Web-based Supplementary Materials for "A Systematic Review and Meta-Analysis of Outdoor Fine Particles and Nonfatal Strokes"

by

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eTable 1. Short- and Long-term studies pooled

Author	Stroke Outcome	Publication year	Risk ratio	Lower limit	Upper limit
Short-Term Studies					
Anderson et	Cerebrovascular	2001	0.99	0.97	1.02
Bell et al.[29]	Cerebrovascular	2008	0.99	0.97	1.01
Chan et al.[30]	Cerebrovascular	2006	1.00	0.98	1.01
Chan et al.[30]	Hemorrhagic	2006	0.96	0.91	1.01
Chan et al.[30]	Ischemic	2006	1.03	0.99	1.07
Dominici et	Cerebrovascular	2006	1.01	1.00	1.01
Haley et al.[32]	Cerebrovascular	2009	1.00	0.99	1.01
Halonen et al.[33]	Cerebrovascular	2009	1.00	0.97	1.03
Jalaludin et al.[34]	Cerebrovascular	2006	0.98	0.95	1.01
Kim et al.[35]	Cerebrovascular	2012	1.00	0.99	1.02
Kloog et al.[36]	Cerebrovascular	2012	1.00	1.00	1.01
Lippman et al.[37]	Cerebrovascular	2000	1.01	0.98	1.04
Lisabeth et al.[38]	Ischemic	2008	1.06	0.99	1.13
Metzger et al.[39]	Cerebrovascular	2004	1.05	1.01	1.09
Moolgavkar[40]	Cerebrovascular	2000	1.01	1.00	1.02
Villeneuve et	Hemorrhagic	2012	1.02	0.86	1.20
Villeneuve et al.	Ischemic	2012	1.07	0.95	1.21
Villeneuve et al.	Hemorrhagic	2006	1.11	0.97	1.27
Villeneuve et al.	Ischemic	2006	1.02	0.94	1.10
Wellenius et al.	Ischemic	2012	1.18	1.02	1.36
Long-Term Studies					
Kloog et al. [36]	Cerebrovascular	2012	1.03	1.01	1.07
Lippsett et al. [43]	Hemorrhagic and ischemic	2011	1.10	0.93	1.31
Miller et al. [6]	Hemorrhagic and ischemic	2007	1.28	1.02	1.61
Atkinson et al.	Hemorrhagic	2013	1.08	0.92	1.27

[a]*For simplicity, we report the national pooled estimate from Dominici here, but pooled the 202 city-specific risk estimates.*

eAppendix: Bayesian Approach for meta-analysis

We present an approach to summarize the uncertainty in the association between exposure to $PM_{2.5}$ and the incidence of nonfatal strokes using a 2-stage Bayesian hierarchical model. It is assumed the true but unknown risks are exchangeable among the selected studies. The unknown true risks (i.e. true study-specific risk) can have any distribution in the sense of Bayesian perspective. In this meta-analysis study, we consider two distributions in particular, a normal (non-informative prior) and a gamma (semi-informative prior) distributions. We then develop a strategy (called "Hybrid Bayesian-Frequentist approach") to select reasonable prior distributions for the gamma risk distribution when we have a limited number of studies but there is toxicological or clinical literature to support a causal relationship.

We assume that β=(β_1,..., β_K), representing the stroke risks for the K studies, are exchangeable. In other words, our prior belief about β_i (risk for the *i*-th study) and β_j (risk for the *j*-th study) are identical. This implies the unknown true stroke risks are considered to have the same nature regardless of place (North America vs Asia), size (big vs small country in population), or time (in the 80s vs 90s). Due to our inability to separate those differences, we start with this general assumption.

We construct an exchangeable prior by assuming that β is a random sample from a reasonable statistical distribution, normal versus gamma, as mentioned earlier. The reported study-specific risk estimate ($\hat{\beta}_k$) is then assumed to vary about the true risk (β_k) in equation (A1), and the individual β_k is assumed to be random variables from a distribution conditional on additional parameters called hyperparameters (A3-N, A3-G, and A3-G*). The β_k is assumed to be a random variable from a normal distribution specified by mean and variance parameters (A2-N) and from a gamma distribution specified by shape and scale parameters (A2-G). The gamma distribution, which is not a typical choice, is selected for the true risk since we believe the association between the adverse health outcomes (strokes) and exposure to $PM_{2.5}$ is positive. The gamma distribution also can characterize variation in risk among studies in a non-symmetric manner, a pattern often observed. No matter what distribution is assumed, the β_k has mean (μ_β) and between study variation (σ^2_β), which is the inter-study difference or heterogeneity among studies.

At the first stage of the 2-stage Bayesian hierarchical model, we assume for the *k*-th study:

$$\hat{\beta}_k \mid \beta_k \sim N(\beta_k, \hat{v}_k^2) \text{ for k} = 1,..,K, \qquad \text{(A1)}$$

where $\hat{\beta}_k$ is the reported risk estimates, β_k is the unknown true risk, and $\hat{v}_k^2$ is the known estimated sampling variance of $\hat{\beta}_k$ conditional on β_k, $\hat{\text{var}}(\hat{\beta}_k \mid \beta_k)$, of the *k*-th study. The normality assumption in (A1) is derived from a meta-regression model, where the stroke risk estimate has a normal distribution, and thus (A1) is shared by both normal and gamma priors.

At the second stage, the true risks, $\beta_1, \ldots, \beta_K$, are assumed in two ways: a random sample from a normal distribution with mean (μ_β) and variation (σ_β^2) or from a gamma distribution with shape and scale parameters, $\alpha>0$ and $\theta>0$, respectively. Here the hyperparameters μ_β and σ_β^2 are assumed to be independent.

First, the normal prior for the stroke risk is written: for any *k*,

$$\beta_k \mid \mu_\beta, \sigma_\beta^2 \sim N(\mu_\beta, \sigma_\beta^2) \qquad \text{(A2-N)}$$

The model specification is completed by prior distributions for the hyperparameters

$$\mu_\beta \sim N(0, I_\mu) \text{ and } \sigma_\beta^2 \sim IG(\phi, \pi) \qquad \text{(A3-N)}$$

where IG is an Inverse Gamma distribution with shape and scale parameters ϕ and π for variance σ_β^2. The posterior distributions for μ_β and σ_β^2 are insensitive to the specification of I_μ but highly sensitive to the values of (ϕ, π). One selects non-informative priors as follows:

$$I_\mu = 1000, \ \phi = 0.001, \text{ and } \pi = 0.001. \qquad \text{(A4-N)}$$

Two examples on short-term risk, ischemic and hemorrhagic strokes, were used for four different values of ϕ and π but keeping $I_\mu = 1000$ fixed as the results were insensitive to the prior for μ_β. The typical non-informative priors in equation (A4-N) are expected to have little influence on the eventual posteriors, but this is often untrue if only small number of studies is available.

As shown in eTable 2, the 95% posterior ranges for μ_β and σ_β^2 are quite different over the change in the prior for σ_β^2, and the results from this non-informative prior (A4-N) are shaded.

eTable 2: Example results from Bayesian normal model (A3-N)

cause	Prior[1]	parameter	mean	sd	Q2.5	Q50	Q97.5	observed variance
Ischemic (number of study=5)	1.0E-04	overall risk[2]	0.0467	0.0266	0.0005	0.0453	0.1030	0.0033
	1.0E-04	Hetero[3]	0.0019	0.0090	0.0001	0.0006	0.0111	0.0033
	0.001	overall risk	0.0521	0.0362	-0.0134	0.0506	0.1274	0.0033
	0.001	hetero	0.0046	0.0171	0.0004	0.0021	**0.0225**	0.0033
	0.01	overall risk	0.0597	0.0624	-0.0592	0.0587	0.1849	0.0033
	0.01	hetero	0.0171	0.0483	0.0026	0.0097	0.0731	0.0033
	0.1	overall risk	0.0646	0.1445	-0.2195	0.0645	0.3499	0.0033
	0.1	hetero	0.1010	0.2309	0.0190	0.0622	0.4064	0.0033
Hemorrhagic	1.0E-04	overall risk	0.0069	0.1267	-0.1365	0.0009	0.1851	0.0056
	1.0E-04	hetero	0.0448	2.0916	0.0001	0.0033	0.1594	0.0056

(number of study=3)	0.001	overall risk	0.0146	0.1550	-0.1770	0.0107	0.2271	0.0056
	0.001	hetero	0.0694	2.4949	0.0007	0.0073	**0.2544**	0.0056
	0.01	overall risk	0.0224	0.2384	-0.3017	0.0209	0.3573	0.0056
	0.01	hetero	0.1672	3.5516	0.0040	0.0241	0.6745	0.0056
	0.1	overall risk	0.0266	0.4765	-0.6931	0.0258	0.7503	0.0056
	0.1	hetero	0.6848	15.0711	0.0278	0.1385	2.9690	0.0056

[1]prior values of ϕ and π for equation (A4-N)

[2]pooled risk (mean risk) among studies (μ_β)

[3]heterogeneity between studies (σ_β^2)

Second, the gamma prior for the stroke risk is written: for any *k*,

$$\beta_k \mid \alpha,\theta \sim G(\alpha,\theta). \qquad \text{(A2-G)}$$

The mean (μ_β) and variance (σ_β^2) of G(α,θ) are $\alpha\theta$ and $\alpha\theta^2$, respectively. To compare with the normal prior in (A2-N), we re-parameterize them by changing the shape and scale parameters to μ_β and σ_β^2 as follows:

$$\beta_k \mid \mu_\beta,\sigma_\beta^2 \sim G(\mu_\beta^2/\sigma_\beta^2, \sigma_\beta^2/\mu_\beta).$$

We apply non-informative prior distributions for both μ_β and σ_β^2 using the uniform distribution and diffuse the prior distributions by taking large values of the uniform distribution:

$$\mu_\beta \sim U(0, I_\mu) \text{ and } \sigma_\beta^2 \sim U(0, I_{\sigma^2}). \qquad \text{(A3-G)}$$

As with the normal distributional assumption on the true stroke risks, in practice the posterior distributions for μ_β and σ_β^2 are insensitive to the specification of I_μ but highly sensitive to the values of I_{σ^2}. We borrow a philosophy from the Frequentist's approach by noting that the heterogeneity in risk among studies should be less than the observed variance between the $\hat{\beta}_k$. To ensure our method adheres to this philosophy we identify a value of I_{σ^2} such that the 0.975 percentile of the posterior distribution of σ_β^2 is close to but not greater than the observed variance of the $\hat{\beta}_k$.

I_μ=1000, and I_{σ^2} depends on observed variance of the $\hat{\beta}_k$. (A4-G)

In comparison to the normal priors in (A3-N), the same two examples on short-term risk were used for four different values of I_{σ^2} but keeping $I_\mu = 1000$ in (A3-G). The results are summarized in eTable 3. Again the results are very sensitive to the prior for σ_β^2, as predicted above due to the small number of studies. We propose an empirical prior based

on the observed variance in the last column and the 97.5th percentile column shaded to decide the value for I_{σ^2} : the 97.5th percentile of the posterior distribution of heterogeneity is close to but less than the observed variance as indicated in bold in the table.

eTable 3: Example results from Bayesian gamma model (A3-G)

cause	Prior[1]	parameter	mean	sd	Q2.5	Q50	Q97.5	observed variance
Ischemic (number of study=5)	1.0E-04	overall risk[2]	0.0405	0.0145	0.0123	0.0403	0.0694	0.0033
	1.0E-04	Hetero[3]	0.0000	0.0000	0.0000	0.0000	0.0001	0.0033
	0.001	overall risk	0.0460	0.0173	0.0141	0.0453	0.0816	0.0033
	0.001	hetero	0.0005	0.0003	0.0000	0.0005	**0.0010**	0.0033
	0.01	overall risk	0.0652	0.0271	0.0203	0.0626	0.1248	0.0033
	0.01	hetero	0.0043	0.0029	0.0001	0.0040	0.0097	0.0033
	0.1	overall risk	0.1094	0.0583	0.0251	0.1004	0.2424	0.0033
	0.1	hetero	0.0459	0.0301	0.0010	0.0445	0.0972	0.0033
Hemorrhagic (number of study=3)	1.0E-04	overall risk	0.0139	0.0113	0.0010	0.0111	0.0422	0.0056
	1.0E-04	hetero	0.0001	0.0000	0.0000	0.0001	0.0001	0.0056
	0.001	overall risk	0.0197	0.0147	0.0021	0.0162	0.0560	0.0056
	0.001	hetero	0.0005	0.0003	0.0000	0.0006	**0.0010**	0.0056
	0.01	overall risk	0.0362	0.0254	0.0055	0.0302	0.0990	0.0056
	0.01	hetero	0.0056	0.0028	0.0005	0.0058	0.0098	0.0056
	0.1	overall risk	0.0802	0.0523	0.0159	0.0671	0.2113	0.0056
	0.1	hetero	0.0562	0.0275	0.0056	0.0584	0.0981	0.0056

[1]prior values of I_{σ^2} for equation (A3-G)

[2]pooled risk (mean risk) among studies (μ_β)

[3]heterogeneity between studies (σ_β^2)

eFigure 1 on sensitivity analysis for short-term effects: For short-term effects in this paper 221 risk estimates were used for pooled risk estimate. Among them 202 estimates were drawn from the Dominici et al. multi-city study.[31] To assess the influence of this multi-city study, we excluded 202 risk estimates and then pooled across the remaining study risk estimates (N=19) and for the cerebrovascular endpoint alone (N=11).

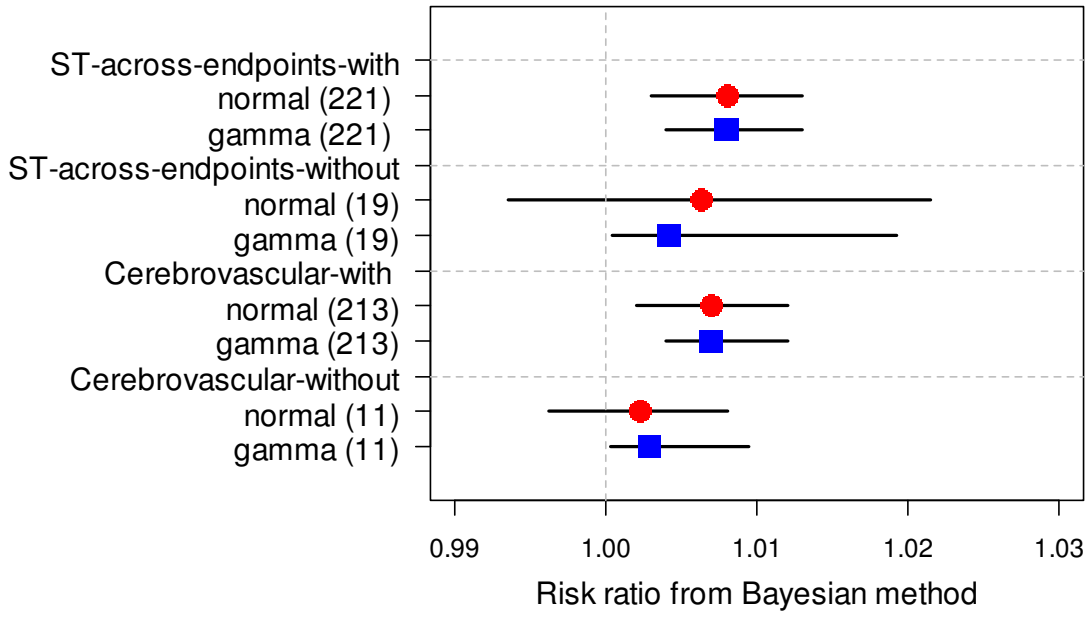
Note that 5 out of 19 studies (26%) across all stroke endpoints reported negative point estimates, and also 4 out of 11 studies (36%) on cerebrovascular stroke reported negative point estimates. These are relatively high rates of negative risk estimate, and thus for stable computations we used original hyperparameters (shape and scale) of the gamma prior distribution (A3-G*) instead of using its mean (μ_β) and variance (σ_β^2) in (A3-G).

Again we apply non-informative prior distributions for both shape and scale using a uniform distribution as follows:

$$\beta_k \mid \alpha, \theta \sim G(\alpha, \theta), \quad \text{(A2-G)}$$

$$\alpha \sim U(0, I_\alpha) \text{ and } \theta \sim U(0, I_\theta). \quad \text{(A3-G*)}$$

The comparisons with and without the multi-city study are displayed in eFigure 1. Both prior distributions, normal and gamma, returned comparable posterior medians (represented by dots in circle and square, respectively) but the normal prior returned wider posterior intervals when the multi-city study was excluded.



eFigure 1. Risk ratio of short-term exposure to $PM_{2.5}$ (per 10 μg/m^3) with and without multi-city study[31]: Bayesian approach with normal and gamma prior distributions for across-all strokes and cerebrovascular stroke alone (number of studies included).

To estimate the unknown parameters, we ran three sequences (chains) of the Gibbs sampler using different initial values, each chain for 11,000 iterations and removed the first 1000 burn-in samples to reach convergence. We assessed the convergence through the use of trace and Gelman-Rubin statistic plots. All estimates were obtained by WinBUGS (version 1.4.3)[e1] and a R package R2WinBUGS[e2]. All figures were generated also by R (version 2.15.2)[e3].

eREFERENCES

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