



HHS Public Access

Author manuscript

J Expo Sci Environ Epidemiol. Author manuscript; available in PMC 2015 November 17.

Published in final edited form as:

J Expo Sci Environ Epidemiol. 2013 ; 23(3): 268–274. doi:10.1038/jes.2012.106.

Structural equation modeling of the inflammatory response to traffic air pollution

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Abstract

Several epidemiological studies have reported conflicting results on the effect of traffic-related pollutants on markers of inflammation. In a Bayesian framework, we examined the effect of traffic pollution on inflammation using structural equation models (SEMs). We studied measurements of C-reactive protein (CRP), soluble vascular cell adhesion molecule-1 (sVCAM-1), and soluble intracellular adhesion molecule-1 (sICAM-1) for 749 elderly men from the Normative Aging Study. Using repeated measures SEMs, we fit a latent variable for traffic pollution that is reflected by levels of black carbon, carbon monoxide, nitrogen monoxide and nitrogen dioxide to estimate its effect on a latent variable for inflammation that included sICAM-1, sVCAM-1 and CRP. Exposure periods were assessed using 1-, 2-, 3-, 7-, 14- and 30-day moving averages previsit. We compared our findings using SEMs with those obtained using linear mixed models. Traffic pollution was related to increased inflammation for 3-, 7-, 14- and 30-day exposure periods. An

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

Supplementary Information accompanies the paper on the Journal of Exposure Science and Environmental Epidemiology website (<http://www.nature.com/jes>)

inter-quartile range increase in traffic pollution was associated with a 2.3% (95% posterior interval (PI): 0.0–4.7%) increase in inflammation for the 3-day moving average, with the most significant association observed for the 30-day moving average (23.9%; 95% PI: 13.9–36.7%). Traffic pollution adversely impacts inflammation in the elderly. SEMs in a Bayesian framework can comprehensively incorporate multiple pollutants and health outcomes simultaneously in air pollution–cardiovascular epidemiological studies.

Keywords

bayesian; directed acyclic graphs; inflammation; traffic air pollution; structural equation models

INTRODUCTION

Epidemiological studies have linked increased levels of traffic-related pollution to increased cardiovascular mortality and morbidity and have also identified traffic-related pollution as a risk factor.¹ Although the physiological mechanisms of this association have not been fully explained, scientific evidence increasingly suggests that altered cardiac autonomic control, vascular endothelial cell injury and systemic inflammation have significant roles.^{2,3} For instance, Madrigano *et al.*⁴ found that serum levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) were positively associated with black carbon (BC), a marker of ambient pollution from traffic. Delfino *et al.*⁵ also found in elderly people with coronary artery disease that exposure to the traffic pollutants, BC, carbon monoxide (CO) and nitrogen dioxide (NO₂), were associated with increased C-reactive protein (CRP) level, a marker of systemic inflammation.

These findings, however, are not definitive, as other studies have reported inverse or null associations between air pollution exposure and these adverse health outcomes.^{5–7} Even within a given study, conclusions have varied with the surrogate marker of traffic pollution or of endothelial injury or inflammation.⁸ This heterogeneity across and within studies suggests the need for comprehensive methods to consider multiple traffic pollutants and multiple health biomarkers simultaneously.

To address this issue, we used structural equation models (SEMs), which represent a family of statistical techniques that allows one to estimate association among multiple latent variables, to examine the association between traffic pollution and inflammation. For our analyses, we used latent variables to conceptualize traffic pollution and inflammation. These latent variables, traffic pollution and inflammation, are not observed directly but are correlated with measured traffic-related pollutants and markers of inflammation, respectively. Notably, the latent variables correspond to what is “common” among the parameters measured and do not preclude, for example, CRP and sVCAM-1 representing in part different biological processes. SEMs have been used in studies that assessed source-specific health effects of air pollution^{9,10} and in health effects of methyl mercury¹¹ and lead to neurodevelopment.^{12,13} Notably, SEMs reduce the attenuation due to measurement error in models with 3 or more surrogates of the latent exposure,¹⁴ which is an ongoing concern in air pollution studies.

In this paper, we develop repeated measures SEMs in a Bayesian framework to examine the impact of short-term changes in traffic pollution on inflammation among participants in the Normative Aging Study (NAS). We compare and contrast the results of the SEM to more conventional linear mixed models (LMMs) in both the Frequentist and Bayesian framework.

MATERIALS AND METHODS

Study Population

The NAS is an ongoing longitudinal study of aging established by the Veterans Administration in 1963.¹⁵ Briefly, 2,280 healthy, community-dwelling men living in the Greater Boston area were enrolled between 1963 and 1968. Every 3–5 years, after an overnight fast and abstention from smoking, participants visited the clinic for an extensive physical examination, blood collection, laboratory tests and a self-administered questionnaire on medical history, alcohol consumption, medication usage, food intake, smoking history and other factors that could affect health.

From January 2000 to December 2009, soluble intracellular adhesion molecule-1 (sICAM-1), sVCAM-1 and CRP measurements were obtained during each participant's regularly scheduled visit. sVCAM-1 and sICAM-1 were measured in plasma by an ELISA assay (R&D Systems, Minneapolis, MI, USA) with a sensitivity of 2.0 and 0.35 ng/ml, respectively. High-sensitive CRP concentrations were also measured in the serum by an immunoturbidimetric assay on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN, USA), using reagents and calibrators from Denka Seiken (Niigata, Japan). To date, sICAM-1, sVCAM-1 and CRP measurements are available from 749 participants. Of these participants, 212 had one measurement, 174 had two measurements, 339 participants had three measurements and 24 individuals had four measurements, for a total of 1673 valid measurements. All participants gave written consent and this study had Institutional Review Board approval.

We measured concentrations of ambient BC continuously at the Harvard University Countway Library stationary ambient monitoring site, located <1 km from the clinical laboratory, where subjects were examined. Hourly ambient CO, nitrogen monoxide (NO) and NO₂ concentrations were obtained from the Massachusetts Department of Environmental Protection for monitoring stations within 20 km of the clinical laboratory, including those in Boston (Roxbury, Bremen, Kenmore Square and North-End), Lynn and Waltham MA. We used data from these sites to calculate the mean hourly concentrations of each pollutant. We obtained data on ambient temperature and dew point temperature from the first-order National Weather Service station at Boston Logan airport. We calculated apparent temperature (ATemp), an index of human discomfort¹⁶ as: $ATemp = -2.653 + (0.994 \times Temp) + (0.0153 \times DPT^2)$, where Temp is the ambient temperature in Celsius and DPT is the dew point temperature in Celsius.

Statistical Analysis

We examined the association between latent traffic pollution and latent inflammation using SEMs in Bayesian framework that account for repeated measures. This approach links

estimation of parameters in an integrated approach through estimation of parameters characterizing the joint distribution of multiple outcomes and exposures. SEMs consist of two main components, a measurement model part, which shows the relation between latent constructs and their indicators/markers and a structural model part, which shows the association dependencies between two latent constructs, between a latent construct and a measured variable or between two measured variables. As standard SEMs typically assume that all continuous variables are normally distributed, sICAM-1, sVCAM-1 and CRP were log-transformed to satisfy this assumption.

SEM in Bayesian Framework with Repeated Measures—We examined associations between traffic-related pollution and markers of inflammation using SEMs, parametric-directed acyclic graphs (DAGs) that contain specified paths connecting latent and observed variables.^{14,17} In a Bayesian framework, the SEMs consist of (1) probability models for the observed variables, given latent variables and model parameters, (2) distributional assumptions on the latent variables and (3) prior distributions for the parameters. The SEMs also specify linear models relating the unknown means of the latent traffic pollution and latent inflammation variables to fixed covariates (e.g. confounding factors), other latent variables and a subject-level random intercept to accommodate the repeated measures design of the study. For the effect of traffic pollution on inflammation, exposure periods were assessed and modeled separately using 1-, 2-, 3-, 7-, 14- and 30-day moving average pre-visit, given results from earlier studies that show effects at similar exposure windows.^{4,18,19}

We specified measurement models describing the relationships between the latent variables and the observed measures. We first modeled the relationship between the latent exposure variable Traffic and the traffic-related observed measures, mainly BC, CO, NO and NO₂ (Figure 1). For moving average concentration pre-visit measurement of participants $i = 1, \dots, I$, of traffic-related pollutants $j = 1, \dots, J$, on participant's scheduled time visits $t = 1, \dots, T$,

$$X_{ijt} \sim N(\mu_{ijt}^X, \tau_j^X) \quad (1)$$

where X_{ijt} is the normally distributed traffic-related exposure variable for moving average concentration pre-visit measurement of participant i of traffic-related pollutant j on participant's scheduled time visit t , with unknown mean μ_{ijt}^X and variance τ_j^X . The mean exposure of traffic-related pollutant j , μ_{ijt}^X , was related to the latent exposure variable Traffic through a linear model,

$$\mu_{ijt}^X = \lambda_{0j} + \lambda_{1j} \text{Traffic}_{it} \quad (2)$$

where Traffic_{it} is the normally distributed latent exposure variable Traffic for scheduled time visit t for participant i , with unknown mean $\mu_{it}^{\text{Traffic}}$ and variance τ^{Traffic} ,

$$\text{Traffic}_{it} \sim N(\mu_{it}^{\text{Traffic}}, \tau^{\text{Traffic}}) \quad (3)$$

The mean Traffic exposure, $\mu_{it}^{\text{Traffic}}$, was related to confounding factors, through a linear model,

$$\mu_{it}^{\text{Traffic}} = \varphi_1 \text{Sine} [2\pi\theta(t)/365.24] + \varphi_2 \text{Cosine} [2\pi\theta(t)/365.24] + \varphi_3 \text{Residual}(ATemp)_t + \varphi_4 \text{Residual}^2(ATemp)_t \quad (4)$$

where the sine and cosine terms capture seasonal trends in traffic pollution, $\theta(t)$ is the calendar day of the year the participant visited the clinic, ATemp is the apparent temperature averaged across the same exposure window, and residual (ATemp) is the residual of a model regressing ATemp against sine and cosine terms of the calendar day of the year in the study. This approach was taken because temperature data is highly seasonal, and this avoids substantial collinearity between the seasonal terms and temperature, which would otherwise be present in the model. In addition, Eq. (4) appears as it does not vary with participant i but it does vary because the scheduled time visits t are unique to that participant.

We also modeled the relationship between latent outcome variable Inflammation and its observed markers, mainly CRP, sICAM-1 and sVCAM-1 (Figure 1). For blood-sampled measurement of participants $i = 1, \dots, I$, of inflammation markers $k = 1, \dots, K$, on participant's scheduled time visit $t = 1, \dots, T$,

$$Y_{ikt} \sim N(\mu_{ikt}^Y, \tau_k^Y) \quad (5)$$

where Y_{ikt} represents the normally distributed markers of inflammation for blood-sampled measurement of participant i of inflammation marker k on participant's scheduled time visit t , with unknown means μ_{ikt}^Y and variances τ_k^Y . For inflammation marker k , the mean outcome, μ_{ikt}^Y , was related to the latent outcome variable Inflammation through a linear model,

$$\mu_{ikt}^Y = a_{0k} + a_{1k} \text{Inflammation}_{it} \quad (6)$$

where Inflammation_{it} is the normally distributed latent outcome variable Inflammation for scheduled time visit t for participant i , with unknown mean $\mu_{it}^{\text{Inflammation}}$ and variance $\tau^{\text{Inflammation}}$,

$$\text{Inflammation}_{it} \sim N(\mu_{it}^{\text{Inflammation}}, \tau^{\text{Inflammation}}) \quad (7)$$

The mean Inflammation outcome, $\mu_{it}^{\text{Inflammation}}$, was related to the latent exposure variable Traffic_{it} , confounding factors, predictors of the latent outcome variable and a subject-level random intercept, b_i , through a linear model,

$$\begin{aligned} \mu_{it}^{\text{Inflammation}} = & \gamma_1 \text{Traffic}_{it} \\ & + \gamma_2 X_{1it} \\ & + \dots + \gamma_{m+1} X_{mit} \\ & + \gamma_{m+2} \text{Sine} [2\pi\theta(t)/365.24] \\ & + \gamma_{m+3} \text{Cosine} [2\pi\theta(t)/365.24] \\ & + \gamma_{m+4} \text{Residual}(ATemp)_t \\ & + \gamma_{m+5} \text{Residual}^2(ATemp)_t + b_i \end{aligned} \quad (8)$$

where the fixed covariates (X_{jit} , ..., X_{mit}) included age, body mass index (BMI), smoking status (ever/never), pack-years smoked, diabetes status (defined as having a doctor's diagnosis of disease or fasting blood glucose > 126 mg/dL), an indicator of statin usage (yes/no), an indicator of hypertension usage (yes/no) and 2 servings of alcohol per day (yes/no). These covariates were chosen a priori as potentially important predictors of inflammation. To account for seasonal variation in inflammation, a function of calendar date {sine $[2\pi\theta(t)/365.24]$ +cosine $[2\pi\theta(t)/365.24]$, where $\theta(t)$ is the calendar day of the year the participant visited the clinic} was used. To account for temperature variation in inflammation, we regressed ATemp on sine $(2\pi\theta(t)/365.24)$ + cosine $(2\pi\theta(t)/365.24)$ and used the linear (Residual (ATemp) $_t$) and quadratic (Residual² (ATemp) $_t$) residuals of the equation as part of the fixed effects of the model. To accommodate the repeated measures design of the study, we also included a subject-level random intercept, b_i , to represent subject-specific permanent effects for each participant. Furthermore, Eq. (8) implicitly depends on participant i because the scheduled time visits t depend on participant i .

For model identifiability, the location of all the latent variables was centered and set to 0 (i.e. ϕ_0 and $\gamma_0 = 0$). Because latent variables are constructed from multiple measured parameters, which have different scales of variation, a scale must be specified for each latent variable. We chose BC as the reference scale for Traffic pollution, and sVCAM-1 as the scale for Inflammation. To set the reference scale for Traffic and Inflammation and for identifiability and interpretation of these latent variables, β^{BC} and $\alpha^{sVCAM-1}$ were also constrained to be equal to 1.¹¹ See Figure 1 for the DAG diagram of the SEM.

LMMs in Bayesian and Frequentist Framework—To compare the results from the SEM with repeated measures in Bayesian framework to those obtained from a standard univariate analysis, the association between traffic-related air pollutant BC and mean marker of inflammation (sVCAM-1) was also estimated using LMMs with random subject-specific intercepts in Bayesian (BLMMs) framework. Moreover, to demonstrate that our Bayesian approach to estimation yields trustworthy parameter estimates, we also compared the results from the above BLMMs to frequentist framework estimates (LMMs) obtained from LME in R (<http://www.r-project.org>). The same fixed and random covariates used in SEMs were included in all the BLMMs and LMMs. To allow more direct comparison for the SEMs, BLMMs and LMMs, effect size estimates were reported for an inter-quartile range (IQR) increase in Traffic pollution or BC.

We specified a model for the measured health effect outcome, sVCAM-1. The mean sVCAM-1 for participant i on participant's scheduled time visit t , $sVCAM-I_{it}$, was related to BC_{it} , confounding factors and predictors of the health effect outcome, and a subject-level random intercept, b_i , through a linear model,

$$\begin{aligned}
sVCAM - 1_{it} = & \beta_0 + \beta_1 BC_{it} \\
& + \beta_2 X_{1it} \\
& + \dots + \beta_{n+1} X_{nit} \\
& + \beta_{n+2} \text{Sine} [2\pi\theta(t) / 365.24] \\
& + \beta_{n+3} \text{Cosine} [2\pi\theta(t) / 365.24] \\
& + \beta_{n+4} \text{Residual}(ATemp)_t \\
& + \beta_{n+5} \text{Residual}^2(ATemp)_t + b_i.
\end{aligned}$$

Results were quantified and characterized in terms of the strength of the following hypothesized relationships: positive relationships between BC and sVCAM-1, and between Traffic pollution and Inflammation. In terms of Bayesian inference, results were presented as probability statements, providing evidence that coefficients describing BC or Traffic pollution are positive based on the hypothesized relationship. For descriptions of prior distributions of parameters and implementation particulars, see Supplementary Section for details.

RESULTS

Eligible study participants included 749 NAS participants, who had valid CRP and cellular adhesion molecules measurements available for analysis. Subjects were male with a mean age of 74.9 years (SD = 6.7 years), were mostly overweight with a mean BMI of 28.1 kg/m² (SD = 4.2 kg/m²) and were mostly ever cigarette smokers (70.4%) (Table 1). Table 2 shows the descriptive statistics for markers of inflammation, and ambient air pollutant measures. Traffic pollutant concentrations averaged over 1 day and over 30 days before blood collection were strongly correlated, with CO averaged over 1 day and 30 days having the highest correlation (Spearman correlation coefficient, ρ 0.74). The correlation between markers of inflammation was highest for sICAM-1 and sVCAM-1 (ρ = 0.42) (see Supplementary Table 1 for details).

Measurement Models of Traffic Pollution and Inflammation

Table 3 tabulates the results of the factor loadings (λ_{Ij} and a_{Ij} coefficients of Eqs. (2) and (6)) of the measurement models for the relation of Traffic and Inflammation latent variables to its various marker variables, it also includes the corresponding variance of latent ($1/\tau^{\text{Traffic}}$ of Eqs. (3) and $(1/\tau^{\text{Inflammation}}$ of Eq. (7)) and its marker ($1/\tau_j^X$ of Eq. (1) and $1/\tau_k^Y$ of Eq. (5)) variables. Using sVCAM-1 as the reference marker, Inflammation was strongly represented by CRP with a coefficient as factor loading of 1.88 (95% posterior interval (PI): 1.52, 2.26) (Figure 2a). In using BC as the reference marker, for the 1-day moving average exposure, the highest reliability measure of Traffic was CO (coefficient as factor loading of 0.95; 95% PI: 0.87, 1.05), whereas the lowest reliability measure of Traffic was NO₂ (0.02; 95% PI: 0.02, 0.02). Furthermore, for the 30-day moving average exposure, CO predominantly represented Traffic (3.40; 95% PI: 2.88, 4.01), whereas NO₂ was still the lowest reliability measure of Traffic (0.07; 95% PI: 0.06, 0.08) (Figure 2b). Moreover, the variance of latent Inflammation variable was lower (0.008; 95% PI: 0.006, 0.010) compared

with the variance of the 1-day moving average latent Traffic variable, which was slightly higher (0.038; 95% PI: 0.031, 0.045). For the traffic-related pollutants, the variance of the 1-day moving average BC was highest (0.132; 95% PI: 0.122, 0.142), whereas NO₂ was the lowest in variance (3.0E-5; 95% PI: 2.7E-5, 3.2E-5) for all the pollutants. Of the three markers of inflammation, the variance of CRP was the highest (1.102; 95% PI: 1.027, 1.183) and the variance of sICAM-1 was the lowest of the three markers (0.005; 95% PI: 0.002, 0.010).

Effect of Traffic Pollution on Inflammation

Table 4 shows the estimated percent change in inflammation per IQR increase in traffic pollution for various daily moving averages. For a 1-day moving average, an IQR increase in traffic pollution exposure was associated with a 0.9% (95% PI: – 1.0 to 2.8%) increase in inflammation (posterior probability 0.82). The magnitude of the association increased with longer moving averages, resulting in a 23.9% (95% PI: 13.9–36.7%) increase in inflammation for exposures averaged over the 30 days before the blood measurement (posterior probability 1.00). Figure 3a presents the posterior probability distribution of the SEMs. As the averaging period increases from 1 day to 30 days, the variability or spread of the distribution also increased, as evidenced by the wider posterior probability distributions.

Model Comparison

Ordinary LMMs were fitted to double check the estimates and PIs from the BLMMs. The results from LMMs and BLMMs produced almost identical estimates and confidence/posterior intervals (See Supplementary Table 2 for LMM results on the effects of traffic-related pollutants on sVCAM-1). Table 4 compares the posterior mean and 95% PI from SEMs to the posterior mean and 95% PI from BLMMs. The effect estimates were higher for SEMs as compared with BLMMs for longer moving averages (7-, 14- and 30-day). However, for shorter moving averages (1-, 2- and 3-day) the effect estimates were higher for BLMMs as compared with SEMs (see Figure 3). For example, a 23.9% (95% PI: 13.9–36.7%) increase in inflammation (reference marker: sVCAM-1) was observed for an IQR increase in traffic (reference pollutant: BC) for the 30-day exposure window using SEM, as compared with a 7.0% (95% PI: 4.1–10.0%) increase in sVCAM-1 using BLMM. In contrast, for the 1-day moving average exposure window, an IQR increase in traffic (reference pollutant: BC) was associated with a 0.9% (95% PI: – 1.0 to 2.8%) increase in inflammation (reference marker: sVCAM-1) for the SEM and a 4.4% (95% PI: 2.5–6.4%) increase in sVCAM-1 observed for an IQR increase in BC using BLMM.

DISCUSSION

Using SEMs, we found traffic pollution, as reflected by BC, CO, NO and NO₂, to have a strong and positive association with inflammation, as measured by CRP, sVCAM-1 and sICAM-1, at longer exposure windows (3-, 7-, 14- and 30-day). As increased inflammation has been shown to predict cardiovascular disease among older men, our findings suggest that air pollution may adversely impact cardiovascular health through the inflammation pathway.

Our results are consistent with the results from BLMMs and LMMs based on BC as the sole marker of traffic pollution and on sVCAM-1 as the individual marker of inflammation. For example, we found significant impacts of BC on sVCAM-1 using LMMs in both the Bayesian and Frequentist approaches. Impacts assessed using the LMMs were, however, similar across all examined exposure windows (except for the 30-days moving average) as compared with those obtained using the SEM, which had an increasing monotonic effect, as evidenced by their respective estimated means (Table 4). Our results indicate the need to examine the cumulative/simultaneous effect of multiple traffic-related pollutants in addition to the effects of a single pollutant. The differences in the findings we observed between the LMM approach and the SEM approach implies that the effect of traffic on inflammation is not the same as the effect of BC on sVCAM-1 (Figure 3). In addition, we also ran LMMs to check the effect of the other pollutants on sVCAM-1. We hypothesize that other traffic-related pollutants (CO, NO and NO₂) contribute to the effect of traffic on inflammation, especially at the longer moving averages (7, 14 and 30 days) where the effect estimates of the other traffic-related pollutants (CO, NO and NO₂) on sVCAM-1 are higher compared with their effect estimates at shorter moving averages (Supplementary Table 2). In addition, long-term average CO over weeks at low concentrations is likely representative of longer-term exposure to things in auto exhaust other than CO, as low-level CO exposure is actually used therapeutically and is an antioxidant. At shorter moving averages (1, 2 and 3 days), our finding of larger significant impact of BC on sVCAM-1 using the LMMs as compared with SEMs implies that other traffic-related pollutants may not have an effect. However, alternatively, the longer-term effect may represent the increasing role of other inflammatory markers than sVCAM-1 at longer exposure windows. For example, in a cross-sectional analysis of this data Zeka *et al.*²⁰ showed that BC was related to CRP, but only at longer moving averages such as 4 weeks. CRP may not be responding to shorter-term excursions in traffic exposure.²⁰ More research that examines the concurrent use of the two approaches (SEMs and LMMs) is needed to verify our results.

In addition to greater impacts of traffic on inflammation using SEMs at longer averaging times (7, 14 and 30 days), we also found wider PIs in SEMs as compared with BLMMs. Wider PIs are likely due to our use of multiple indicators to measure the latent variables (Traffic and Inflammation) in our SEMs and the reduction in temporal variability for longer averaging times, which could contribute to the decrease in precision/wider PI. Reduced bias introduced by measurement error correction, which occurs in SEMs with three or more surrogates for a latent variable, would result in a de-attenuated posterior mean and larger variance of the posterior probability distribution for the main effect of traffic pollution on inflammation, both effects we observed at longer moving averages (Table 4). This is a typical phenomenon in measurement error corrections; it tends to de-attenuate point estimates coupled with wider posterior/confidence intervals due to reflecting additional uncertainty due to measurement error correction. The hope is that the total mean-squared error (bias squared + variance) is lower than the uncorrected estimate.^{14,21}

Our findings are consistent with previous studies of the NAS cohort.^{4,19} While using a LMM, Madrigano *et al.*⁴ found a significant association between 2-day moving average BC concentrations and an increase in sVCAM-1. Although not statistically significant at the $P <$

0.05 level, 1- and 3-day moving average BC were also associated with an increase in sVCAM-1. In another study that used a validated spatio-temporal land use regression model to estimate BC exposure at the residential address of each NAS participant, Alexeeff and coworkers¹⁹ reported associations of BC and sICAM-1 at longer moving averages of 4, 8 and 12 weeks. Further, both Alexeeff *et al.*¹⁹ and Madrigano *et al.*⁴ used sVCAM-1 and sICAM-1 data from 1999 to 2008. In our analysis, we removed the 1999 measurements because we found inconsistency in the method of blood collection/handling that could have affected the sICAM-1 and sVCAM-1 measurements. However, we included measurements from 2009, which became available for our study. Our finding of significant effects of traffic on inflammation at longer exposure windows was likely due to our use of the SEMs, which potentially reduced bias introduced by measurement error and increased our power to detect the effect of traffic pollution on inflammation at all examined exposure windows.

To our knowledge, our study is the first to show simultaneous impacts of multiple traffic-related pollutants on inflammation, a cardiovascular health outcome that has the ability to predict cardiovascular morbidity and mortality. SEM estimates all the coefficients in the model simultaneously, an advantage in using SEM. Therefore, one is able to assess and measure the strength and the significance of a particular relationship (i.e. effect of BC on sVCAM-1 (γ_1) or effect of BC on CRP ($\gamma_1 \times \alpha_1^{CRP}$)) in the framework of the complete model. Our study showed that multiple markers of traffic pollution and inflammation can be analyzed concurrently using SEMs that account for repeated measures, potentially minimizing discrepancies and conflicting results that may arise from multiple comparisons of individual markers of exposure or health outcome. In addition, the models benefit from a reduction in measurement error bias. In using SEMs in a Bayesian framework, our study was able to integrate data and to account for variations in one probabilistic framework. In addition, we showed that SEMs in Bayesian framework also have the capability to analyze unbalanced longitudinal data, with either multiple exposure and/or outcome markers. Furthermore, our study used a random subject intercept which means that the contrasts are a mixture of within and between subjects; for this reason, confounding factor bias should be small relative to that in a purely cross-sectional study design.²² This comprehensive approach, however, is not needed for research study designs that only have one traffic-related pollutant exposure variable and have one measured outcome variable, for which LMM and linear regression model will still be the preferred method of analysis for repeated and longitudinal studies, and cross-sectional studies, respectively. Nevertheless, more studies are needed to verify and validate the structural equation modeling approach in air pollution epidemiological studies.

There are several limitations in our study. First, exposures in our study were estimated using concentrations measured at a single ambient monitoring site for BC and at several monitoring sites for CO, NO and NO₂, which will not capture spatial variation in air pollutant concentrations. Because participants lived up to 22 km from our ambient monitoring site, this spatial variation may result in exposure measurement error that would probably be non-differential and could bias the results in either direction.²³ In addition, bias due to residual or unmeasured confounding and predictor factors cannot be ruled out, and the potential for larger variance and wider PI should also be considered if SEMs and not

LMMs are to be used in air pollution epidemiologic studies.^{14,21} Lastly, as the study population consists of a high proportion of ever-smoker older males who are predominately white and are mostly veterans that have special occupational exposure, the results may not be generalizable to younger individuals, women, never smokers or other racial and ethnic groups. The effect of traffic pollution on inflammation on these other populations should be tackled in future studies.

In conclusion, this study documented the positive associations between traffic pollution (BC, CO, NO₂ and NO) exposure and inflammation (CRP, sICAM-1 and sVCAM-1). The study also showed that SEMs in a Bayesian framework would be a plausible and alternative method for repeated measures and longitudinal studies in air pollution epidemiology that looks at the effect of traffic pollution exposure on multiple health effect outcomes. The Bayesian approach allowed us to incorporate the mixed-effect model structure within the SEM framework. Furthermore, this study provides further evidence that traffic pollutants via the inflammation pathway may have a critical role in cardiopulmonary toxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This study was supported in part by grants from the National Institute of Environmental Health Sciences (ES014663-01A2, ES-015172, ES015774 and PO1 ES09825) and from the U.S. Environmental Protection Agency (EPA R827353 and R 83479801).

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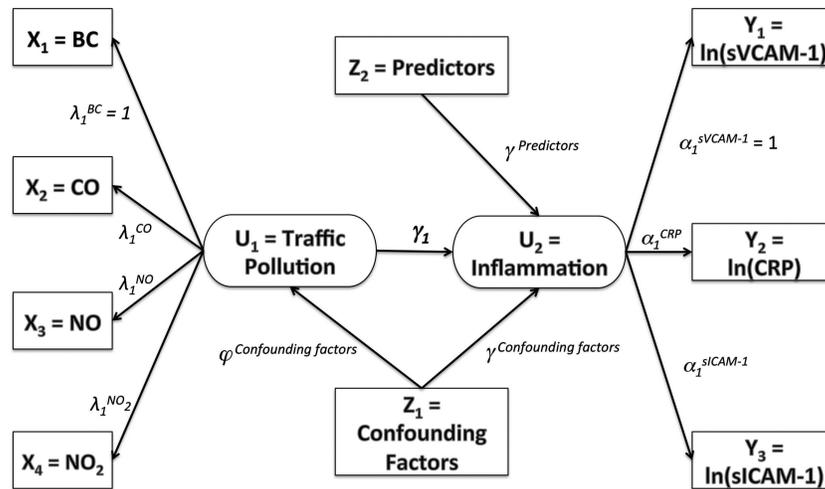


Figure 1. Path diagram for the effect of traffic pollution on inflammation. Ellipses are used to denote latent constructs, rectangles are used to denote the observed variables measuring and affecting these constructs, and single-headed arrows are used to denote directional relationships, from predictor to outcome.

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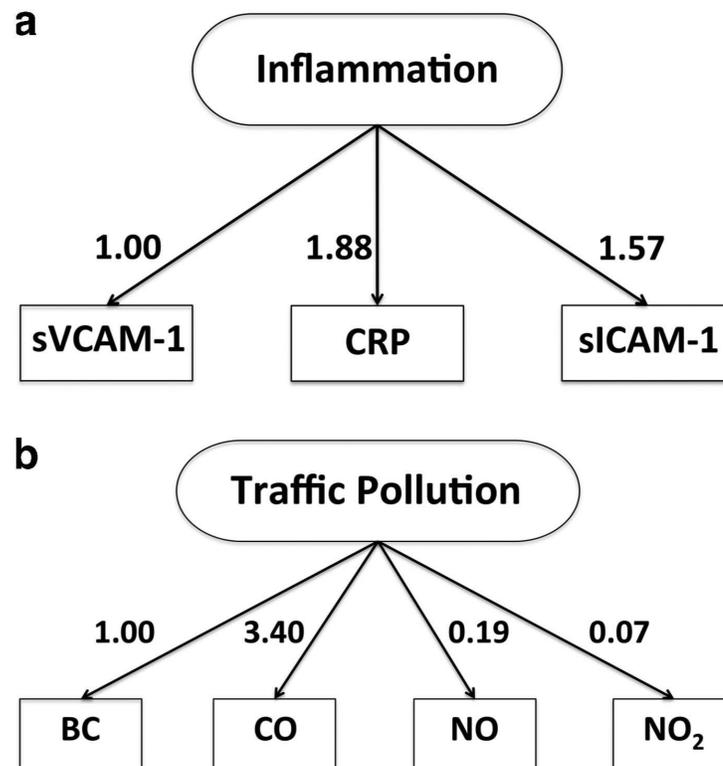


Figure 2. Relation of latent variables of Inflammation (for a 1-day moving average exposure) (a) and Traffic (for a 30-day moving average exposure) (b) to marker variables as factor loading values.

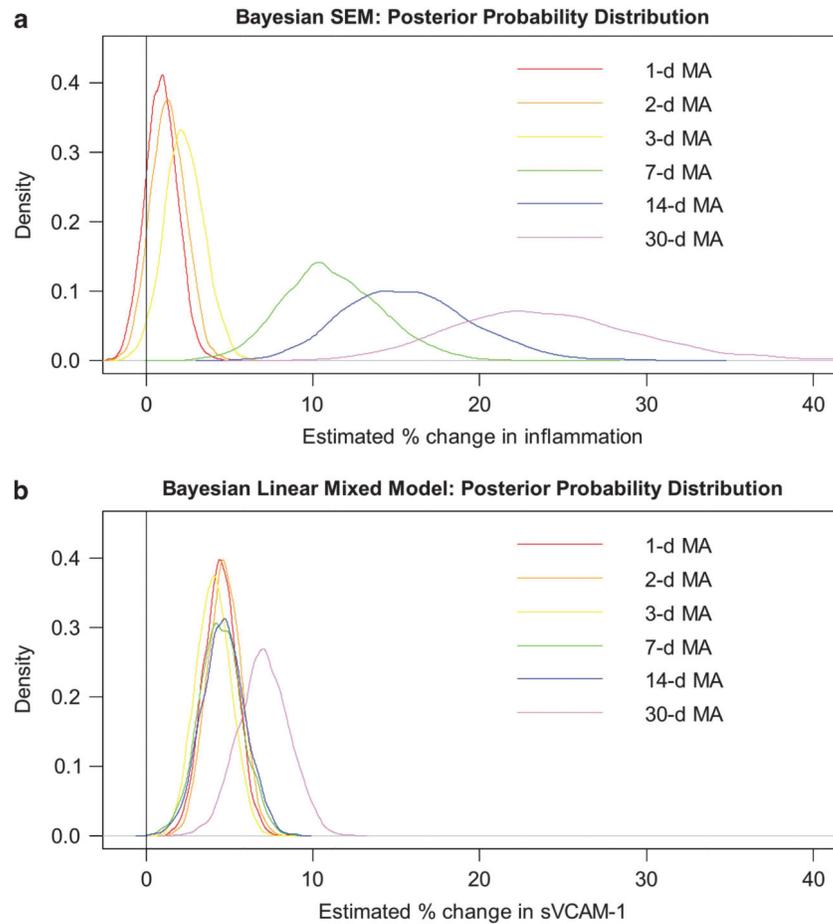


Figure 3. Density plots of posterior estimated percentage change in inflammation or sVCAM-1 associated with an IQR increase in BC (reference pollutant of latent traffic pollution) exposure at different daily moving averages (MA). **(a)** SEM in Bayesian Framework: effect of traffic pollution on inflammation and **(b)** Bayesian LMM: effect of BC on sVCAM-1.

Table 1

Characteristics of study population ($N = 749$), Normative Aging Study 2000–2009.

Characteristic	Value (mean \pm SD) or (%)
Age, years	74.9 \pm 6.7
Body mass index, kg/m ²	28.1 \pm 4.2
30 kg/m ² (%)	26.5
Mean arterial pressure, mmHg	90.1 \pm 11.0
Cholesterol, mg/dL	185.6 \pm 38.5
Glucose fasting, mg/dL	105.9 \pm 22.4
Ever diabetic (%) ^a	19.6
Cumulative cigarette pack-years, years	20.3 \pm 24.4
Ever cigarette smoker (%)	70.4
Two drinks per day (%)	18.6
Antihypertensive user (%)	65.4
Statin user (%)	47.2

^aReport of doctor's diagnosis of disease or FBG > 126 mg/dL.

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Table 2

Summary statistics for inflammation and ambient air pollutant measures.

	Average	Median	SD	5%	95%	IQR
<i>Inflammation measure^a</i>						
ln(sVCAM-1)	6.9	6.9	0.4	6.4	7.5	0.4
ln(sICAM-1)	5.7	5.7	0.3	5.3	6.1	0.3
ln(CRP)	0.5	0.5	1.1	-1.2	2.3	1.4
<i>Air pollution measure^b</i>						
BC	0.73	0.73	0.17	0.47	1.00	0.24
CO	0.37	0.36	0.16	0.14	0.67	0.19
NO	0.016	0.014	0.008	0.007	0.034	0.009
NO ₂	0.018	0.019	0.004	0.013	0.024	0.005

^a Abbreviations: CRP, C-reactive protein; IQR, inter-quartile range; sVCAM-1, soluble vascular cell adhesion molecule-1; sICAM-1, soluble intracellular adhesion molecule-1.

^b 30-day moving average ambient air pollution measurements from January 2000 to December 2009.

Table 3

Factor loadings (λ_{lj} and α_{lk} coefficients) of the measurement models for the relation of Traffic and Inflammation latent variables to its various marker variables and the corresponding variance of latent ($1/\tau^{\text{Traffic}}$ and $1/\tau^{\text{Inflammation}}$) and its marker ($1/\tau_j^X$ and $1/\tau_k^Y$) variables.

Moving average	Latent variable/markers	Factor loading (λ_{lj}) (95% PI)	Variance (95% PI)	Latent variable/markers	Factor loading (α_{lk}) (95% PI)	Variance (95% PI)
1-day	Traffic/		0.038 (0.031, 0.045)	Inflammation/		0.008 (0.006, 0.010)
	BC ^a	1.00	0.132 (0.122, 0.142)	sVCAM-1 ^a	1.00	0.099 (0.093, 0.107)
	CO	0.95 (0.87, 1.05)	0.010 (0.008, 0.012)	sICAM-1	1.57 (1.41, 1.73)	0.005 (0.002, 0.010)
	NO	0.07 (0.06, 0.07)	1.1E-4 (1.0E-4, 1.2E-4)	CRP	1.88 (1.52, 2.26)	1.102 (1.027, 1.183)
	NO ₂	0.02 (0.02, 0.02)	3.0E-5 (2.7E-5, 3.2E-5)			
2-day	Traffic/		0.024 (0.019, 0.029)	Inflammation/		0.008 (0.006, 0.010)
	BC	1.00	0.098 (0.092, 0.106)	sVCAM-1	1.00	0.099 (0.092, 0.106)
	CO	1.03 (0.94, 1.14)	0.009 (0.008, 0.011)	sICAM-1	1.57 (1.39, 1.75)	0.006 (0.002, 0.012)
	NO	0.07 (0.06, 0.07)	7.3E-5 (6.6E-5, 8.0E-5)	CRP	1.88 (1.52, 2.26)	1.104 (1.029, 1.182)
	NO ₂	0.02 (0.02, 0.03)	2.6E-5 (2.4E-5, 2.8E-5)			
3-day	Traffic/		0.016 (0.013, 0.019)	Inflammation/		0.008 (0.006, 0.010)
	BC	1.00	0.072 (0.067, 0.078)	sVCAM-1	1.00	0.099 (0.092, 0.106)
	CO	1.15 (1.03, 1.27)	0.008 (0.007, 0.010)	sICAM-1	1.55 (1.37, 1.74)	0.006 (0.002, 0.013)
	NO	0.07 (0.06, 0.07)	5.5E-5 (5.0E-5, 6.0E-5)	CRP	1.89 (1.53, 2.27)	1.106 (1.031, 1.183)
	NO ₂	0.03 (0.02, 0.03)	2.4E-5 (2.2E-5, 2.5E-5)			
7-day	Traffic/		0.003 (0.002, 0.004)	Inflammation/		0.008 (0.006, 0.010)
	BC	1.00	0.042 (0.040, 0.046)	sVCAM-1	1.00	0.099 (0.092, 0.106)
	CO	2.17 (1.86, 2.54)	0.009 (0.008, 0.010)	sICAM-1	1.57 (1.39, 1.76)	0.006 (0.002, 0.012)
	NO	0.12 (0.10, 0.14)	3.8E-5 (3.4E-5, 4.1E-5)	CRP	1.89 (1.53, 2.28)	1.107 (1.035, 1.186)
	NO ₂	0.04 (0.04, 0.05)	2.0E-5 (1.9E-5, 2.2E-5)			
14-day	Traffic/		0.001 (0.001, 0.002)	Inflammation/		0.008 (0.006, 0.010)
	BC	1.00	0.032 (0.030, 0.035)	sVCAM-1	1.00	0.099 (0.092, 0.106)
	CO	2.76 (2.35, 3.27)	0.009 (0.008, 0.010)	sICAM-1	1.57 (1.39, 1.77)	0.006 (0.002, 0.012)
	NO	0.15 (0.13, 0.18)	3.3E-5 (3.0E-5, 3.6E-5)	CRP	1.90 (1.53, 2.29)	1.107 (1.032, 1.186)
	NO ₂	0.06 (0.05, 0.07)	1.9E-5 (1.8E-5, 2.0E-5)			
30-day	Traffic/		7.7E-4 (5.3E-4, 0.001)	Inflammation/		0.008 (0.006, 0.010)
	BC	1.00	0.027 (0.025, 0.029)	sVCAM-1	1.00	0.099 (0.092, 0.106)
	CO	3.40 (2.88, 4.01)	0.008 (0.007, 0.009)	sICAM-1	1.56 (1.38, 1.75)	0.006 (0.002, 0.012)
	NO	0.19 (0.16, 0.22)	2.9E-5 (2.7E-5, 3.2E-5)	CRP	1.89 (1.53, 2.27)	1.107 (1.030, 1.187)
	NO ₂	0.07 (0.06, 0.08)	1.8E-5 (1.7E-5, 1.9E-5)			

Abbreviations: BC, black carbon; CO, carbon monoxide; CRP, C-reactive protein; 95% PI: 95% posterior intervals; NO, nitrogen monoxide; NO₂, nitrogen dioxide; sICAM-1, soluble intracellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1.

^aReference marker.

Table 4

Effect estimates of % change in health effect outcome (inflammation or sVCAM-1) associated with an IQR^a increase in exposure (black carbon (reference pollutant of latent traffic pollution)).

Exposure outcome	Moving average	% Change in mean (95% posterior interval)	Posterior probability ^b
<i>Structural equation model^c</i>			
Traffic inflammation	1-day	0.9 (-1.0, 2.8)	0.824
	2-day	1.3 (-0.7, 3.4)	0.895
	3-day	2.3 (0.0, 4.7)	0.972
	7-day	11.1 (5.7, 17.6)	1.000
	14-day	15.7 (8.9, 24.1)	1.000
	30-day	23.9 (13.9, 36.7)	1.000

Exposure outcome	Moving average	% Change in mean (95% posterior interval)	Posterior probability ^d
<i>Bayesian linear mixed model^e</i>			
BC/sVCAM-1	1-day	4.4 (2.5, 6.4)	1.000
	2-day	4.7 (2.7, 6.6)	1.000
	3-day	4.0 (2.0, 6.1)	1.000
	7-day	4.4 (1.9, 7.0)	1.000
	14-day	4.6 (2.1, 7.2)	1.000
	30-day	7.0 (4.1, 10.0)	1.000

Abbreviations: BC, black carbon; sVCAM-1, soluble vascular cell adhesion molecule-1.

^aInter-quartile range (IQR): 1-day = 0.54; 2-day = 0.46; 3-day = 0.40; 7-day = 0.32; 14-day = 0.26; 30-day = 0.24.

^bPosterior probability that $\gamma_1 > 0$.

^cSEM in Bayesian framework: effect of traffic pollution on inflammation.

^dPosterior probability that $\beta_1 > 0$.

^eBayesian linear mixed model: effect of black carbon on sVCAM-1.