Original Article

Monte Carlo Sensitivity Analysis for Adjusting Multiple-bias in the Longitudinal Cardiovascular Study

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Epidemiologic findings by conventional statistical methods reflect uncertainty due to random error but omit uncertainty due to biases, such as unmeasured confounding, selection bias, and misclassification error. One approach for addressing this problem is to perform sensitivity analyses. We used MCSA (Monte Carlo sensitivity analysis) to analyze data from a large population-based cohort study, Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine. The effects of the blood pressure on arteriosclerotic disease were examined among 21,949 subjects accounting for both misclassification of exposure and unmeasured confounding. We used a Poisson regression model to estimate the gender-specific incidence rate ratio (IRR) of each blood pressure category adjusted for several measured risk factors. The prior information on the misclassified blood pressure and the unmeasured diabetes mellitus history was obtained from sub-cohort members. Sequential correction of two biases by the MCSA led to large decrease of IRR among pre-hypertensive men ($IRR = 1.79$ [95% limits = $0.22 - 3.78$]) and women (1.15 [$0.28 - 2.25$]), and large increase of IRR among stage 2 hypertensive men (7.24 [$3.50 - 11.2$]) and women (4.12 [$2.14 - 6.89$]). Our expanded MCSA provides valuable approach for bias analysis, which makes explicit and quantifies sources of uncertainty.

Key words: sensitivity analysis, uncertainty, misclassification error, unmeasured confounding, Monte Carlo method.

1. Introduction

Most epidemiologic findings suffer from a large amount of uncertainty due not only to random error, but also to biases such as confoundings, measurement error, and selection bias (Taubes, 1995; Rothman et al., 2008). Conventional statistical methods reflect the uncertainty associated with random sampling of subjects from a hypothetical population, but omit the other sources of

uncertainty and rely on assumptions that are not testable from the observed data, such as the assumption that there are no unmeasured confounders or the assumption of missing at random.

One approach for addressing these issues is to perform sensitivity analyses, where omitted sources of uncertainty are added as sensitivity parameters or are used to adjust the data (Greenland, 1996; Copas and Li, 1997; Lin et al., 1998). Quantitative assessments of bias can provide more realistic estimates of the total uncertainty, and can help the investigator illustrate the possible extent of such biases. That is, simple sensitivity analysis estimates what the true exposure effect would be in light of observed data and hypothetical bias parameters, and produces one or more adjusted point estimates for the exposure effect under several scenarios. While conducting simple sensitivity analysis is an improvement over ignoring bias, it treats all scenarios equally regardless of plausibility, and thus the results can be sensitive to the chosen range of a parameter. Furthermore, it can become difficult to summarize results as the number of sensitivity parameters increases (Greenland, 1996; Rothman et al., 2008).

An alternative approach for addressing the limitations of simple sensitivity analysis is to perform Monte Carlo Sensitivity Analysis (MCSA), which specifies a probability distribution for each sensitivity parameter, draws a set of those parameters, and repeats the conventional analysis for multiple draws (Lash, 2000; Greenland, 2001; 2005; 2009; Lash, 2003; Steenland and Greenland, 2004). If the data provide negligible information on the bias parameters and if sampling error is properly incorporated into the final distribution, such MCSA can approximate Bayesian results (Greenland, 2001; 2005; 2009).

In this article, we develop bias correction formulas for both misclassification of exposure with more than two categories and unmeasured confounders. Using these formulas, we apply MCSA to the data from the Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine project (JALS Group, 2008) to examine the effects of blood pressure on arteriosclerotic disease while accounting for both misclassification error of exposure (blood pressure) and an unmeasured confounder (history of diabetes mellitus) using a reasonable prior distribution of each sensitivity parameter.

2. Study Population and Definitions

2.1 Study Population (JALS-ECC)

The aim of the Japan Arteriosclerosis Longitudinal Study (JALS) is to investigate the risk factors for arteriosclerotic disease specific to the Japanese population (JALS Group, 2008). The JALS is composed of two studies: one is a combination of existing cohorts (Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine; JALS-ECC), a collaborative pooling project based on individual participant data from existing prospective cohort studies that have been conducted between 1985 and December 2001, the other is a prospective cohort study that began in 2002 and is ongoing. In this article, we used data from the former study. Quality control of collected cohort data was performed at the JALS Coordinating Center. Consequently, individual

records for each of the 66,691 participants in 21 cohort studies were included in this project, with 82.7% of the participants from 17 community-based cohorts and 17.3% from four worksite-based cohorts. Baseline records for all participants included age (years), gender, BMI (body mass index; kg/m^2), SBP and DBP (systolic and diastolic blood pressure; mmHg; Chobanian et al., 2003). The participants also had data from several medical check-ups, including medical history and laboratory tests. Permission to submit each cohort's data to the JALS central office was obtained from each institute's ethical review board.

2.2 Exclusion Criteria for this Article

In this article, we evaluated the effect of blood pressure on the occurrence of arteriosclerotic disease. The primary endpoint was the first occurrence of arteriosclerotic disease, comprising fatal and nonfatal events of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, and myocardial infarction. Of the 17 community-based cohorts included in JALS-ECC, we excluded eight because they didn't measure all four primary endpoints (40,563 participants excluded). We also excluded participants from the analyses based on the following criteria: those under 40 or over 89 years of age (1,234 participants excluded), and those for whom data on TC (total cholesterol; mg/dL) and smoking history were not available (2,945 participants excluded). The population for the final analysis consisted of 8,538 men and 13,411 women. Table 1 shows the characteristics of this population. The incidence (rate/year) for arteriosclerotic events was 6.16×10^{-3} for men and 3.71×10^{-3} for women.

Table 1. Characteristics of Analysis Population Stratified by Gender

Characteristics	Men (N = 8,538)	Women (N = 13,411)
Age (Year)	58.7 ± 11.0	58.3 ± 11.3
BMI (Kg/m^2)	23.0 ± 3.0	23.3 ± 3.3
SBP (mmHg)	135.3 ± 19.8	132.8 ± 19.9
DBP (mmHg)	81.5 ± 11.7	78.2 ± 11.1
TC (mg/dL)	190.5 ± 34.5	206.4 ± 36.6
Smoking history (%)		
Non-smoker	23.3	92.3
Ex-smoker	23.4	1.4
Current Smoker	53.3	6.3
No. of arteriosclerotic event	406	390
Total person-year	65,944	105,105

Results expressed as mean $\pm$ SD (standard deviation) unless otherwise indicated.

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol.

3. Methods

3.1 Crude Model Assuming No Systematic Errors

We used a Poisson regression model to estimate the incidence rate ratio (IRR) and 95% confidence interval (CI) of blood pressure groups adjusted for age, BMI, TC, and smoking history, which were measured at the start of the study. All analyses were stratified by gender. According to the seventh report of the Joint National Committee (JNC 7th; Chobanian et al., 2003), blood pressure is divided into four categories: normal (SBP < 120 and DBP < 80 mmHg), pre-hypertension ($120 \leq \text{SBP} < 140$ or $80 \leq \text{DBP} < 90$ mmHg), stage 1 hypertension ($140 \leq \text{SBP} < 160$ or $90 \leq \text{DBP} < 100$ mmHg), and stage 2 hypertension ($160 \leq \text{SBP}$ or $100 \leq \text{DBP}$ mmHg). We divided age into five categories in 10-year intervals and treated it as a time-dependent covariate. BMI and TC were treated as continuous covariates. We classified smoking status into three categories: nonsmoker, ex-smoker, and current smoker.

Let Y be the event variable for each participant ($Y = 1$ if arteriosclerotic disease is observed, $Y = 0$ otherwise), $\mathbf{X}$ be the dummy variable vector for blood pressure category (3x1 vector; reference category is the normal group), and $\mathbf{Z}$ be a vector of covariates (age, BMI, TC and smoking status). We assume the following crude model, in which there are no misclassification errors in $\mathbf{X}$ and all confounders are included in $\mathbf{Z}$ within each gender:

$$E(Y | \mathbf{X}, \mathbf{Z}) = T \exp(\beta_0 + \beta_1' \mathbf{X} + \beta_2' \mathbf{Z}) \quad (1)$$

where T is a person-year of follow-up and β_1 and β_2 are the regression parameters corresponding to $\mathbf{X}$ and $\mathbf{Z}$. Note that β_1 is a vector: $\beta_1' = (\beta_{11}, \beta_{12}, \beta_{13})$.

3.2 Adjusting the Model for Misclassification

Because the values of blood pressure based on the mercurial manometer are subject to large measurement errors (Pickering, 2005), it is important to conduct a sensitivity analysis for exposure misclassification. We assumed the following Poisson regression model based on the observed misclassified exposure $\mathbf{X}^*$:

$$E(Y | \mathbf{X}^*, \mathbf{Z}) = T \exp(\beta_0^* + \beta_1^{*'} \mathbf{X}^* + \beta_2^{*'} \mathbf{Z}) \quad (2)$$

where β^* represents the regression parameters. Here, we assume that exposure misclassification is non-differential, which is independent of disease status because blood pressure was measured before events occurred, and so the distribution of the surrogate variable $\mathbf{X}^*$ depends only on $\mathbf{X}$ and not on the outcome variable Y .

Under the assumption of non-differential exposure misclassification, whereby $\mathbf{X}^*$ and Y are conditionally independent given $\mathbf{X}$, there is the following relationship between model (1) which is the expected response given true blood pressure category and $\mathbf{Z}$, and model (2) which is the expected response given observed blood pressure category and $\mathbf{Z}$ (Gustafson, 2004):

$$E(Y | \mathbf{X}^*, \mathbf{Z}) = E[E(Y | \mathbf{X}, \mathbf{Z}) | \mathbf{X}^*, \mathbf{Z}]$$

$$= E[T \exp(\beta_0 + \beta'_1 \mathbf{X} + \beta'_2 \mathbf{Z}) \mid \mathbf{X}^*, \mathbf{Z}] \quad (3)$$

Comparing model (2) with (3), the correction formula for true exposure effects can be developed, and magnitude of the misclassification can be described by the predictive probabilities $H_{ts} = \Pr(\mathbf{X} = t \mid \mathbf{X}^* = s)$:

$$\begin{bmatrix} \exp(\beta_0) \\ \exp(\beta_0 + \beta_{11}) \\ \exp(\beta_0 + \beta_{12}) \\ \exp(\beta_0 + \beta_{13}) \end{bmatrix} = \begin{bmatrix} H_{00} & H_{10} & H_{20} & H_{30} \\ H_{01} & H_{11} & H_{21} & H_{31} \\ H_{02} & H_{12} & H_{22} & H_{32} \\ H_{03} & H_{13} & H_{23} & H_{33} \end{bmatrix}^{-1} \begin{bmatrix} \exp(\beta_0^*) \\ \exp(\beta_0^* + \beta_{11}^*) \\ \exp(\beta_0^* + \beta_{12}^*) \\ \exp(\beta_0^* + \beta_{13}^*) \end{bmatrix} \quad (4)$$

where s ($s = 0, \dots, 3$) and t ($t = 0, \dots, 3$) are observed and true categories for blood pressure, respectively. $s = 0$ or $t = 0$ represent $\mathbf{X} = (0, 0, 0)'$. The derivation of equation (4) is given in Appendix. Note that the predictive probabilities H_{ts} can be written via the misclassification probabilities, $\pi_{st} = \Pr(\mathbf{X}^* = s \mid \mathbf{X} = t)$, that is, $H_{ts} = \frac{\Pr(\mathbf{X} = t)}{\Pr(\mathbf{X}^* = s)} \pi_{st}$. Therefore, if reasonable estimates of misclassification probabilities and prevalence of true exposure are obtained from an internal validation subsample of the study participants, we can adjust exposure misclassifications based on (4). When the exposure category is binary, (4) is equivalent to the correction formula given by Gustafson (Gustafson, 2004).

3.3 Adjusting the Model for an Unmeasured Confounder

History of diabetes mellitus (DM) is a known risk factor for arteriosclerotic disease (Karapanayiotides et al., 2004; Romero-Carral et al., 2006). However, in our study, different measurements were used to obtain data on DM. Five sub-cohorts (37.3% of 8,869 men and 62.7% of 11,839 women) define DM using both of blood sugar and past DM history, while other sub-cohorts have only partial information about blood sugar or past DM history. We defined the five sub-cohorts as having adequately measured DM history data. It is an important limitation of most studies that an unmeasured confounder is treated as if it were independent of the measured confounders. On the other hand, we have the five sub-cohorts with measurement of DM status adequately. We can assess its effect in this sub-cohorts, treat it as related to the measured and controlled covariates, and use that to calibrate the results for the remaining cohorts.

Therefore, in the crude model (1), we omitted the DM variable from the measured confounders $\mathbf{Z}$. In this subsection, we treat the history of DM as an unmeasured confounder, denoted by U , and consider a formula for exposure effects with adjustment for U .

We assumed the following two Poisson regression models; one is adjusted for U ($U = 0, 1$) and the other is not adjusted for U :

$$E(Y \mid \mathbf{X}, \mathbf{Z}, U) = T \exp(\gamma_0 + \gamma'_1 \mathbf{X} + \gamma'_2 \mathbf{Z} + \gamma'_3 U) \quad (5)$$

$$E(Y \mid \mathbf{X}, \mathbf{Z}) = T \exp(\gamma_0^* + \gamma_1^{*'} \mathbf{X} + \gamma_2^{*'} \mathbf{Z}) \quad (6)$$

where γ and γ^* are the regression parameters. By the law of conditional expectation, the relationship between models (5) and (6) is:

$$\begin{aligned} E(Y | \mathbf{X}, \mathbf{Z}) &= \int_{-\infty}^{\infty} E(Y | \mathbf{X}, \mathbf{Z}, U) dF(U | \mathbf{X}, \mathbf{Z}) \\ &= T \exp(\gamma_0 + \gamma'_1 \mathbf{X} + \gamma'_2 \mathbf{Z}) [\exp(\gamma_3) P_{XZ} + (1 - P_{XZ})] \end{aligned} \quad (7)$$

where $F(U | \mathbf{X}, \mathbf{Z})$ is the distribution function of U given $\mathbf{X}$ and $\mathbf{Z}$, and P_{XZ} is the prevalence of the unmeasured confounder U in the exposure $\mathbf{X}$ and covariates $\mathbf{Z}$. Comparing model (6) with (7), a correction formula for true exposure effects can be developed (Lin et al., 1998):

$$\exp(\gamma_{1s}) = \frac{\exp(\gamma_3) P_{0Z} + (1 - P_{0Z})}{\exp(\gamma_3) P_{sZ} + (1 - P_{sZ})} \exp(\gamma_{1s}^*) \quad (8)$$

where γ_{1s} is a component of γ_1 corresponding to blood pressure category s ($s = 0, \dots, 3$. $s = 0$ represent $\mathbf{X} = (0, 0, 0)'$). Thus, if reasonable estimates of the effect for an unmeasured confounder U and prevalence of U are obtained, we can adjust an unmeasured confounder based on (8).

3.4 Monte Carlo Sensitivity Analysis (MCSA)

MCSA repeatedly re-estimates the effect measure of interest based on the observed data and the priors for bias sources. As shown in (4) and (8), the bias-adjusted IRR relating blood pressure to arteriosclerotic disease can be obtained from the crude IRR multiplied by the bias factor. For example, the bias factor in (8) is a function of the DM prevalence in each blood pressure category (P_{XZ}) as well as the IRR for the effect of DM on arteriosclerotic disease ($\exp(\gamma_3)$). One must assign prior distributions to these unknown parameters. To account for random error, the distribution of the crude IRR relating blood pressure to arteriosclerotic disease ($\exp(\gamma_{1s}^*)$) is estimated using conventional methods, that is, the logarithm of the crude IRR is taken to be normally distributed with a mean and variance estimated by the usual maximum likelihood methods. One can then repeatedly sample from the priors for the bias parameters and from the estimated distribution of the crude IRR, each time constructing a bias factor and then using this factor to adjust the crude IRR (Greenland, 2001; 2003; 2005; Steenland and Greenland, 2004). The point estimate of the adjusted IRR can be calculated from the 50th percentile for the generated distribution of the parameter of interest, and the 95% Monte Carlo limits can be calculated from the 2.5th and 97.5th percentiles.

3.5 Single and Sequential Corrections of Multiple-bias

First, we consider the adjustment of blood pressure misclassification error based on (4). Although there are several ways to measure error-free blood pressure values (Pickering et al., 2005), it is difficult to use such instruments in the health checkup setting, and the mercurial manometer is usually used. In Japan, it is recommended that blood pressure is measured twice when using the mercurial manometer, so we regarded the mean of the two consecutive measurements as the expected true value. In our data, two measurements on the same day were obtained in four

Table 2. Distributions of Blood Pressure between True Value and First Measurement among Four Sub-cohorts

		True Value (Mean of Two Measurements)			
		Normal	Pre-hypertension	Stage 1 Hypertension	Stage 2 Hypertension
First Measurement	Men	Normal	84 (2.71%)	6 (0.19%)	0 (0.00%)
		Pre-hypertension	19 (0.61%)	205 (6.61%)	9 (0.29%)
		Stage 1 Hypertension	0 (0.00%)	287 (9.26%)	1,295 (41.76%)
		Stage 2 Hypertension	0 (0.00%)	0 (0.00%)	325 (10.48%)
	Women	Normal	178 (4.08%)	4 (0.09%)	0 (0.00%)
		Pre-hypertension	33 (0.76%)	301 (6.89%)	12 (0.27%)
		Stage 1 Hypertension	0 (0.00%)	510 (11.68%)	1,805 (41.32%)
		Stage 2 Hypertension	0 (0.00%)	1 (0.02%)	493 (11.29%)

Percentage is gender-specific proportion in each category (Total subject is 3,101 in men and 4,368 in women).

sub-cohorts (35.0% of 8,869 men and 36.9% of 11,839 women). Table 2 shows the distribution of the blood pressure categories between the expected true values and the first measurements in that sub-cohort.

To repeatedly estimate the bias factor in (4), we assumed the multinomial distribution with 16 parameters shown in Table 2, and drew 10,000 random samples from that distribution for each gender. The prior distribution for the crude IRR ($\exp(\beta_1^*)$) was computed from model (2), in which the first measurement of blood pressure was used as $\mathbf{X}^*$ for all participants. The 10,000 crude IRRs were sampled from a multivariate normal distribution with a mean vector equal to the logarithm of the maximum likelihood estimates, and a variance matrix equal to the inverse of the Fisher information at the estimates. Each of the sampled parameters was used to estimate the misclassification-adjusted IRR via (4).

Next, we consider the adjustment of an unmeasured confounder (DM history) based on (8). In our study, the adequate definition of DM history was adopted in five sub-cohorts. Therefore, the prior distribution for the bias factor was obtained from that sub-cohort. Table 3 shows the prevalence of DM history in each blood pressure category. We assumed the multinomial distribution with four parameters shown in Table 3, and drew 10,000 random samples from the distribution for each gender. The effect of DM history ($\exp(\gamma_3)$) was estimated by applying model (5) to the data from the five sub-cohorts. The IRR for DM history was 1.53 (95% CI = 1.10 – 2.13) for men and 1.52 (95% CI = 1.02 – 2.26) for women. The 10,000 IRRs for the effect of DM history were sampled from a normal distribution with a mean equal to the logarithm of the above estimates, and a standard deviation equal to the standard error of that estimate. Similar to the adjustment for misclassification, to account for random error we estimated the distribution of the crude IRR relating blood pressure to arteriosclerotic disease ($\exp(\gamma_{1s}^*)$) by applying model (6) to all participants, and sampling 10,000 crude IRRs from a multivariate normal distribution.

Table 3. Prevalences of DM History in Each Blood Pressure Category among Four Sub-cohorts

Blood Pressure Category	Men			Women		
	No. of DM History	Total No.	Prevalence	No. of DM History	Total No.	Prevalence
Normal	58	785	0.074	66	1,847	0.036
Pre-hypertension	166	1,710	0.097	157	3,149	0.050
Stage 1 Hypertension	124	1,065	0.116	115	1,617	0.071
Stage 2 Hypertension	70	536	0.131	55	647	0.085

Each of the sampled parameters was used to estimate the DM-adjusted IRR via (8).

Sequential correction of multiple-bias is performed by repeating the above stated single correction procedure in sequence. The corrections should be made in the reverse order from the order in which biases enter a particular study (Phillips, 2003; Greenland, 2005; 2009). For example, suppose that the data generation process is one in which true causal effects are biased due to confounding factors, the study participants are a limited population without non-responders, and finally the responding participants are classified with error (Phillips, 2003; Greenland, 2005; 2009). This phenomenon of accumulating uncertainty suggests that we should correct misclassification first, then non-response, and then unmeasured confounders. In this sequential correction, the misclassification-adjusted IRRs based on (4) are considered to be the crude IRRs relating blood pressure to arteriosclerotic disease in (8), where an unmeasured confounder is adjusted. All analyses were carried out with SAS (version 9.1; SAS Institute Inc, Cary, NC).

4. Results

The results from the crude model assuming no systematic errors are shown in Table 4. After adjustment of several measured confounders, associations between blood pressure and arteriosclerotic events were observed in all categories. The linear trend of the blood pressure effect was found for men and women.

Three MCSA were conducted for each gender. One was a sequential correction for both biases and the other two were single corrections for each bias. The results are shown in Table 5. Bias adjusted-IRR (median) with the 95% Monte Carlo limits of each blood pressure category relative to normal are shown by gender. Results should be compared with those of the crude model (Table 4). Using the single correction for blood pressure misclassification, we observed larger effects in the stage 2 hypertension groups for both genders. Adjusting for the DM history using the single correction for an unmeasured confounder, the IRR decreased compared with the crude one in the pre-hypertension and stage 1 hypertension groups for men, and in the pre-hypertension group for women. Compared with the crude results, the sequential correction of both biases in men resulted in the decrease of IRR in the pre-hypertension and stage 1 hypertension groups and an increase in the stage 2 hypertension group. Similarly, in women, IRR in the pre-hypertension group decreased, while that of the stage 2 hypertension group increased.

Table 4. Conventional Poisson Regression Models Assuming No Systematic Errors

Variable	Men		Women	
	IRR	95% CI	IRR	95% CI
Blood Pressure (mmHg)				
Normal*	1.0		1.0	
Pre-hypertension	2.31	1.47, 3.64	1.33	0.92, 1.92
Stage 1 Hypertension	3.61	2.30, 5.67	1.87	1.29, 2.70
Stage 2 Hypertension	4.49	2.83, 7.14	2.54	1.71, 3.75
Age (years)				
40-49	0.34	0.18, 0.62	0.69	0.35, 1.35
50-59*	1.0		1.0	
60-69	1.66	1.23, 2.56	3.21	2.15, 4.81
70-79	3.22	2.37, 4.36	6.63	4.47, 9.83
80-89	5.36	3.69, 7.80	10.79	6.94, 16.76
BMI (per 5 kg/m ²)	1.17	0.99, 1.38	1.14	0.99, 1.31
TC (per 10 mg/dL)	1.05	1.02, 1.08	1.00	0.97, 1.03
Smoking History				
Non-smoker*	1.0		1.0	
Ex-smoker	0.98	0.72, 1.34	1.24	0.83, 1.87
Current Smoker	1.56	1.20, 2.04	1.76	0.99, 3.12

*Reference category; IRR: Incidence rate ratio; CI: Confidence interval;
 BMI: Body mass index; TC: Total cholesterol

Table 5. Bias Adjusted-IRR Relating Blood Pressure to Arteriosclerotic Disease Based on Single and Sequential MCSA

MCSA Methods	Blood Pressure Category	Men			Women		
		Median	2.5th	97.5th	Median	2.5th	97.5th
Single adjustment (Misclassification)	Normal*	1.00			1.00		
	Pre-hypertension	2.46	1.28	4.16	1.46	0.77	2.38
	Stage 1 Hypertension	4.42	2.48	7.28	2.39	1.33	4.10
	Stage 2 Hypertension	8.35	4.89	11.8	4.97	2.64	8.05
Single adjustment (Uncontrolled Confounding)	Normal*	1.00			1.00		
	Pre-hypertension	1.24	0.21	2.56	0.98	0.23	1.79
	Stage 1 Hypertension	2.72	1.06	5.20	2.05	1.00	3.67
	Stage 2 Hypertension	5.39	2.87	8.98	3.58	1.86	5.74
Sequential adjustment	Normal*	1.00			1.00		
	Pre-hypertension	1.56	0.22	3.24	1.15	0.28	2.30
	Stage 1 Hypertension	3.85	1.63	5.99	2.29	1.23	4.13
	Stage 2 Hypertension	8.04	4.48	12.2	4.85	2.46	9.03

*Reference category; 2.5th and 97.5th means 2.5th percentiles and 97.5th percentiles of the Monte Carlo samples, respectively.

For the overall effect of blood pressure on arteriosclerotic events, we found a quadratic trend rather than a linear one by simultaneously adjusting for both biases. All MCSA results gave wider intervals of effects than those of the conventional ones, reflecting the addition of uncertainty beyond random error.

5. Discussion

Sensitivity analysis is a quantitative extension of the qualitative speculations that characterize good discussions of study results. If it is clear that the biases are small or if the conventional confidence intervals are so wide that nothing can be inferred even in the absence of bias, these qualitative discussions may be sufficient. However, if there are concerns that biases may be large or if conventional results appear very precise, the quantitative assessment of biases can play a crucial role in forming inferences (Greenland, 1996; Steenland and Greenland, 2004). The MCSA is an expanded version of simple sensitivity analysis, which can provide a distribution for the bias-adjusted estimate and can be easily conducted with statistical software such as SAS.

In this article, MCSA for two different biases were combined into a joint analysis. In many epidemiologic studies, there are missing or inaccurately measured data for a subset of participants. In such cases, usual analyses will be conducted based on complete cases, with or without adjustment for such a confounder. These analyses implicitly assume that missing confounders are random or that such a variable is not an important confounder. As shown in this article, the MCSA can adequately account for uncertainty by considering such confounders as an unmeasured one. Although only two sources of bias were considered in this article, selection bias, including response and follow-up bias, is another important problem. Adjusted formulas for selection bias such as (4) and (8) can be developed (Greenland, 1996; 2005; 2009), and sequential corrections for all biases can be conducted if data on the selection probability are available.

To conduct the MCSA, it is necessary to specify a probability distribution for each sensitivity parameter. In our analyses, the prior distribution for misclassified blood pressure was obtained from participants whose blood pressure was measured twice on the same day. There are two limitations of this prior information. First, the blood pressure values for such participants tended to be high. However, because it is clinically known that participants with high blood pressure are likely to be misclassified (Pickering, 2005), such a prior distribution would provide significant information about the target participants. To evaluate the sensitivity of the results in Table 5 to this prior distribution, we also conducted the MCSA based on another prior distribution in which misclassification probabilities were nearly the same in each category, confirming that the results (not shown) were not different from those shown in Table 5. Adjusting for the misclassification alone closely resembled the results from the regression calibration method (not shown). The second limitation in the prior information that we considered was that we used the mean of two blood pressure values as the expected true value. Refinement of the prior distribution will be possible if more accurate information on the expected true value is obtained in the validation

sub-cohort using serial measurements by the oscillometric method.

There may be other unmeasured confounders in addition to DM history. However, because of the strength of its effect and its relatively high prevalence, we think that DM history is the main potential unmeasured confounder in our analysis. When some confounders are measured in a subset of the cohort, it is preferable to apply our expanded MCSA method. We also conducted the MCSA with the value of urinary acid considered as an unmeasured confounder because this was measured only in about half of the participants. The IRRs of each blood pressure category adjusted by the single MCSA (not shown) were almost the same as the crude results in Table 4. Therefore, the effect of urinary acid on the conclusion will be minimal.

In our analyses of the JALS-ECC data, the correction of the misclassified blood pressure led to larger IRRs among stage 2 hypertensive participants. Because participants with high blood pressure are likely to be misclassified, the effects of the adjustment for misclassification will be large in the high blood pressure category. When the exposure has more than two categories, the non-differential misclassification of exposure for a given comparison may bias results away from the null value, and can even reverse the direction of a trend (Dosemeci, 1990). However, as shown in Tables 4 and 5, exposure misclassification biased the results toward the null value in all comparisons. In our data, trend reversal would not occur because the mean blood pressure measurement increased with the expected true value (Weinberg, 1994). The Monte Carlo limits were wider than those from the crude analysis because they reflected uncertainty which is not considered in the crude analysis.

The effects of adjusting for an unmeasured confounder were observed among mildly hypertensive participants. In particular, after adjustment for DM history, associations observed in the pre-hypertensive group relative to the normal one disappeared. This implies that pre-hypertension may not be a serious risk factor for arteriosclerotic disease after controlling for DM history. In fact, the IRR of the pre-hypertension group relative to the normal one estimated from the five sub-cohorts (5,871 men and 9,645 women) where DM history was adequately measured, was 1.86 (95% CI = 0.97 – 2.84) for men and 1.79 (95% CI = 0.96 – 2.26) for women.

In conclusion, we developed the MCSA for multiple-bias and applied it to the data from JALS-ECC to examine the effects of blood pressure on arteriosclerotic disease and account for both misclassification of blood pressure and the unmeasured confounding of DM history. We believe that this type of bias analysis, which makes explicit and quantifies sources of uncertainty, is useful and should be adopted by epidemiologists.

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REFERENCES

- Chobanian A.V., Bakris G.L., Black H.R., et al. (2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *The Journal of the American Medical Association* **289**: 2560-2572.
- Copas J.B., Li H.G. (1997). Inference for non-random samples (with discussion). *Journal of the Royal Statistical Society, Series B* **59**: 55-95.

- Dosemeci M., Wacholder S., Lubin J.H. (1990). Does non-differential misclassification of exposure always bias a true effect toward the null value? *American Journal of Epidemiology* **132**: 746-748.
- Greenland S. (1996). Basic methods for sensitivity analysis of biases. *International Journal of Epidemiology* **25**: 1107-1116.
- Greenland S. (2001). Sensitivity analysis, Monte Carlo risk analysis, and Bayesian uncertainty assessment. *Risk Analysis* **21**: 579-583.
- Greenland S. (2003). The impact of prior distributions for uncontrolled confounding and response bias: A case study of the relation of wire codes and magnetic fields to childhood leukemia. *Journal of the American Statistical Association* **98**: 47-54.
- Greenland S. (2005). Multiple-bias modeling for analysis of observational data (with discussion). *Journal of the Royal Statistical Society, Series A* **168**: 267-306.
- Greenland S. (2009). Bayesian perspectives for epidemiologic research: III. Bias analysis via missing-data methods. *International Journal of Epidemiology* **38**: 1662-1673.
- Gustafson G. (2004). *Measurement Error and Misclassification in Statistics and Epidemiology*, Chapman and Hall/CRC: New York.
- Japan Arteriosclerosis Longitudinal Study (JALS) Group (2008). Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC). *Circulation Journal* **72**: 1563-1568.
- Karapanayiotides T., Piechowski-Jozwiak B., van Melle G. et al. (2004). Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. *Neurology* **62**: 1558-1562.
- Lash T.L., Silliman R.A. (2000). A sensitivity analysis to separate bias due to confounding from bias due to predicting misclassification by a variable that does both. *Epidemiology* **11**: 544-549.
- Lash T.L., Fink A.K. (2003). Semi-automated sensitivity analysis to assess systematic errors in observational epidemiologic data. *Epidemiology* **14**: 451-458.
- Lin D.Y., Psaty B.M., Kronmal R.A. (1998). Assessing sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* **54**: 948-963.
- Phillips C.V. (2003). Quantifying and reporting uncertainty from systematic errors. *Epidemiology* **14**: 459-466.
- Pickering T., Hall J., Apple L., et al. (2005). Recommendations for blood pressure measurement in humans and experimental animals. *Hypertension*, **45**: 142-161.
- Romero-Corral A., Somers V.K., Korinek J., et al. (2006). Update in prevention of atherosclerotic heart disease: management of major cardiovascular risk factors. *Revista de investigación clínica* **58**: 237-244.

Rothman K., Greenland S., Lash T.L. (2008). *Modern Epidemiology*. 3rd ed, Lippincott Williams and Wilkins: Philadelphia.

Steenland K., Greenland S. (2004). Monte Carlo sensitivity analysis and Bayesian analysis of smoking as an unmeasured confounder in a study of silica and lung cancer. *American Journal of Epidemiology* **160**: 384-392.

Taubes G. (1995). Epidemiology faces its limits. *Science* **269**: 164-169.

Weinberg C.R., Umbach D.M., Greenland S. (1994). When will nondifferential misclassification of an exposure preserve the direction of a trend? *American Journal of Epidemiology* **140**: 565-571.

Appendix

Derivation of the equation (4).

To make the derivation simple, we omit covariates $\mathbf{Z}$ from the equation.

We can change the expression of model (3) as,

$$\begin{aligned} E(Y | \mathbf{X}^*) &= E[T \exp(\beta_0 + \beta'_1 \mathbf{X}) | \mathbf{X}^*] \\ &= \exp(\beta_0) E(T | \mathbf{X}^*) E[\exp(\beta'_1 \mathbf{X} | \mathbf{X}^*)] \end{aligned}$$

where $E(T | \mathbf{X}^*) = \sum_{t=0}^3 T_t \Pr(\mathbf{X} = x_t | \mathbf{X}^* = x_s^*) = \sum_{t=0}^3 \frac{T_t \Pr(\mathbf{X} = x_t) \pi_{st}}{\Pr(\mathbf{X}^* = x_s^*)} = E(T_s^*)$.

When we fix $\mathbf{X} = x_s$,

$$\begin{aligned} E[\exp(\beta'_1 \mathbf{X} | \mathbf{X}^* = x_s^*)] &= \sum_{t=0}^3 \exp(\beta'_1 \mathbf{X}) \Pr(\mathbf{X} = x_t | \mathbf{X}^* = x_s^*) \\ &= \frac{\Pr(\mathbf{X} = x_0) \pi_{s0}}{\Pr(\mathbf{X}^* = x_s^*)} + \sum_{t=1}^3 \exp(\beta_{1t}) \frac{\Pr(\mathbf{X} = x_t) \pi_{st}}{\Pr(\mathbf{X}^* = x_s^*)} \end{aligned}$$

where $\beta'_1 = (\beta_{11}, \beta_{12}, \beta_{13})$, $\mathbf{X} = x_0 = (0, 0, 0)'$.

Based on the above-mentioned, model (3) with fixed $\mathbf{X}^*$ can be expressed as,

$$\begin{aligned} E(Y | \mathbf{X}^* = x_s^*) &= T^* \exp(\beta_0^* + \beta^{*'} \mathbf{X}^*) \\ &= \exp(\beta_0) E(T_s^*) \left\{ \frac{\Pr(\mathbf{X} = x_0) \pi_{s0} + \sum_{t=1}^3 \exp(\beta_{1t}) \Pr(\mathbf{X} = x_t) \pi_{st}}{\Pr(\mathbf{X}^* = x_s^*)} \right\}. \end{aligned}$$

For $x_s = x_0$,

$$\exp(\beta_0) = \frac{\exp(\beta_0^*) \Pr(\mathbf{X}^* = x_0^*)}{\{\Pr(\mathbf{X} = x_0) \pi_{0|0} + \sum_{t=1}^3 \exp(\beta_t) \Pr(\mathbf{X} = x_t) \pi_{0|t}\}},$$

and for $x_s = x_k$ ($k \neq 0$),

$$\exp(\beta_{1k}^*) = \frac{\Pr(\mathbf{X}^* = x_0^*)}{\Pr(\mathbf{X}^* = x_k^*)} \left\{ \frac{\Pr(\mathbf{X} = x_0) \pi_{k|0} + \sum_{t=1}^r \exp(\beta_{1t}) \Pr(\mathbf{X} = x_t) \pi_{k|t}}{\Pr(\mathbf{X} = x_0) \pi_{0|0} + \sum_{t=1}^r \exp(\beta_{1t}) \Pr(\mathbf{X} = x_t) \pi_{0|t}} \right\}.$$

These two can be rewritten as equation (4).