} X^\top Y | Z \big]
= E\big[ (X^\top X)^{-1} X^\top (X\beta + U + \varepsilon) | Z \big]
= \beta + E\big[ (X^\top X)^{-1} X^\top U | Z \big]
= \beta + (X^\top X)^{-1} X^\top E[U|Z]. \tag{3}
\]

Examining \( (3) \), and considering \( E(\hat{\beta}) = E[E(\hat{\beta}|Z)] \), we see that \( \hat{\beta} \) will be biased for \( \beta \) since the second term will be non-zero for correlated \( U, Z \).

When \( U \) is omitted from the regression model, the component of \( U \) not attributed to \( Z \) will be incorporated in the residuals. Since \( U \) is spatially structured, residuals of the regression of \( Y \) on \( Z \) will also be spatially correlated. In an effort to account for residual spatial correlation, spatial linear mixed models are often adopted. Typically, such models represent mechanisms similar in form to \( (2) \), but in which all right-hand-side variables are assumed to be independent, and some assumptions are made about the form of \( \text{Var}[U] = \text{Var}[U|Z] \). These models aim to explain the spatial correlation in the residuals and they are often effective at improving efficiency and adjusting standard errors. However, as we show below, they do not alleviate the omitted variable bias. If \( \text{Var}[Y|Z] \) (which depends on \( \text{Var}[U] \)) is known, the generalized least squares (GLS) estimator of \( \beta \) is

\[
\tilde{\beta} = \{X^\top \text{Var}[Y|Z]^{-1} X\}^{-1} X^\top \text{Var}[Y|Z]^{-1} Y. \tag{4}
\]

with conditional expected value

\[
E(\tilde{\beta}|Z) = \beta + \{X^\top \text{Var}[Y|Z]^{-1} X\}^{-1} X^\top \text{Var}[Y|Z]^{-1} E[U|Z]. \tag{5}
\]

Therefore, even if \( \text{Var}[Y|Z] \) is known, \( \tilde{\beta} \) remains biased. This result indicates that including a spatial random effect in the regression model does not necessarily mitigate or eliminate bias arising from unmeasured spatial confounders.
4 Affine Estimator to Account for Omitted Spatial Variables

In the previous section we discussed how spatial correlation in the outcome model residuals might arise due to spatial predictors of \( Y \). Further, we discussed how commonly used approaches to estimate \( \beta_1 = \mu'(z) \) are biased in the presence of unmeasured confounding by a spatial variable \( U \). Based on the above, it is now clear that mitigating bias from unmeasured spatial variables cannot be achieved based solely on an outcome regression model without making additional assumptions, nor by harvesting spatial information found solely in the outcome model residuals.

In this section, we propose an estimator that is inspired by the form of the bias in (3) and (5). As we will see, the estimator includes a component that depends on \( U \). For that reason, identifiability of this component, and as a result our ability to calculate the value of the estimator, requires additional assumptions. We provide a set of assumptions that suffice for identification. These assumptions pertain to the joint distribution of \( (U, Z) \), and they allow us to identify the unobserved component of the estimator utilizing the spatial correlation structure in the exposure and the outcome model residuals. A restriction on the spatial scales of the exposure and spatial confounder aims to ensure that the effect of the exposure is not wrongfully attributed to the spatial confounder, and that we do not adjust for potential spatial mediating variables, as we will discuss in more detail in Section 4.7.

4.1 The affine estimator

An investigation of the formulas in (3) and (5) shows that bias of both least squares estimators arises from the non-zero correlation between \( U \) and \( Z \). We propose using the affine estimator

\[
\tilde{\beta} = \left\{ X^T (\text{Var}[Y|Z])^{-1} X \right\}^{-1} X^T (\text{Var}[Y|Z])^{-1} \{ Y - \text{E}[U|Z] \},
\]

which replaces \( Y \) by \( Y - \text{E}[U|Z] \) and is unbiased if \( \text{E}[U|Z] \) is known, or more practically, consistent if \( \text{E}[U|Z] \) is consistently estimated. Note that since \( U \) is unmeasured, direct modeling of \( \text{E}[U|Z] \) based on traditional estimation methods is not possible. Instead, we present a class of estimators based on Gaussian Markov random field theory.

4.2 A Gaussian Markov random field construction of the joint distribution

In this section we present a set of assumptions on the joint distribution of \( (U, Z) \) which allows us to identify \( \text{E}[U|Z] \) and calculate \( \tilde{\beta} \) based on the observed data, as we will show in Section 4.3. Different or weaker assumptions for identification of \( \text{E}[U|Z] \) are likely possible, but we proceed with these for ease of illustration.

In viewing the model from a spatial perspective and following common spatial statistics practice, we assume that the marginal distributions of \( Z, U, \) and \( \varepsilon \) are all Gaussian with mean zero, and that \( (U, Z) \) is normal. We recognize that joint normality might be a strong assumption and we discuss an approach to relax it in Section 7. However, here, we retain it for simplicity and to better align to the spatial modeling literature. Further, we make the following assumptions about the joint distribution of \( (U, Z) \):

1. Cross-Markov property: \( p(Z_i|Z_{-i}, U) = p(Z_i|Z_{-i}, U_i) \),
2. Constant conditional correlation: \( \text{Cor}(U_i, Z_i|U_{-i}, Z_{-i}) = \rho \).
The first assumption states that \( Z_i \) depends on \( U \) only through its value at location \( i \), \( U_i \), conditional on the values of \( Z \) at all other locations. Thus, it accommodates correlation between nearby treatments, but it does not allow \( U_j \) to directly affect the value of \( Z_i \) for \( i \neq j \). The second assumption states that the conditional correlation between \( U_i \) and \( Z_i \) does not vary by location. In the joint distribution of \((U, Z)\), these assumptions can be incorporated in the precision matrix. Specifically, if

\[
\begin{pmatrix} U \\ Z \end{pmatrix} \sim \mathcal{N} \left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} G & Q \\ Q^\top & H \end{pmatrix}^{-1} \right),
\]

the cross-Markov assumption is equivalent to diagonal \( Q \), and along with the constant conditional correlation assumption implies

\[
q_{ij} = \begin{cases} -\rho \sqrt{g_{ii} h_{ii}}, & i = j, \\ 0, & i \neq j. \end{cases}
\]

In order to ensure positive definiteness of the precision matrix, \( \rho \) has to be constrained. Even though no convenient form of such constraint is available, a conservative one is given by

\[
|\rho| < \frac{\min \left\{ \min_i \{ \lambda_{G,i} \}, \min_i \{ \lambda_{H,i} \} \right\}}{\sqrt{\max_i \{ g_{ii} h_{ii} \}}},
\]

where \( \lambda_{G,i} \) and \( \lambda_{H,i} \) are the \( i \)th eigenvalues of \( G \) and \( H \), respectively (see Appendix B for the derivation of the bound on \( \rho \)).

Given the above framework, the joint model for \( U \) and \( Z \) is completed by specifying \( G \) and \( H \), the precision matrices of \( U \mid Z \) and \( Z \mid U \) respectively, up to some unknown parameters that will be estimated from the data. For areal data like the ones in Section 6, we adopt conditional autoregressive structures (CAR; Besag (1974)) for \( G \) and \( H \), a common assumption in standard spatial analysis models. In the analysis of point-referenced data, the precision matrices of \( U \mid Z \) and \( Z \mid U \) can be specified based on a correlation function decaying in geographical distance. In either case, since \( U \) includes all unmeasured spatial variables \( C_u \), the correct specification of its precision matrix \( G \) becomes harder for a larger number of unmeasured spatial covariates.

In Table 1 we present the full set of assumptions based on which \( \mu'(z) \) is identifiable from observed data, even in the presence of unmeasured spatial variables.

### 4.3 Linear effect estimator

From (2), and using the conditional distribution \( U \mid Z \) acquired from (7), the joint model for the observed data (integrating \( U \mid Z \) out) can be factored as

\[
\begin{align*}
Y \mid Z & \sim \mathcal{N} [X \beta - G^{-1} Q Z, G^{-1} + R^{-1}], \\
Z & \sim \mathcal{N} [0, (H - Q^\top G^{-1} Q)^{-1}].
\end{align*}
\]

where \( R^{-1} = \text{Cov}(\varepsilon) \). See Appendix C for the derivation of (10). From (10), we see that the likelihood depends on \( U \) only through the components of the precision matrix in (7). Note that, even though our focus is in estimating parameters of the outcome model \( (\beta) \), an exposure model is also adopted to provide information on the spatial structure of \( U \).
Table 1: Set of assumptions based on which the causal exposure-response curve derivative is identifiable using observed data and can be estimated using the affine estimator.

| Causal Assumptions                  | Structural Assumptions          |
|-------------------------------------|---------------------------------|
| Temporal Order                     | Outcome Additivity              |
| Confounders are temporally precedent to the exposure, and the exposure is temporally precedent to the outcome | The exposure and measured covariates do not interact with the unmeasured covariates. |
| SUTVA                               | Normality                       |
| No interference between units, no hidden levels of the treatment | $Z, U, \varepsilon$ are jointly normal |
| Consistency of potential outcomes   | Cross-Markov                    |
| $Y_i = Y_i(Z_i)$                    | $Z_i \perp \perp U_{-i}|U_i, Z_{-i}$, where $U_{-i} = (U_1, U_2, \ldots, U_{i-1}, U_{i+1}, \ldots, U_n)^T$, $Z_{-i}$ defined similarly |

Following a common approach to estimation for mixed models, variance parameters are estimated based on the restricted likelihood derived from (10), and the estimates are used to calculate the bias-adjusted affine estimator $\hat{\beta}$ in (6). Specifically, let $V = \text{Var}[Y|Z] = G^{-1} + R^{-1}$, $A = \text{Var}[Z] = (H - Q^T G^{-1} Q)^{-1}$, and $B = -G^{-1}Q$. The restricted likelihood is then

$$RL \propto |V| \cdot |A| \cdot |X^T V^{-1} X|^{-1/2} \times \exp \left[ -\frac{1}{2} \left\{ (Y - BZ)^T (V^{-1} - V^{-1} X (X^T V^{-1} X)^{-1} X^T V^{-1}) (Y - BZ) + Z^T A^{-1} Z \right\} \right]. \quad (11)$$

(Derivation of (11) is in Appendix D). If $\hat{V}$ and $\hat{B}$ are the maximizers of the restricted likelihood in (11) subject to appropriate range constraints like the ones in (9), we calculate $\hat{\beta} = \left(X^T \hat{V}^{-1} X\right)^{-1} X^T \hat{V}^{-1} (Y - \hat{B}Z)$.

Here, it is worth making a connection between our approach and mixed effects models often used in spatial statistics. If $\rho = 0$, the model in (7) reduces to the case where $U, Z$ are independent, and the restricted likelihood estimation method would lead to the estimator $\hat{\beta}$. A non-zero correlation $\rho$ between $U$ and $Z$ leads to the inclusion of the $-G^{-1}Q$ component in the coefficient of $Z$, corresponding exactly to the bias correction term $E[U|Z] = -G^{-1}QZ$. 

4.4 Approximate standard errors accounting for correlation between parameter estimates

For the GLS estimator $\tilde{\beta}$, approximate standard errors are often constructed assuming known variance parameters: $\text{Var}(\tilde{\beta}) \approx (X^T\tilde{V}^{-1}X)^{-1}$. We do not recommend applying this idea directly to $\tilde{\beta}$ due to the fact that the estimates of $\rho$ and $\beta_1$ are strongly correlated. We account for such correlation with a small modification. If all variance parameters except $\rho$ are treated as known, then

$Y|Z \sim N[X\beta - \rho G^{-1}Q^*Z, G^{-1} + R^{-1}]$, \hspace{1cm} (12)

where $Q^*$ is diagonal with elements $q^*_{ii} = -\sqrt{g_{ii}h_{ii}}$ known and independent of $\rho$. Then, treating $\rho$ exclusively as a coefficient, we can write $D = (X| - G^{-1}Q^*Z)$ via concatenation, and obtain an estimated variance $\hat{\text{Var}}\left(\begin{pmatrix} s\beta \\ s\rho \end{pmatrix}\right) = (\hat{D}^T\hat{V}^{-1}\hat{D})^{-1}$, from which an estimate of the variance of $s\beta$ can be acquired. Based on the estimated variance of $\tilde{\beta}$, Wald-type confidence intervals can be obtained.

4.5 Regularization of the joint precision matrix

Although direct restricted maximum likelihood (REML) estimation is possible, we recommend proceeding by maximizing the restricted likelihood multiplied by a weakly informative prior density for the purposes of regularization. This approach is known as maximum a posteriori or Bayes modal (Chung et al., 2015) estimation.

The estimation of the joint precision matrix of $(U, Z)$, $P$, is critical in mitigating bias due to the unobserved spatial confounder $U$. However, the present setting is a “low-information” one, as we neither observe $U$ directly nor obtain independent replicates. In such settings, the restricted likelihood may be maximized at the boundary of allowed values. For example, Chung et al. (2013) noted that it is not unusual in random effects meta-analysis for the REML estimate of the between-study standard deviation to be zero, and suggested regularizing the REML estimate by multiplying the restricted likelihood by a weakly-informative gamma prior for the between-study variance, yielding a so-called “Bayes modal” estimator. The name is derived from the observation that the restricted likelihood is the posterior of the variance parameters under flat priors marginalized over the regression coefficients (again under flat priors).

Along another thread, Won et al. (2013) considered estimating the covariance matrix in high-dimensional settings where maximum likelihood estimates of such covariance matrices are often ill-conditioned and cannot be inverted accurately. They propose a constrained maximum likelihood approach using the constraint $\kappa(\Sigma) \leq \kappa_{max}$, where $\kappa(\Sigma)$ is the condition number (the ratio of the largest to the smallest eigenvalue) and $\kappa_{max}$ is pre-specified. They note that this optimization problem is equivalent to maximizing the likelihood times an exponential prior on $\kappa(\Sigma)$ left-truncated at 1. An advantage of this approach is that it directly addresses the ill-conditioning problem, which we have found to be the primary nuisance in estimating $P$. For our purposes, we adopt a truncated exponential prior for $\kappa(P)$ with rate 1/10 and range $(1, \infty)$. With this specification, the difference in log prior density between $\kappa(P) = 1$ and $\kappa(P) = 10$ is 0.9, while that between $\kappa(P) = 1$ and $\kappa(P) = 100$ is 9.9.
4.6 Spatial scale restriction for the unmeasured spatial confounder

On the particular topic of spatial confounding bias of spatial regression estimators, Paciorek (2010) shows that the bias and variance of spatial model estimators depend on the relative spatial scales of the exposure and the residual including the confounder, $z + U$. Paciorek (2010) recommends only fitting spatial models when there is exposure variation on a spatial scale smaller than that of the unmeasured confounder. In an attempt to capture some of this larger-scale spatial structure in the confounder while de-emphasizing the small-scale structure in the same problems, we recommend using a version of the affine estimator in which we enforce—even when incorrect—that the spatial scale of the confounder is larger than that of the exposure.

From a spatial perspective, the spatial scale restriction ensures that we do not mistakenly attribute all spatial variability of the outcome residuals to the unmeasured spatial confounding when it is truly due to the exposure. From a causal perspective, this restriction is imposed because estimation of the causal effect of $Z$ on $Y$ in the presence of a confounder $U$ is only possible if there is variability in $Z$ within levels of $U$.

In Section 4.7, we discuss how the spatial scale restriction is also useful in settings where spatial variables mediate the effect of interest. In Section 5, we investigate the performance of the GLS and affine estimators employing the spatial scale restriction.

4.7 Spatially correlated mediating variables

From model (10) and the form of the restricted likelihood in (11), it is evident that information about the elements $(G, Q)$ in the bias correction term $-G^{-1}QZ$ is found in the spatial variability of $Z$ and the outcome model’s residuals. However, the estimation procedure described in Section 4.2 and Section 4.3 does not differentiate between spatial structure arising from spatial confounders (temporally precedent of $Z$) or variables found on the causal pathway between $Z$ and $Y$ (mediators). If $Z$ and $Y$ are measured within a small time window, it is reasonable to assume that there are no spatial covariates mediating the effect of $Z$ on $Y$, and for that reason, our estimates correspond to estimates of $\beta_1 = \mu'(z)$.

On the other hand, in the presence of spatial intermediate variables, estimates using the affine estimator might more closely resemble the direct effect of $Z$ on $Y$, not due to changes to the spatial mediators (Baron and Kenny, 1986). In this setting, the spatial scale restriction provides some protection against adjustment for spatial mediators since variation in spatial scales smaller than that of the exposure is not adjusted for. Therefore, the spatial scale restriction allows for unmeasured spatial confounder bias mitigation while protecting us from adjusting for variables on the causal pathway between $Z$ and $Y$.

4.8 Semiparametric effect estimator

Up to now, we have assumed that the true exposure-response relationship is linear. However, to better accommodate continuous exposures, we flexibly model the exposure-response relationship using penalized regression splines. Penalized regression splines may be represented as linear mixed models (Ruppert et al., 2003), allowing for the linear effect assumption in (2) to be relaxed to

$$
Y = 1\beta_0 + f(Z) + U + \varepsilon,
$$

(13)
where $f(Z) = (f(Z_1), \ldots, f(Z_n))$ and $f$ is a smooth function of $Z$. Our radial basis penalized spline model for $f$ may then be written

$$
\tilde{f}(z) = \sum_{d=1}^{D} \beta_d z^d + \sum_{k=1}^{K} l_k |z - \xi_k|^D,
$$

(14)

where $D$ is the degree of the spline and the $\xi_k$ are pre-specified knots. Letting

$$
X = \begin{pmatrix}
1 & z_1 & \cdots & z_n^D \\
\vdots & \vdots & \ddots & \vdots \\
1 & z_1 & \cdots & z_n^D
\end{pmatrix}, \quad L = \begin{pmatrix}
|z_1 - \xi_1|^D & \cdots & |z_1 - \xi_K|^D \\
\vdots & \ddots & \vdots \\
|z_n - \xi_1|^D & \cdots & |z_n - \xi_K|^D
\end{pmatrix},
$$

(15)

and $V = \varphi^{-1}LL^\top + G^{-1} + R^{-1}$, where $\varphi > 0$ is a roughness penalty, the restricted likelihood is as in (11) with updated components $X$ and $V$. Letting $M = (X L)$ and $D$ be a diagonal matrix with the first $D + 1$ elements equal to 0 and the rest equal to 1 (corresponding to penalization of the $\beta$ and $l$, respectively), the estimate of $\theta = (\beta_0, \beta_1, \ldots, \beta_D, l_1, l_2, \ldots, l_K)$ is $\hat{\theta} = (M^\top V^{-1} M + \varphi D)^{-1} M^\top V^{-1} (Y - \hat{B}Z)$. Approximate standard errors for $\hat{\theta}$ may be obtained as in Section 4.4 by augmenting $M$ with $-G^{-1}Q^\top Z$ and $\theta$ with $\rho$.

### 4.9 The affine estimator in the presence of unmeasured non-spatial confounders

Within framework (1), assuming positivity, and using the affine estimator, any set of assumptions that suffice for identification of $E[U|Z]$ would also allow identification of the causal parameter $\mu'(z)$. In Section 4.2 and Table I, we presented a set of assumptions on $(U, Z)$ that achieve that.

However, the identifiability of $E[U|Z]$ is highly dependent on the assumptions regarding the unmeasured confounder, and it is not always guaranteed. One such situation arises when unmeasured confounding (and as a result $U$) is not spatial. Even though the mathematical derivations are included in Appendix E, we present the core of the result here. Assume that $U_i$ are independent and identically distributed random variables (exhibiting no spatial structure) with $G = \tau_U I$. Further, assume that $Z$ and $\varepsilon$ are not spatially structured with precision matrices $H = \tau_Z I$ and $R = \tau_\varepsilon I$. In Appendix F, we show that the parameter vector $(\tau_U, \tau_Z, \tau_\varepsilon, \rho)$ in the restricted likelihood is reduced to $(\sigma^2, \varphi) = (\tau_U^{-1} + \tau_\varepsilon^{-1}, \tau_Z(1 - \rho^2))$, and the parameters in $(\tau_U, \tau_\varepsilon)$ and in $(\tau_Z, \rho)$ are not separately identifiable. Thus, when there is no spatial structure, $\hat{\beta} = (X^\top X)^{-1}X^\top (Y - \rho \sqrt{\tau_\varepsilon} Z)$ is not identifiable either.

This result is intuitively obvious. If $U$ is not spatially structured, there is no information in the observed data to differentiate outcome model residuals’ variability due to $U$ from that due to $\varepsilon$, and similarly nothing to differentiate intrinsic variability in $Z$ from variability due to $U$. In such case, $E[U|Z]$ is not identifiable based on observed data indicating that adjustment for $U$ is not possible if the unmeasured confounders do not exhibit spatial structure.

In the case where some of the unmeasured confounders in $C^u$ are spatial and others are not, identifiability (or lack thereof) of $E[U|Z]$ based on the observed data should be derived directly from the assumptions on the joint distribution and from the form of the restricted likelihood. Even though intuition may urge us to be skeptical of the identifiability of $E[U|Z]$, at this point we are unable to categorically prove (non-)identifiability in such cases.
5 Simulation Study

5.1 Linear effect

We perform simulations to compare the affine estimator to the ordinary and generalized least squares estimators under several generative models (GMs). Four GMs reflect $(U, Z)$ generation according to (7) and (8), with $U|Z$ and $Z|U$ being one-dimensional CAR models (detailed in Appendix F). The within-variable dependence parameters are denoted by $\varphi_U$ and $\varphi_Z$, and precision parameters by $\tau_U = \tau_Z = 1$. For the first of these models, we make $U$ and $Z$ independent ($\rho = 0$) with $\varphi_U = 0.5$ and $\varphi_Z = 0.2$. This corresponds to a scenario where the unmeasured variables are not confounders of the exposure-response relationship. For the remaining three CAR models, we specify cross-variable dependence ($\rho = 0.5$), and vary within-variable dependence parameter pair ($\varphi_U, \varphi_Z$) at (0.5, 0.2), (0.2, 0.5), and (0.35, 0.35). The fifth and sixth GMs represent situations in which the analysis model is mis-specified. For the fifth GM, $U$ was generated such that it marginally follows a one-dimensional CAR model with $\varphi_U = 0.5$ and $\tau_U = 1$, and $Z|U \sim \mathcal{N}[U, I]$. Under GM 5, the model (7) is mis-specified in that $G$ does not describe the true precision matrix of $U|Z$, and the assumption of constant conditional correlation is violated. However, the precision matrix of $Z|U$ is still correctly specified, and the cross-Markov property holds. In the sixth GM, log $U$ takes the place of $U$ in (7), so that the joint normality assumption on $(U, Z)$ is violated. In all six GMs, the outcome is generated according to (2) with $\beta = (0, 1)$ and $\varepsilon \sim \mathcal{N}[0, I]$.

Under each GM we generate 1000 datasets of size $n = 100$ and fit the OLS, GLS and affine estimators. When assumptions on the forms of variances are required, we assume CAR structures, and for the affine estimator we assume that $Q$ is of the Markov form (8). For the GLS and affine estimators, we evaluate variations with and without the restriction that $\varphi_Z < \varphi_U$ discussed in Section 4.6, with the restricted estimators denoted by (-RS).

For both the GLS and affine estimators there are cases in which the restricted likelihood is maximized at the boundary of the parameter space. Such occurrences often result in singular or near-singular variance matrices and erratic behavior by estimators. We considered two approaches to address the ill-conditioning problem in the covariance matrices. The first, which we adopted in the simulations presented here, follows from the discussion in Section 4.5 and considers an exponential prior on the condition number $\kappa$ of the precision matrix. We use this prior for the GLS-RS, affine, and affine-RS estimators, but results shown for the GLS estimator do not use this regularization prior. Note that for the GLS estimator, this prior couples the distributions of $U$ and $Z$ which is not usually a feature in spatial analyses, and we wanted to represent the GLS estimator’s performance as implemented usually in practice. (When fitting the GLS estimator using the prior, results were not substantially different.) An alternative approach is to proceed without a regularization prior, and when $\kappa$ is large, say, greater than 100, “fall back” to a simpler estimator. In Appendix G we present a smaller battery of simulation results based on this approach yielding similar conclusions to those presented here.

Table 2 displays the simulation results in terms of bias, standard deviation of estimates across data sets, root mean squared error (RMSE) and empirical coverage of 95% confidence intervals. We first note that there is minimal difference among the OLS, GLS, and GLS-RS estimators in all simulation scenarios. In all cases, the standard errors of the affine estimators are larger than those of the OLS, GLS, and GLS-RS estimators.

For the unconfounded GM 1, all estimators are unbiased and have approximately correct confidence
Table 2: Simulation results from 1000 data sets of size $n = 100$. The -RS suffix indicates estimators with the restriction $\varphi_Z \leq \varphi_U$.

| Mechanism | Estimator | Bias | Std. Err. | RMSE | 95% CI Coverage |
|-----------|-----------|------|-----------|------|-----------------|
| GM 1      | Independent OLS | 0.00 | 0.19 | 0.19 | 0.94 |
|           | GLS | 0.00 | 0.19 | 0.19 | 0.93 |
|           | GLS-RS | 0.00 | 0.19 | 0.19 | 0.93 |
|           | Affine | 0.01 | 0.34 | 0.34 | 0.98 |
|           | Affine-RS | 0.01 | 0.35 | 0.35 | 0.98 |
| GM 2      | Large-scale confounder OLS | 0.67 | 0.15 | 0.69 | 0.00 |
|           | GLS | 0.64 | 0.15 | 0.65 | 0.01 |
|           | GLS-RS | 0.63 | 0.14 | 0.64 | 0.01 |
|           | Affine | 0.49 | 0.47 | 0.68 | 0.81 |
|           | Affine-RS | 0.24 | 0.36 | 0.43 | 0.96 |
| GM 3      | Large-scale exposure OLS | 0.56 | 0.12 | 0.57 | 0.01 |
|           | GLS | 0.55 | 0.12 | 0.57 | 0.01 |
|           | GLS-RS | 0.54 | 0.13 | 0.56 | 0.02 |
|           | Affine | 0.56 | 0.28 | 0.63 | 0.87 |
|           | Affine-RS | 0.30 | 0.59 | 0.66 | 0.88 |
| GM 4      | Same scales OLS | 0.60 | 0.14 | 0.62 | 0.01 |
|           | GLS | 0.59 | 0.14 | 0.61 | 0.01 |
|           | GLS-RS | 0.58 | 0.14 | 0.59 | 0.02 |
|           | Affine | 0.55 | 0.37 | 0.66 | 0.85 |
|           | Affine-RS | 0.31 | 0.47 | 0.56 | 0.92 |
| GM 5      | Non-constant conditional correlation OLS | 0.37 | 0.09 | 0.38 | 0.03 |
|           | GLS | 0.36 | 0.09 | 0.37 | 0.04 |
|           | GLS-RS | 0.36 | 0.09 | 0.37 | 0.04 |
|           | Affine | 0.21 | 0.32 | 0.38 | 0.95 |
|           | Affine-RS | 0.09 | 0.27 | 0.28 | 0.98 |
| GM 6      | Non-normal joint distribution OLS | 1.15 | 0.50 | 1.25 | 0.01 |
|           | GLS | 1.03 | 0.45 | 1.13 | 0.01 |
|           | GLS-RS | 1.07 | 0.48 | 1.17 | 0.01 |
|           | Affine | 0.74 | 0.63 | 0.97 | 0.84 |
|           | Affine-RS | 0.59 | 0.56 | 0.81 | 0.90 |
interval coverage, but both affine estimators have much larger standard errors and therefore RMSE. In all GMs with confounding (2–6), the Affine-RS estimator mitigates bias relative to the OLS estimator, whereas the GLS and GLS-RS estimators do not. The results for the unrestricted Affine estimator are mixed—it mitigates bias when the scale of the confounder is larger than that of the covariate (including in the misspecified cases), but not when it is of a smaller or equal scale. Even when the unrestricted Affine estimator mitigates bias, it does not do so as well as the Affine-RS estimator. When the restricted scale assumption is correct, the Affine-RS estimator has a smaller standard error than the unrestricted Affine estimator. Additionally, the Affine-RS estimator has a smaller RMSE than all other estimators except in the case of a large-scale exposure where its scale restriction is false. However, both affine estimators have far superior confidence interval coverage rates.

5.2 Nonlinear effect

The bias-variance trade-off observed between the GLS and affine estimators in the linear case was also observed for a non-linear exposure-response curve. We generated 1000 data sets of size 300 where \( U, Z \) are generated from (7) with \( (\tau_U, \varphi_U, \tau_Z, \varphi_Z, \rho) = (1, 0.5, 1, 0.2, 0.5) \), and \( Y \) is generated according to (13), with \( \beta_0 = 0, f(z) = 2/(1 + e^{-6z}) - 1 \), and \( \sigma^2 = 1 \). Therefore, the true exposure-response is an anti-symmetric sigmoid curve with asymptotes \(-1\) and \(1\). We fit the restricted-scale semiparametric GLS and affine estimators using a penalized cubic spline model with a radial basis and used the same truncated exponential prior on the condition number \( \kappa \) as in the linear simulations.

Figure 2 displays a graphical summary of the simulation results. For the most part, both estimators capture the general shape of the mean response curve. However, the GLS-RS estimator shows substantial bias across the exposure range, apart from exposure values near 0. On the other hand, the Affine-RS estimator is much less biased, but exhibits substantially greater variability, especially for exposure ranges with limited available data.

![Figure 2: Nonlinear effect simulation results. 1000 datasets of size \( n = 100 \).]
6 Estimating the effect of HyADS relative coal exposure and relative humidity on ambient PM$_{2.5}$ concentrations in New England

PM$_{2.5}$ pollution consists of particles with diameter less than 2.5 micrometers emitted by various sources, including power plants, vehicles, and forest fires. Due to its very small size, PM$_{2.5}$ can travel far into the human body. For that reason, it has been associated with various adverse health outcomes such as cardiovascular and respiratory hospitalizations and mortality (see for example Laden et al. (2000); Dominici et al. (2006) among others). Thus, PM$_{2.5}$ is one of the key regulated air pollutants, with some policies aimed at reducing emissions from coal-fired power plants.

We evaluate the effectiveness of reductions in coal power plant emissions on ambient PM$_{2.5}$ concentrations in New England (Maine, Massachusetts, Rhode Island, Connecticut, New Hampshire, Vermont) in 2012, while accounting for the potential threat from unmeasured spatial confounding. To best illustrate our methodology in the air pollution setting, we also evaluate the causal relationship between relative humidity and ambient PM$_{2.5}$ levels. Computational restrictions did not allow us to evaluate these relationships in the entire U.S.

6.1 Exposure information and data linkage

We use 2012 exposure information from the HYSPLIT average dispersion model (HyADS), a recently developed reduced-complexity pollution transport model (Henneman et al., 2019a). HyADS uses wind speed and direction, among other information, to trace the movement of particles from individual sources and create a source-receptor matrix expressing particle concentrations in each zip code and from every EGU. The source-receptor matrix is weighted by EGU emissions, and it is further aggregated over the year and over all sources polluting in a zip code. Therefore, HyADS expresses a zip-code specific unitless measure of emissions-weighted parcel concentrations, referred to as the HyADS relative coal exposure. Recently, HyADS exposure information was used in estimating the health effects of coal emissions on health (Henneman et al., 2019b).

Fine resolution ambient PM$_{2.5}$ concentrations in 2012, which were developed by combining output from the GEOSChem chemical transport model, ground-based measurements, satellite observations, and other information were retrieved from van Donkelaar et al. (2016); Boys et al. (2014); Van Donkelaar et al. (2014). We acquire 2012 weather and geographic information (average annual temperature, dew point, relative humidity, and altitude) from the Automated Surface Observing System (ASOS) of the National Oceanic and Atmospheric Administration, and demographic information from the 2000 Census. ASOS monitors were linked to zip codes whose centroids were located within 100 kilometers. Data were aggregated to the county level in order to reduce computational complexity of the spatial models without reducing the geographical area of study.

Figure 3 shows maps of HyADS, PM$_{2.5}$, and relative humidity over the study area. Since HyADS exhibits limited small-scale spatial variability, we expected that spatial models would lack power to identify the spatial structure of any confounders. Thus, we plotted maps of temperature, altitude, relative humidity, and dew point, and identified relative humidity as the environmental variable with the highest small-scale spatial variability. For that reason, we estimated the relationship between relative humidity and ambient PM$_{2.5}$. This relationship is not “causal” in the sense that it is not feasible to directly intervene on relative
humidity, although it is possible in theory for relative humidity to change while other variables in our dataset remain constant.

6.2 Unmeasured spatial confounding in the analysis of PM$_{2.5}$ concentrations

In both analyses, unmeasured spatial confounding could arise if missing atmospheric, weather, or other spatially varying covariate is a confounder of the exposure-PM$_{2.5}$ relationship. We group measured covariates in two groups: demographic and environmental variables. Environmental variables are likely to be confounders of the effects of HyADS and humidity on PM$_{2.5}$. These covariates are temperature and altitude when evaluating the effect of humidity, and further include humidity and dew point when HyADS is the exposure of interest. Demographic variables are possible confounders of the effect of HyADS but are less likely to confound the relationship between humidity and PM$_{2.5}$. Demographic variables are total population, population density measured as population per square mile, median household income, and population percentages of urban residents, high school graduates, white, poor, and female populations, and migration to the area within the last five years. In all analyses, an indicator for island counties (Nantucket and Dukes County, MA) is included. In order to evaluate the affine estimator’s performance in mitigating bias from unmeasured spatial confounders we estimate the effect of exposure on the outcome employing the OLS, GLS and affine estimators adjusting for no covariates, demographics only, environmental only, and both demographic and environmental covariates.

For the GLS and affine estimators, neighboring counties are defined as counties that share a geographical border, as recorded by the 2010 United States Census. We use the proper conditional autoregressive model for both the exposure and confounder models, and the joint confounder-exposure model structure described by (7) and (8). Variance parameters are estimated via maximum a posteriori estimation, maximizing the product of the restricted likelihood and the truncated Exp[1/10] prior density on the condition number of the joint precision matrix $P$, as evaluated in the simulation study.

Figure 3: Spatial distribution of HyADS exposure, ambient PM$_{2.5}$ concentrations, and relative humidity in New England in 2012.
6.3 Results

Figure 4 displays the OLS, GLS, GLS-RS, and affine-RS estimates and 95% confidence intervals for the linear effect of the HyADS relative coal exposure on PM$_{2.5}$ concentrations using each set of covariates. Point estimates correspond to the expected change in PM$_{2.5}$ concentrations for one standard deviation increase in the exposure. When all potential confounders are adjusted for, one standard deviation increase in HyADS exposure is estimated to lead to an increase in PM$_{2.5}$ by 0.48 (95% CI: 0.27 to 0.69) $\mu g/m^3$ according to the OLS estimator, and by 0.28 (−0.35 to 0.91) according to the affine estimator.

Across methods and confounding adjustment sets point estimates are positive, indicating that coal-fired power plant emissions lead to increases in ambient PM$_{2.5}$ concentrations. Generally, the OLS and GLS estimates and corresponding 95% confidence intervals are similar and non-overlapping zero, while the GLS-RS and affine-RS estimates are slightly closer to zero with wider confidence intervals. In all cases, the profile restricted likelihood for $\rho$ is sharply peaked near or at zero, and so the GLS-RS and affine-RS point estimates are similar or identical, but confidence intervals based on the affine estimator are larger than their GLS-RS counterparts. An estimate for $\rho$ close or at zero could indicate that unmeasured spatial confounding is not present in this setting, or that the spatial variability in the observed data does not allow us to identify common residual spatial structure.

Similarly, Figure 5 displays the estimates and 95% confidence intervals of the effect of average relative humidity on PM$_{2.5}$. In these analyses, the estimate of $\rho$ is small but negative indicating the presence of unmeasured spatial confounding. When both demographic and environmental variables are included, all spatial estimates (GLS, GLS-RS, Affine-RS) are very close to zero, while the OLS estimate is still somewhat negative, though not statistically significant. When neither demographic nor environmental variables are explicitly included, the OLS and GLS estimates are similar, negative, and statistically significant, while the GLS-RS and affine-RS estimates are substantially closer to zero. This indicates that, when demographic and environmental variables are not included in the outcome model, the GLS-RS and affine-RS estimators still return point estimates close to the estimate from the OLS estimator when these variables are explicitly...
adjusted for. Again, the estimated standard errors for the GLS-RS estimates are larger than those of the OLS and GLS estimates, and those for the affine-RS estimates are larger still.

Interestingly, the relationship between the GLS-RS estimate and the other estimates differ when demographic variables are included versus when environmental variables are included. When demographic but not environmental variables are included, the GLS-RS estimate is similar to the OLS and GLS estimates. Conversely, when environmental but not demographic variables are included, the GLS-RS estimate is more similar to the affine-RS estimate. Thus, in this dataset the GLS-RS estimator appears to be able to recognize outcome spatial dependence due to the outcome predictors (demographic variables), but not the spatial confounders (environmental variables).

Appendix H includes a subset of analogous results using semiparametric mean structure in Section 4.8 to estimate the effects of HyADS exposure and relative humidity on PM$_{2.5}$ concentrations, adjusting for no additional covariates. The conclusions are similar. In short, when estimating the causal effect of HyADS exposure, the affine estimates mirror the corresponding OLS estimates. However, when estimating the effect of relative humidity on PM$_{2.5}$ concentrations, the OLS estimated curve has a steeper decline than the curve estimated using the affine estimator.

7 Discussion

Unmeasured confounding is a threat to most studies utilizing observational data, and one of the main arguments used against air pollution epidemiology. A powerful approach to assessing the robustness of estimated effects to unmeasured confounding is sensitivity analysis (Rosenbaum and Rubin, 1983a; Rosenbaum, 2002; Imbens and Rubin, 2015). Even though sensitivity analysis can provide a measure of robustness for estimated effects, it does not directly adjust effect estimates for the presence of such confounders.

When the study of interest, data, and unmeasured confounders are spatial in nature, we discussed an estimator that, based on assumptions, mitigates bias from unmeasured spatial confounders. Our approach is
rooted in the causal inference framework and exploits spatial statistics tools that can be used to directly adjust for structured unmeasured confounding. We hope that our work contributes to the growing bridge between spatial data analysis and causal inference. The methodology is intended to be amenable to researchers accustomed to the usual spatial statistics literature, but could potentially be useful in situations calling for mixed models more generally, with appropriate modifications. For that reason, the proposed approach may be widely applicable to scenarios in spatial statistics, time-series analyses, and spatio-temporal settings.

We discussed a set of assumptions that allowed for identification of the bias correction term using only the observed data, while providing a simple expression for the expected value of the confounder conditional on the exposure: joint normality of the spatial confounder and exposure of interest, the cross-Markov and constant conditional correlation assumptions. There are several ways in which these assumptions could be relaxed. First, joint normality may be relaxed by assuming joint normality of an underlying random effect process, with the realizations of both the exposure and covariates arising from other distributions. For example, exponential family distributions would admit generalized linear mixed model representations for which Laplace approximations exist for the resulting restricted likelihoods (Wood, 2011). Furthermore, spatial Dirichlet processes may be used as a more flexible, nonparametric alternative to the multivariate normal form of the random effect structure, both in point-referenced (Gelfand et al., 2005) and areal (Kottas et al., 2008) data. The cross-Markov assumption may be relaxed by, for example, treating the joint distribution of the exposure and confounder as a multivariate conditional autoregressive process (Gelfand and Vounatsou, 2003) and expanding the allowable neighbor relations. The constant conditional correlation assumption may be relaxed by allowing the conditional correlation to vary smoothly in space or based on the number of neighboring locations.

Researchers would need to verify that the set of assumptions they decide on is reasonable within the context of their study suffices for identification of the bias correction term. We consider this to be the most pressing topic of future study: what are the general conditions under which causal effects are identifiable in the presence of unmeasured spatial confounding, and to what extent bias mitigation is robust to model misspecification. We have illustrated situations in which the causal effect is and is not identifiable, but at this point such a determination must be made through direct study of the restricted likelihood or simulation, as more approachable criteria are not known.

Last, some challenges in applying the proposed approach arise as a result of using the two-step estimation procedure of restricted maximum likelihood or maximum a posteriori estimation of variance parameters followed by affine estimation of regression parameters. Future work could focus on testing whether the conditional correlation $\rho$ is zero, which is not a topic treated here. In such cases, a purely Bayesian estimation approach could prove useful.

Publicly available data and code

The air pollution dataset and analysis code are available at https://github.com/schnellp/causal-spatial.

Acknowledgements

We would like to thank Dr. Lucas R.F. Henneman for supplying the data and providing valuable discussion on the interpretation of our results. We would also like to thank Dr. James S. Hodges for his valuable
thoughts and input during various stages of the manuscript. This work was partially supported by grant R01MH118927 from the National Institutes of Health.

Appendices

A Identifiability of causal estimands

Here, we review causal identifiability of $\mu(z) = E[Y(z)]$, the expected value of the potential outcome for a fixed treatment $z$ over some population, for a binary treatment $z \in Z = \{0, 1\}$. Note that we do not observe $Y(z)$ for everyone and $\mu(z)$ is an expectation including many unobserved quantities.

A causal estimand is referred to as identifiable under a set of assumptions if it can be written as a function of observables. For $\mu(z)$, on set of assumptions is (1) consistency of potential outcomes, (2) positivity and (3) no unmeasured confounding, since

$$
\mu(z) = E[Y(z)] = E[E[Y(z)|W]] = E[E[Y(z)|Z = z, W]] = E[E[Y|Z = z, W]],
$$

where the third equation holds because of the no unmeasured confounding assumption, and the fourth equation holds because of the causal consistency assumption. So $\mu(z)$ is written as a function of the observed outcomes among those with $Z = z$, and for that reason it is identifiable.

B Conservative bounds on the conditional correlation

Given positive definite $G$ and $H$, and $Q$ as defined in (8), $\rho$ needs to be restricted such that $P = \begin{pmatrix} G & Q \\ QT & H \end{pmatrix}$ is also positive definite. Letting

$$
S = \begin{pmatrix} G & 0 \\ 0 & H \end{pmatrix} \quad \text{and} \quad T = \begin{pmatrix} 0 & Q \\ Q & 0 \end{pmatrix},
$$

we constraint $S, T$ such that for any vector $v \neq 0$ of length $2n$, $v^T P v = v^T S v + v^T T v > 0$. Let $C = \{v : |v| = 1\}$. It suffices to show that $\min_{v \in C} v^T S v > -\min_{v \in C} v^T T v$. Note that $\min_{v \in C} v^T S v$ is the minimum eigenvalue of $S$, and similarly for $T$. Also, since $S$ is block diagonal, $\min_i \{\lambda_S, \lambda_H\} = \min[\min_i \{\lambda_G, \lambda_H\}]$. The eigenvalues of $T$ are the roots of $|\lambda I_{2n} - T| = |\lambda I_n - \rho^2 QQ| = \prod_{i=1}^n (\lambda^2 - \rho^2 g_{ii} h_{ii})$, i.e., $\lambda = \pm \rho \sqrt{g_{ii} h_{ii}}$. Thus $-\min_{v \in C} v^T T v = |\rho| \sqrt{\max_i \{g_{ii} h_{ii}\}}$, and

$$
|\rho| < \frac{\min[\min_i \{\lambda_G, \lambda_H\}]}{\sqrt{\max_i \{g_{ii} h_{ii}\}}}
$$

guarantees positive definite $P$. 

20
C Hierarchical factorization

Based on (7) the covariance matrix is

$$\begin{pmatrix} G & Q \\ Q^T & H \end{pmatrix}^{-1} = \begin{pmatrix} G^{-1} + G^{-1}Q(H - Q^TG^{-1}Q)^{-1}Q^TG^{-1} & -G^{-1}Q(H - Q^TG^{-1}Q)^{-1} \\ -(H - Q^TG^{-1}Q)^{-1}Q^TG^{-1} & (H - Q^TG^{-1}Q)^{-1} \end{pmatrix}.$$ 

Based on the properties of the multivariate normal distribution,

$$U | Z \sim N(\mu_{U|Z}, \Sigma_{U|Z})$$

where

$$\mu_{U|Z} = -G^{-1}Q(H - Q^TG^{-1}Q)^{-1}(H - Q^TG^{-1}Q)^{-1}Z = -G^{-1}QZ$$

$$\Sigma_{U|Z} = G^{-1} + G^{-1}Q(H - Q^TG^{-1}Q)^{-1}Q^TG^{-1} - G^{-1}Q(H - Q^TG^{-1}Q)^{-1}(H - Q^TG^{-1}Q)(H - Q^TG^{-1}Q)^{-1}Q^TG^{-1} = G^{-1}.$$

Based on the above, the marginal variance of $Z$ is $(H - Q^TG^{-1}Q)^{-1}$, and the $\text{Var}[Y|Z] = \text{Var}[U|Z] + \text{Var}[\varepsilon|Z] = G^{-1} + R^{-1}$. Further, $E[U|Z] = -G^{-1}QZ$ leading to the following outcome model integrating $U|Z$ out:

$$Y|Z \sim N(X\beta + E[U|Z], \text{Var}[U|Z] + \text{Var}[\varepsilon]) = N(X\beta - G^{-1}QZ, G^{-1} + R^{-1}).$$

(16)

D Restricted likelihood

The full data likelihood can be factored as $f(y, u, z; \beta) = f(y|u, z; \beta) f(u|z) f(z)$. Using the outcome model in (16) and defining $B = -G^{-1}Q$, $A = \text{Var}[Z] = (H - Q^TG^{-1}Q)^{-1}$, and $V = G^{-1} + R^{-1}$, we have

$$f(Y|Z; \beta) \propto |V|^{-1/2} \exp \left[ -\frac{1}{2} \begin{pmatrix} Y - BZ - X\beta \end{pmatrix}^T V^{-1} \begin{pmatrix} Y - BZ - X\beta \end{pmatrix} \right],$$

(17)

leading to the following restricted likelihood conditional on $Z$,

$$r(Y|Z) \propto (|V| \cdot |X^TV^{-1}X|)^{-\frac{1}{2}} \exp \left[ -\frac{1}{2} (Y - BZ)^T \begin{pmatrix} V^{-1} - V^{-1}X(X^TV^{-1}X)^{-1}X^TV^{-1} \end{pmatrix} (Y - BZ) \right].$$

(18)

Since $f(Z)$ does not depend on $\beta$, we can write the full restricted likelihood as

$$RL = r(Y|Z) f(Z),$$

$$\propto |V| \cdot |A| \cdot |X^TV^{-1}X|^{-1/2} \exp \left[ -\frac{1}{2} \begin{pmatrix} (Y - BZ)^T (V^{-1} - V^{-1}X(X^TV^{-1}X)^{-1}X^TV^{-1}) (Y - BZ) \\ + Z^TA^{-1}Z \end{pmatrix} \right].$$

(19)
E Identifiability in the absence of spatial structure

We illustrate the way in which the proposed method fails to adjust for confounding in the absence of spatial structure. Suppose that $G = \tau_U I$, $H = \tau_Z I$, and $R = \tau_e I$ are all scalar matrices. We then have $Q = -\rho \sqrt{\tau_U \tau_Z}$, and in the notation of (11), $V = (\tau_U^{-1} + \tau_e^{-1})I$, $A = \tau_Z^{-1}(1 - \rho^2)^{-1}I$, and $B = \rho \sqrt{\tau_U} I$. Note that $A$ does not depend on $\tau_U$. Various simplifications to (11) are then available:

\[
|V| \cdot |A| \cdot |X^T V^{-1} X| = (\tau_U^{-1} + \tau_e^{-1})^{n-p} [\tau_Z^{-1}(1 - \rho^2)^{-1}]^n \|X^T X\|;
\]

\[
V^{-1} - V^{-1} X (X^T V^{-1} X)^{-1} X^T V^{-1} = (\tau_U^{-1} + \tau_e^{-1})^{-1} [I - X (X^T X)^{-1} X^T],
\]

\[
Z^T A^{-1} Z = \tau_Z (1 - \rho^2) Z^T Z.
\]

The log restricted likelihood is then

\[
\log RL = C - \frac{n - p}{2} \log(\tau_U^{-1} + \tau_e^{-1}) - \frac{n}{2} \log(\tau_Z^{-1}(1 - \rho^2)^{-1})
- \frac{1}{2} \left[ (\tau_U^{-1} + \tau_e^{-1})^{-1} \left( Y - \rho \sqrt{\tau_Z \tau_U} Z \right)^T \{I - X (X^T X)^{-1} X^T\} \left( Y - \rho \sqrt{\tau_Z \tau_U} Z \right) \right]
- \frac{1}{2} \tau_Z (1 - \rho^2) Z^T Z,
\]

\[
= C - \frac{n - p}{2} \log(\tau_U^{-1} + \tau_e^{-1}) + \frac{n}{2} \log(1 - \rho^2)
+ \frac{1}{2} (\tau_U^{-1} + \tau_e^{-1})^{-1} Y^T \{I - X (X^T X)^{-1} X^T\} Y
+ (\tau_U^{-1} + \tau_e^{-1})^{-1} \rho \sqrt{\tau_Z \tau_U} Z^T \{I - X (X^T X)^{-1} X^T\} Y
- \frac{1}{2} (\tau_U^{-1} + \tau_e^{-1})^{-1} \rho^2 \sqrt{\tau_Z \tau_U} Z^T \{I - X (X^T X)^{-1} X^T\} Z
- \frac{1}{2} \tau_Z (1 - \rho^2) Z^T Z
\]

(20)

where the last equation holds because $Z$ is a column of $X$, and therefore $Z^T \{I - X (X^T X)^{-1} X^T\} = 0$.

Treating the restricted likelihood as a function of $\rho$, due to the term $\frac{n}{2} \log(1 - \rho^2)$, the log restricted likelihood approaches $-\infty$ as $\rho \to \pm 1$, and so all maxima on $\rho \in [-1, 1]$ are in the interior.

Writing $(\tau_U^{-1} + \tau_e^{-1}) = \sigma^2$ and $\varphi = \tau_Z(1 - \rho^2)$ we then have

\[
\log RL = C - \frac{n - p}{2} \log \sigma^2 - \frac{1}{2} \sigma^{-2} Y^T \{I - X (X^T X)^{-1} X^T\} Y + \frac{n}{2} \log \varphi - \frac{1}{2} \varphi Z^T Z,
\]

\[
\frac{\partial}{\partial \sigma^2} \log RL = -\frac{n - p}{2 \sigma^2} + \frac{1}{2 \sigma^4} Y^T \{I - X (X^T X)^{-1} X^T\} Y
\]

\[
\frac{\partial}{\partial \varphi} \log RL = \frac{n}{2 \varphi} - \frac{1}{2} Z^T Z.
\]

(21)

Thus $\tau_U$ and $\tau_e$ are not identifiable, and the global maximum is at $\sigma^2 = (n-p)^{-1} Y^T \{I - X (X^T X)^{-1} X^T\} Y$. 

22
Similarly, $\tau_Z$ and $\rho$ are not identifiable, and the global maximum is at $\varphi = n/Z^\top Z$. As a final result, 
\[ \bar{\beta} = (X^\top V^{-1}X)^{-1}X^\top V^{-1}(Y - BZ) = (X^\top X)^{-1}X^\top(Y - \rho \sqrt{\tau_Z} Z) \] is undetermined.

### F Specification of the proper conditional autoregressive model

We briefly describe the univariate (proper) conditional autoregressive model (Besag, 1974; Cressie, 1993) used in simulations and analyses in this paper. The CAR model is most often presented in a conditional specification,

\[ U_i|U_{-i} \sim N\left(\varphi_U \sum_{j \in \partial_i} U_j/|\partial_i|, \sigma^2\right), \quad (22) \]

where $\partial_i$ is the set of $j$ such that $i$ and $j$ are neighbors, and $|\partial_i|$ is the count of those neighbors. A multivariate normal representation of the distribution of $U$ is then available as

\[ U \sim N\left(0, \sigma^2(D - \varphi_U W)^{-1}\right), \quad (23) \]

where $w_{ij} = 1$ if $i$ and $j$ are neighbors, and 0 otherwise, and $D$ is diagonal with entries $|\partial_i|$. This joint distribution is proper as long as $\varphi_U$ is in $(1/\lambda_{(1)}, 1)$, where $\lambda_{(1)}$ is the lowest eigenvalue of $W$.

### G Simulation results for fall-back procedure

One alternative to imposing a prior on the condition number $\kappa$ of the joint precision matrix of the confounder and exposure is to apply a “fall-back” procedure. In this procedure, when the precision matrix is ill-conditioned ($\kappa > 100$), the estimate from a simpler method is used instead. In particular, when the GLS or GLS-RS estimates include an ill-conditioned matrix, the OLS estimator is used instead. Similarly, when the affine or affine-RS estimates include an ill-conditioned matrix, the GLS or GLS-RS estimates are used, respectively unless those too include an ill-conditioned matrix, in which case the OLS estimate is used.

Table G.1 shows simulation results employing the fall-back procedure. As expected, the performance of the GLS estimator using the fall-back procedure falls between the performance of the OLS estimator and the performance of the GLS estimator among data sets where the precision matrix was not ill-conditioned. Similarly for the affine estimator.

### H Semiparametric air pollution estimates

Figure H.1 displays nonlinear estimates and pointwise 95% confidence bands of the exposure-response relationship for both HyADS and relative humidity exposures, and for all values $z$ in the observed exposure range. As in the case of the linear effect estimates, both estimates for the effect of HyADS were similar and positive, while the OLS estimate for the effect of humidity was negative and the Affine-RS estimate null. There is no convincing evidence of substantial deviations from linearity. GLS-RS estimates were similar to Affine-RS estimates though with narrower confidence bands, and the GLS estimates were degenerate, likely due to too many degrees of freedom.
Table G.1: Simulation results using fall-back procedure. 100 datasets of size $n = 100$. 

| Mechanism          | Estimator | Bias  | Std. Err. | RMSE  | 95% CI Coverage |
|--------------------|-----------|-------|-----------|-------|-----------------|
| Independent        | OLS       | 0.00  | 0.19      | 0.19  | 0.96            |
|                    | GLS       | 0.00  | 0.19      | 0.19  | 0.94            |
|                    | GLS-RS    | 0.00  | 0.19      | 0.19  | 0.94            |
|                    | Affine    | 0.00  | 0.74      | 0.73  | 0.95            |
|                    | Affine-RS | −0.01 | 0.66      | 0.66  | 0.95            |
| Large-scale        | OLS       | 0.68  | 0.14      | 0.70  | 0.00            |
| confounder         | GLS       | 0.64  | 0.13      | 0.66  | 0.00            |
|                    | GLS-RS    | 0.64  | 0.14      | 0.65  | 0.00            |
|                    | Affine    | 0.47  | 0.70      | 0.84  | 0.85            |
|                    | Affine-RS | 0.11  | 0.66      | 0.67  | 0.90            |
| Large-scale        | OLS       | 0.56  | 0.11      | 0.57  | 0.00            |
| covariate           | GLS       | 0.56  | 0.11      | 0.57  | 0.00            |
|                    | GLS-RS    | 0.55  | 0.12      | 0.57  | 0.00            |
|                    | Affine    | 0.74  | 0.57      | 0.93  | 0.74            |
|                    | Affine-RS | 0.34  | 0.56      | 0.65  | 0.87            |
| Same scales        | OLS       | 0.61  | 0.13      | 0.62  | 0.00            |
|                    | GLS       | 0.60  | 0.12      | 0.61  | 0.00            |
|                    | GLS-RS    | 0.59  | 0.13      | 0.60  | 0.00            |
|                    | Affine    | 0.56  | 0.57      | 0.79  | 0.83            |
|                    | Affine-RS | 0.27  | 0.56      | 0.62  | 0.92            |
| Non-constant       | OLS       | 0.37  | 0.09      | 0.38  | 0.01            |
| conditional        | GLS       | 0.36  | 0.08      | 0.37  | 0.02            |
| correlation        | GLS-RS    | 0.36  | 0.08      | 0.37  | 0.01            |
|                    | Affine    | 0.08  | 0.52      | 0.52  | 0.88            |
|                    | Affine-RS | 0.00  | 0.49      | 0.49  | 0.90            |
| Non-normal         | OLS       | 1.13  | 0.46      | 1.22  | 0.00            |
| joint              | GLS       | 1.03  | 0.41      | 1.11  | 0.01            |
| distribution       | GLS-RS    | 1.03  | 0.42      | 1.12  | 0.01            |
|                    | Affine    | 0.56  | 0.86      | 1.03  | 0.83            |
|                    | Affine-RS | 0.37  | 0.77      | 0.85  | 0.87            |
Figure H.1: Nonlinear effect estimates and pointwise 95% confidence bands for the relationship between HyADS and relative humidity exposures and PM$_{2.5}$ concentrations. Exposures are presented in terms of standard deviations away from the mean. Points on the x-axis show the distribution of exposure measurements in the observed data. No covariates are included except for island county indicator.

I Including predictors of exposure

In the presence of additional measured covariates $W^m$, that influence $Z$, the affine estimator takes the form:

$$
\hat{\beta} = \left( X^\top (\text{Var}[Y|Z, W^m])^{-1} X \right)^{-1} X^\top (\text{Var}[Y|Z, W^m])^{-1} \{ Y - E[U|Z, W^m] \}.
$$

We can assume a similar structure

$$
\begin{pmatrix}
    U \\
    Z
\end{pmatrix} | W^m \sim \mathcal{N} \left[ \begin{pmatrix} 0 \\ W^m \gamma \end{pmatrix}, \begin{pmatrix} G & Q \\ Q^\top & H \end{pmatrix}^{-1} \right].
$$

And the model for $(Y, Z)|W^m$ becomes

$$
Y|Z, W^m \sim \mathcal{N}[X\beta - G^{-1}Q(Z - W^m\gamma), G^{-1} + R^{-1}],
$$

$$
Z|W^m \sim \mathcal{N}[W^m\gamma, (H - Q^\top G^{-1}Q)^{-1}].
$$

Defining

$$
\begin{align*}
    M &= \begin{pmatrix} G^{-1} + R^{-1} & 0 \\ 0 & (H - Q^\top G^{-1}Q)^{-1} \end{pmatrix}, \\
    C &= \begin{pmatrix} X & G^{-1}QW^m \\ 0 & W^m \end{pmatrix}, \\
    \nu &= \begin{pmatrix} Y + G^{-1}QZ \\ Z \end{pmatrix}, \\
    \theta &= \begin{pmatrix} \beta \\ \gamma \end{pmatrix},
\end{align*}
$$

(26)
we can write the joint distribution of \((Y, Z)\) as

\[
f(Y, Z|\beta, \gamma) \propto |M|^{-\frac{1}{2}} \exp \left[ -\frac{1}{2} (\nu - C\theta)^T M^{-1} (\nu - C\theta) \right],
\]

(27)

and the restricted likelihood as

\[
RL \propto \left( |M| \cdot |C^T M^{-1} C| \right)^{-1/2} \exp \left[ -\frac{1}{2} \nu^T (M^{-1} - M^{-1} C (C^T M^{-1} C)^{-1} C^T M^{-1} ) \nu \right].
\]

(28)

The affine estimator for \((\beta, \gamma)\) is then \((C^T M^{-1} C)^{-1} C^T M^{-1} \nu\), and the approximate standard error of Section 4.4 may be obtained by augmenting \(C\) with \(-G^{-1} Q^* (Z - W^m \gamma)\) and \(\theta\) with \(\rho\).

References

R. M. Baron and D. A. Kenny. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, 51(6):1173–1182, 1986.

J. Besag. Spatial interaction and the statistical analysis of lattice systems. *Journal of the Royal Statistical Society, Series B (Statistical Methodology)*, 36(2):192–236, 1974.

B. Boys, R. Martin, A. Van Donkelaar, R. MacDonell, N. Hsu, M. Cooper, R. Yantosca, Z. Lu, D. Streets, Q. Zhang, et al. Fifteen-year global time series of satellite-derived fine particulate matter. *Environmental Science & Technology*, 48(19):11109–11118, 2014.

Y. Chung, S. Rabe-Hesketh, and I. H. Choi. Avoiding zero between-study variance estimates in random-effects meta-analysis. *Statistics in Medicine*, 32(23):4071–4089, 2013.

Y. Chung, A. Gelman, S. Rabe-Hesketh, J. Liu, and V. Dorie. Weakly informative prior for point estimation of covariance matrices in hierarchical models. *Journal of Educational and Behavioral Statistics*, 40(2):136–157, 2015.

P. Congdon. Assessing the impact of socioeconomic variables on small area variations in suicide outcomes in England. *International Journal of Environmental Research and Public Health*, 10(1):158–177, 2013.

N. Cressie. *Statistics for Spatial Data*. John Wiley & Sons, 1993.

Q. Di, Y. Wang, A. Zabonetti, Y. Wang, P. Koutrakis, C. Choirat, F. Dominici, and J. D. Schwartz. Air pollution and mortality in the Medicare population. *New England Journal of Medicine*, 376(26):2513–2522, 2017.

F. Dominici, R. D. Peng, M. L. Bell, L. Pham, A. McDermott, S. L. Zeger, and J. M. Samet. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *Journal of the American Medical Association*, 295(10):1127–1134, 2006.

A. E. Gelfand and P. Vounatsou. Proper multivariate conditional autoregressive models for spatial data analysis. *Biostatistics*, 4(1):11–15, 2003.

A. E. Gelfand, A. Kottas, and S. N. MacEachern. Bayesian nonparametric spatial modeling with Dirichlet process mixing. *Journal of the American Statistical Association*, 100(471):1021–1035, 2005.

E. M. Hanks, E. M. Schliep, M. B. Hooten, and J. A. Hoeting. Restricted spatial regression in practice: Geostatistical models, confounding, and robustness under model misspecification. *Environmetrics*, 26(4):243–254, 2015.
L. R. Henneman, C. Choirat, C. Ivey, K. Cummiskey, and C. M. Zigler. Characterizing population exposure to coal emissions sources in the United States using the HyADS model. *Atmospheric Environment*, 203: 271–280, 2019a.

L. R. Henneman, C. Choirat, and C. M. Zigler. Decreases in negative health outcomes associated with coal emissions reductions between 2005 and 2012 in the united states. *Epidemiology*, *in press*, pages 1–29, 2019b.

K. Hirano and G. W. Imbens. The propensity score with continuous treatments. 2004.

J. Hodges and B. Reich. Adding spatially-correlated errors can mess up the fixed effect you love. *The American Statistician*, 64(4):325–334, 2010.

J. Hughes and M. Haran. Dimension reduction and alleviation of confounding for spatial generalized linear mixed models. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 75(1):139–159, 2013.

G. W. Imbens and D. B. Rubin. *Sensitivity Analysis and Bounds*, pages 496–510. Cambridge University Press, 2015. doi: 10.1017/CBO9781139025751.023.

L. Keele, R. Titiunik, and J. Zubizarreta. Enhancing a geographic regression discontinuity design through matching to estimate the effect of ballot initiatives on voter turnout. *Journal of Royal Statistical Society, Series A (Statistics in Society)*, 178:223–239, 2015.

A. Kottas, J. A. Duan, and A. E. Gelfand. Modeling disease incidence data with spatial and spatio temporal dirichlet process mixtures. *Biometrical Journal*, 50(1):29–42, 2008.

F. Laden, L. M. Neas, D. W. Dockery, and J. Schwartz. Association of fine particulate matter from different sources with daily mortality in six US cities. *Environmental Health Perspectives*, 108(10):941–947, 2000.

D. Lee and C. Sarran. Controlling for unmeasured confounding and spatial misalignment in long-term air pollution and health studies. *Environmetrics*, 26(7):477–487, 2015.

C. C. Lim, R. B. Hayes, J. Ahn, Y. Shao, D. T. Silverman, R. R. Jones, C. Garcia, and G. D. Thurston. Association between long-term exposure to ambient air pollution and diabetes mortality in the US. *Environmental Research*, 165(February):330–336, 2018.

M. Makar, J. Antonelli, Q. Di, D. Cutler, and J. Schwartz. Estimating the causal effect of fine particulate matter levels on death and hospitalization: Are levels below the safety standards harmful? *Epidemiology*, 28(5):627–634, 2018.

C. J. Paciorek. The importance of scale for spatial-confounding bias and precision of spatial regression estimators. *Statistical Science*, 25(1):107–125, 2010.

G. Papadogeorgou, C. Choirat, and C. M. Zigler. Adjusting for unmeasured spatial confounding with distance adjusted propensity score matching. *Biostatistics*, Online, 2018.

G. Papadogeorgou, M.-A. Kioumourtzoglou, D. Braun, and A. Zanobetti. Low levels of air pollution and health: Effect estimates, methodological challenges, and future directions. *Current Environmental Health Reports*, 2019.

L. Pinault, M. Tjepkema, D. L. Crouse, S. Weichenthal, A. van Donkelaar, R. V. Martin, M. Brauer, H. Chen, and R. T. Burnett. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian community health survey cohort. *Environmental Health*, 15(1):18, dec 2016.

P. R. Rosenbaum. *Sensitivity to Hidden Bias*, pages 105–170. Springer New York, New York, NY, 2002.
P. R. Rosenbaum and D. B. Rubin. Assessing sensitivity to an unobserved binary covariate in an observational study with binary outcome. *Journal of the Royal Statistical Society: Series B (Methodological)*, 45(2): 212–218, 1983a.

P. R. Rosenbaum and D. B. Rubin. The central role of the propensity score in observational studies for causal effects. *Biometrika*, 70(1):41–55, 1983b.

D. B. Rubin. Estimating causal effects of treatments in randomized and nonrandomized studies. *Journal of Educational Psychology*, 66(5):688–701, 1974.

D. B. Rubin. Randomization analysis of experimental data: the Fisher randomization test comment. *Journal of the American Statistical Association*, 75(371):591–593, 1980.

D. Ruppert, M. P. Wand, and R. J. Carroll. *Semiparametric Regression*. Cambridge University Press, 2003.

H. Thaden and T. Kneib. Structural equation models for dealing with spatial confounding. *The American Statistician*, 72(3):239–252, 2018.

A. Van Donkelaar, R. V. Martin, M. Brauer, and B. L. Boys. Use of satellite observations for long-term exposure assessment of global concentrations of fine particulate matter. *Environmental Health Perspectives*, 123(2):135–143, 2014.

A. van Donkelaar, R. V. Martin, M. Brauer, N. C. Hsu, R. A. Kahn, R. C. Levy, A. Lyapustin, A. M. Sayer, and D. M. Winker. Global estimates of fine particulate matter using a combined geophysical-statistical method with information from satellites, models, and monitors. *Environmental Science & Technology*, 50(7):3762–3772, 2016.

N. Verbitsky-Savitz and S. W. Raudenbush. Causal inference under interference in spatial settings: A case study evaluating community policing program in Chicago. *Epidemiologic Methods*, 1(1):105–130, 2012.

J. H. Won, J. Lim, S. J. Kim, and B. Rajaratnam. Condition-number-regularized covariance estimation. *Journal of the Royal Statistical Society, Series B (Statistical Methodology)*, 75(3):427–450, 2013.

S. N. Wood. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *Journal of the Royal Statistical Society, Series B (Statistical Methodology)*, 73(1):3–36, 2011.