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How to use marginal structural models in randomized trials to estimate the natural direct and indirect effects of therapies mediated by causal intermediates

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Abstract

Background Although intention-to-treat analysis is a standard approach, additional supplemental analyses are often required to evaluate the biological relationship among interventions, intermediates, and outcomes. Therefore, we need to evaluate whether the effect of an intervention on a particular outcome is mediated by a hypothesized intermediate variable.

Purpose To evaluate the size of the direct effect in the total effect, we applied the marginal structural model to estimate the average natural direct and indirect effects in a large-scale randomized controlled trial.

Method The average natural direct effect is defined as the difference in the probability of a counterfactual outcome between the experimental and control arms, with the intermediate set to what it would have been had the intervention been a control treatment. We considered 2 marginal structural models to estimate the average natural direct and indirect effects introduced by VanderWeele (*Epidemiology* 2009) and applied them in a large-scale randomized controlled trial—the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J trial)—that compared angiotensin receptor blockers and calcium-channel blockers in high-risk hypertensive patients.

Results There were no strong blood pressure-independent or dependent effects; however, a systolic blood pressure reduction of about 1.9 mmHg suppressed all events. Compared to the blood pressure-independent effects of calcium channel blockers, those of angiotensin receptor blockers contributed positively to cardiovascular and cardiac events, but negatively to cerebrovascular events.

Limitations There is a particular condition for estimating the average natural direct effect. It is impossible to check whether this condition is satisfied with the available data.

Conclusion We estimated the average natural direct and indirect effects through the achieved systolic blood pressure in the CASE-J trial. This first application of estimating the average natural effects in an RCT can be useful for obtaining an in-depth understanding of the results and further development of similar interventions.

Introduction

In randomized controlled trials (RCTs), intention-to-treat analysis is the

standard approach used to compare the treatment effects of an experimental arm to a

control arm. This approach is based on the principle that the effect of an intervening

policy is best assessed by an evaluation based on the intention to treat a subject (*i.e.*, the

planned treatment regimen) rather than the actual intervention used [1]. However,

additional supplemental analyses are often required to evaluate the biological

relationship among interventions, intermediates, and outcomes. For example, if there is

a statistically significant difference in the primary outcome between the two arms, some

investigators examine whether the intervention could work through a hypothesized

mechanism. If no statistically significant difference is found, investigators will

determine which pathway in the intervention did not work well in the RCT. This kind of

analysis is important for an in-depth understanding of the results and further

development of similar interventions.

For this analysis, we need to evaluate whether the effect of an intervention on a

particular outcome is mediated by a hypothesized intermediate variable. Statistically

speaking, this concept relates to the decomposition of the total effect to the direct and

indirect effects. In practice, this investigation has sometimes been conducted using a statistical regression model with adjustment for an intermediate variable. For example, Freedman et al. [2] proposed that the effect of treatment on the clinical outcome after adjustment for the intermediate should be compared with the effect without adjustment. Thereby, they demonstrated that the effect of cholestyramine treatment on coronary heart disease was clearly indicated by the cholesterol-lowering effect of the treatment. However, to adjust such intermediate variables measured after randomization as covariates of standard regression models is considered problematic in most cases [3, 4]. In addition, subtracting the direct effect, estimated from the regression model, from the total effect does not generally yield a quantity that can be interpreted as an indirect or mediated effect [5]. Until recently, there was no statistical method to decompose a total effect into direct and indirect effects, especially when there was a nonlinear relationship between an intervention and an outcome or the interaction between the effects of an intervention and an intermediate on the outcome.

The introduction of a new definition for direct and indirect effects by Robins and Greenland [6] and Pearl [7] promoted assessment of the mediation under the counterfactual framework. If we follow the terminology introduced by Pearl, there are 2 classes of direct effect: "controlled" and "natural" [7]. There are several differences

between these 2 direct effects, which can result in different interpretations when these evaluations are applied to clinical data, for example, in the interpretation as an effect being "prescriptive" or "descriptive" [5, 7]. Moreover, the difference between a total effect and a natural direct effect can be interpreted as an indirect effect but not a controlled direct effect, in general [6-9]. In recent years, there have been many discussions about the conditions to identify a direct and indirect effect, especially in an epidemiologic research, and some analytical methods for this identification have been properly developed on the basis of counterfactual definitions [10-13].

In this article, we will first provide an overview of the statistical methods under the counterfactual model to estimate the direct and indirect effects. To evaluate the size of the direct effect in the total effect, we focus on the estimation of the natural direct and indirect effects. Finally, we apply our analysis strategy based on the marginal structural model proposed by VanderWeele [10] to the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J trial), which is a large-scale RCT that compared the effects of 2 antihypertensive agents on cardiovascular events in high-risk hypertensive patients [14].

Methods

Definition of Direct and Indirect Effects

We first consider an RCT for antihypertensive treatments with 2 drug treatment conditions and 2 outcomes: a blood pressure level as an intermediate outcome and a cardiovascular event as a primary outcome. Let Z denote the randomized interventions (*i.e.,* antihypertensive agents); S, a post-treatment intermediate variable (*i.e.,* blood pressure after treatment); and Y, outcomes of interest in the trial (*i.e.,* cardiovascular events) (Figure 1). Let X denote a set of baseline confounders and U, unmeasured confounders between intermediate-outcome relationships. In the ideal RCT, intervention and both the intermediate condition and outcome have no common causal pathway from other variables. Unfortunately, in the presence of the unmeasured confounders U, the direct and indirect effects are not identifiable [15]. We will assume that there are no unmeasured confounders U between intermediate-outcome relationships or that even if they exist, all unmeasured confounders completely influence the intermediate variables through the measured confounders. Under this assumption, we can remove U from Figure 1. The problem of the unmeasured confounders will be examined in the

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Discussion. Next, we will consider the definitions of direct and indirect effects in this situation.

Hereafter, we will assume that the intervention and outcome are binary and the intermediate is continuous. Robins and Greenland [6] and Pearl [7] formalized the notion of direct and indirect effects in the counterfactual framework. For a random sampled individual i, the observed variables are shown as Z_i, S_i, Y_i, and X_i. $Y_{i,z}$ is an individual's potential outcome if the intervention Z_i is set to z (0 for control treatment, 1 for experimental treatment), and the individual causal total effect is denoted as the difference between the potential outcomes $(Y_{i,1} - Y_{i,0})$. Such potential variables are termed "counterfactual," because only one variable is observed for each individual in reality [16]. Throughout this study, we have assumed that when an individual actually receives a treatment z, the individual's observed outcome Y_i equals the potential outcome $Y_{i,z}$, provided the intervention is set to the same treatment. This assumption connects the observed data to the potential outcomes and is known as a "consistency assumption" [17].

Since it is impossible to observe both counterfactuals in an individual, we consider the marginal distribution for the entire population of the potential outcomes $Y_{i,1}$ and $Y_{i,0}$. The average total effect can be shown as $\Pr(Y_{i,1} = 1) - \Pr(Y_{i,0} = 1)$,

and the unbiased average total effect can be estimated by using the observed data

through an intention-to-treat analysis under the random allocation as follows:

$\Pr(Y_{i,1} = 1) - \Pr(Y_{i,0} = 1) = \Pr(Y_i = 1 | Z_i = 1) - \Pr(Y_i = 1 | Z_i = 0)$ under the

random allocation. Similarly, we further consider the counterfactuals for S and Y as

follows.

$S_{i,z}$: An individual's counterfactual value of the intermediate S if intervention Z is set

to the value z.

$Y_{i,z,s}$: An individual's counterfactual value of the outcome Y if intervention Z is set to

the value z and intermediate S is set to the value s.

Under these counterfactual models, two types of direct effects are formalized: a

controlled direct effect and natural direct effect [6-10]. The individual controlled direct

effect of intervention on outcome, comparing $Z_i = 1$ with $Z_i = 0$ and setting S_i as s,

is defined by $Y_{i,1,s} - Y_{i,0,s}$ and measures the effect of intervention on the outcome not

mediated through the intermediate. Since we cannot calculate the individual controlled

direct effect in reality, we will consider the average controlled direct effect as

$\Pr(Y_{i,1,s} = 1) - \Pr(Y_{i,0,s} = 1)$. This formula shows that the controlled direct effect of

intervention on the outcome can vary from the value of the intermediate to the "set"

value; hence, this type of direct effect has no counterpart indirect effect [7].

On the other hand, another definition of the direct effect, namely, the natural direct effect, has been proposed. The individual natural direct effect of intervention on outcome, comparing experimental with control treatment, under the value of the intermediate "set" to what it would have been if the intervention had been a control treatment, $S_{i,0}$, is formally defined by $Y_{i,1,S_{i,0}} - Y_{i,0,S_{i,0}}$. The average natural direct effect is given as $\Pr(Y_{i,1,S_{i,0}} = 1) - \Pr(Y_{i,0,S_{i,0}} = 1)$. In the case of the average natural direct effect, the average indirect effect can be calculated simply by subtracting the average natural direct effect from the average total effect [7]. If an intervention and intermediate interact to yield the outcome, estimation of the controlled direct effect depends on the level at which the intermediate is set, whereas the average natural direct effect provides a single summary of the average controlled direct effect in the entire population [9]. If there is no interaction between the effects of the intervention and the intermediate on the outcome, the average controlled direct effect and the natural direct effect are equivalent [18].

We will assume that the data strings $(Z_i, S_i, Y_i, X_i, Y_{i,z}, S_{i,z}, Y_{i,z,s})$, $i = 1, ..., N$ are realizations of N independently and are identically distributed random vectors, and henceforth, we will suppress their dependence on the subject index i. In the ideal RCT setting, the randomized intervention Z and potential variables $(S_z, Y_{z,s})$ are

independent from the baseline variables X. Several authors have investigated the

conditions to estimate the average controlled and natural effects. First, we need a

condition such that all confounders between S and $Y_{z,s}$ are measured, that is, $Y_{z,s}|z \in$

$\{0,1\}\coprod S|\{Z,X\}$, in order to estimate both the average controlled and natural direct effect

(no unmeasured confounder condition exists in the intermediate-outcome relationship)

[10]. To estimate the average natural direct effect, we need the additional condition of a

relationship between two potential variables ($Y_{z,s}$ and S_z). Pearl showed that the

average natural direct effect is identifiable if $Y_{z,s}\coprod S_0|X$ holds for all S [7]. This

condition can be interpreted as a potential outcome $Y_{z,s}$ does not depend on the level of

the intermediate in the control arm $Z = 0$ given a set of confounders X.

Marginal structural models

We considered the average causal effect as the contrast of 2 marginal

probabilities. This causal risk difference can be expressed in terms of the parameter of

the linear model like $\Pr(Y_z = 1) = \alpha_0 + \alpha_1 z$. As stated in the previous section, this

causal parameters are equal to the corresponding parameters of the following

association model under the random allocation (no confounding), $\Pr(Y_z = 1|Z = z) =$

$\alpha'_0 + \alpha'_1 z$, and thus it is possible to estimate the causal parameters from the observed

data. The former model is called as a marginal structural model because this models the

marginal distribution (= entire population) of counterfactual random variables. On the

other hand, the latter is called as an associational model because this is a model for

associations observed when comparing subpopulations (defined by levels of treatment)

of the entire population [19]. However, the parameters of the associational model will

not equal to the corresponding causal parameter if there is confounding. Robins et al.

have proposed a weighted analysis procedure for this association model, which in turn

gives unbiased estimates of causal parameter [19]. This weighting technique to estimate

the causal parameter is well known as standardization in epidemiology. Sato and

Matsuyama reviewed why this technique provides an unbiased estimate with a simple

example [20]. We will later describe how to calculate the causal parameters of the

marginal structural model to estimate the direct and indirect effects in our data.

Application Data

We briefly describe the CASE-J trial, which is a prospective, multicenter,

randomized, open-label, active-controlled, 2-arm parallel-group comparison with a

response-dependent dose titration and blinded assessment of the endpoints in high-risk

hypertensive patients [21]. The purpose of this trial was to compare the long-term

effects of the angiotensin receptor blocker candesartan and the calcium-channel blocker

amlodipine on the incidence of cardiovascular events, represented as a composite of

sudden death and cerebrovascular, cardiac, renal, and vascular events in high-risk

hypertensive patients. After informed consent was obtained, 4,728 high-risk

hypertensive patients aged 20–84 years were randomized to receive either of the 2

antihypertensive agents (the candesartan and amlodipine arms) and followed up for at

least 3 years. The same target for the control of blood pressure was set according to the

guidelines proposed by the Japanese Society of Hypertension [22]. Data were collected

every 6 months for blood pressure, medication (treatment period, drug compliance, and

concomitantly used antihypertensive or other drugs), and other clinical conditions. Each

patient had a maximum of 8 follow-up visits, from the baseline to the last visit, and

information on adverse events, dropouts, and cardiovascular events was periodically

collected until the death of the patient or completion of the study (December 2005).

The CASE-J trial revealed that the 2 treatment arms equally suppressed the

incidence of cardiovascular events during the mean follow-up period of 3.2 years, with

a 97.1% follow-up rate. The hazard ratio of the primary endpoint was 1.01 (95%

confidence interval [CI] = 0.79–1.28; P = 0.969) [14]. On the other hand, the achieved

systolic blood pressure at 6 months after enrolment was 143.5 mmHg in the candesartan

arm and 141.4 mmHg in the amlodipine arm. The difference in systolic blood pressure

was 1.7 mmHg after 3 years, and there was a small but statistically significant

difference in the achieved blood pressure between the candesartan and amlodipine arms

in the follow-up period.

Models for Estimating the Natural Direct Effect

To estimate the average natural direct and indirect effects in the CASE-J trial,

we can utilize the marginal structural models introduced by VanderWeele [10]. Figure 2

is a causal graph that represents the CASE-J trial up to time of the second visit. In these

longitudinal settings, data string (Z, S, Y, X, Y_z, S_z, $Y_{z,s}$) corresponds to (Z, S(t),

Y(t + 1), $L(t)$, Y_z(t + 1), S_z(t), $Y_{z,s}$(t + 1)). The visit time (t) is represented as

semiannual visits, and Y(t + 1) is an indicator of the first onset of the outcome between

visit t and t + 1 (t = 0 to 5). The outcomes of interest are the onset of cardiovascular,

cerebrovascular, or cardiac events. Let L(t) be a vector of baseline variables and

time-varying covariates measured before visit t and S(t) be the achieved systolic blood

pressure (intermediate variable) at the visit (t). Therefore, L(t) is measured prior to

S(t) (Figure 2). Let $\overline{S(t)}$ be the historical pattern of the achieved systolic blood pressure. Since the percentage of patients who received more than 80% of the allocated drugs during follow-up was 96.5% and 96.0% for the candesartan and amlodipine, respectively [14], we will consider the randomized intervention Z not to be a time-varying variable.

For the present analysis, $L(0)$ is a vector of the following covariates measured at the baseline: age, sex, body mass index, systolic blood pressure, diastolic blood pressure, pre-existing type 2 diabetes, a history of cerebrovascular events (including stroke or transient ischemic attacks more than 6 months prior to the screening), left ventricular hypertrophy, a history of ischemic heart disease (including angina pectoris or myocardial infarction more than 6 months prior to the screening), renal disease (proteinuria or renal dysfunction), hyperlipidemia, antihypertensive drug use at the time of enrolment, smoking history, and alcohol drinking. $L(t)$ further comprises age and concomitant use of diuretics, beta blockers, alpha-beta blockers, lipid-lowering drugs, and anti-diabetic drugs. The time-varying covariates were carried forward from the most updated value, although there were few missing data in the covariates in the CASE-J trial. We will use $\overline{L(t)}$ as the history of the time-varying covariates up to the time of visit (t), including both the time-varying and non-time-varying covariates measured at

the baseline.

Let $S_z(t)$ denote a counterfactual intermediate after the visit (t) at an intervention Z value of z, and let $Y_{z,\bar{s}}(t+1)$, be a counterfactual outcome at the time of the visit (t+1) at an intervention Z value of z and an intermediate $\overline{S(t)}$ value of the intermediate history $\bar{s}$. In longitudinal settings, the conditions for identifying natural direct and indirect effects at a single point setting need to be generalized for estimating the natural direct and indirect effects. In the ideal RCT setting without time-varying treatment, it follows from the results of VanderWeele [10] that if the following 2 conditions hold the natural direct and indirect effects are identified:

$$Y_{z,\bar{s}}(t+1)|z \in \{0,1\}\coprod S(t)|\{Z,\bar{L}\}$$

$$Y_{z,\bar{s}}(t+1)\coprod S_0(t)|L(0)$$

The first condition requires that for every time period t, the effect of the intermediate $S(t)$ on the outcome Y is not confounded given the covariate history $\bar{L}$ up to time t and the allocated treatment. In this situation, the treatment Z is fixed through the trial. The second condition requires that the treatment should not affect any time-varying confounders in the mediator-outcome relationship for any time t. If the treatment is also time varying, we need to consider the treatment history up to time t and modify these 2 conditions accordingly.

We will apply a weighted pooled logistic regression model with repeated measurement to estimate $\Pr(Y_{1,\bar{S}_0})$ and $\Pr(Y_{0,\bar{S}_0})$. $\bar{S}_0$ denotes the counterfactual intermediate history if the intervention Z is set to control treatment. For this estimation, we need to specify 2 marginal structural models, as follows [10]:

1) $E[S_z(t)|L(0) = l(0)] = \theta_0(t) + \theta_1 z + \theta'_2 l(0)$ and

2) $\text{logit} \Pr\left(Y_{z,s}(t+1)|L(0) = l(0)\right) = \beta_0(t) + \beta_1 z + \beta_2 s(t) + \beta_3 z \times s(t) + \beta'_4 l(0)$.

where $\theta_0(t)$ and $\beta_0(t)$ are time-specific intercepts for each visit. The second model assumes that the outcome depends only on the most recent value of systolic blood pressure, as shown in Figure 2. Note, both models are models for distribution of the counterfactual random variables conditioned by a set of confounders $L(0)$. This conditioning is for substituting $E[S_z(t)]$ in the second marginal structural model at the end, and not for controlling the confounders [10]. Since the CASE-J trial was an RCT and non-compliance for the use of the allocated drugs was negligible, we can assume that there is no confounding between the intervention-intermediate relationships. Therefore, the causal parameters of the first marginal structural model can be estimated by simply fitting a linear model with repeated measurements. On the other hand, we need to adjust for the confounding between the intermediate-outcome relationships to estimate the causal parameters of the second marginal structural model, which models

the marginal distribution of the potential outcome $Y_{z,\bar{s}}$. These parameters can be

unbiasedly estimated by using the inverse probability weighting (IPW) technique, in

which there are no unmeasured confounders between the intermediate and outcome [19,

23, 24]. Each patient's IPW is the inverse of the probability that the systolic blood

pressure level has been controlled to a specific value s_i at visit (t). We specify the

time-varying stabilized weight (sw) as $sw_i(t) = \prod_{k=0}^{t} \frac{f(S(k)=s_i|Z=z_i,L(0)=l_i)}{f(S(k)=s_i|Z=z_i,\bar{L}(k)=l_i)}$, where

$f(S(k)|Z,L(0))$ is the conditional density of the continuous variable $S(k)$, given

Z and $L(0)$. $S(k)$ is assumed to be normally distributed with mean $(\alpha_0 + \alpha_1 Z +$

$\alpha'_2 L(0))$ and variance σ^2. These parameters can be obtained by the least square

regression for each separate visit (k), and $f(S(k)|Z,L(0))$ can be estimated by the

normal density with the estimated means and variance [19]. We further account for the

selection bias, which is due to censoring of loss to follow-up and non-cardiovascular

death. Specifically, let $C(t) = 1$ if a patient was lost to follow-up or died from

non-cardiovascular causes by the time of visit (t), and $C(t) = 0$ otherwise. To

unbiasedly estimate the causal parameters in the second marginal structural model in the

presence of censoring, we use both $sw_i(t)$ and the inverse probability of censoring

weight, that is, $sw^{\dagger}_i(t) = \prod_{k=0}^{t} \frac{Pr(C(k)=0|\bar{C}(k-1)=0,Z=z_i,L(0)=l_i)}{Pr(C(k)=0|\bar{C}(k-1)=0,Z=z_i,\bar{L}(k)=l_i)}$, where $\bar{C}(t) =$

$(C(0),\dots, C(t)) = 0$, and $C(-1) = 0$. Then, the required patient-specific IPW is

$sw_i(t) \times sw^\dagger_i(t)$. Note, $L(0)$ is already included in the denominator of $sw_i(t)$ and

$sw^\dagger_i(t)$, and the most recent covariate values $\bar{L}$ are included as the history of

covariates until the visit (t) in these particular models. We can obtain the causal

parameters in the second marginal structural model by fitting the weighted pooled

logistic model with repeated measurements using the time-varying patient-specific IPW.

In both the first and second marginal structural models, we choose an independent type

variance-covariance matrix of repeated measurements for the same individuals in the

"repeated" statement of SAS "proc genmod" (SAS ver. 9.2; SAS Institute Inc., Cary,

NC, USA).

Finally, we can estimate the probability $\Pr(Y_{z,\bar{S}_0}(t)|l(0))$ by substituting

$E[S_0(t)|l(0)]$ estimated through the first marginal structural model for $S(t)$ in the

second marginal structural model as $\widehat{\Pr}\big(Y_{z,\bar{S}_0}(t)|l(0)\big) = \text{expit}\big[\hat{\beta}_0(t) + \hat{\beta}_1 z +$

$\hat{\beta}_2 E[S_0(t)|l(0)] + \hat{\beta}_3 z \times E[S_0(t)|l(0)] + \hat{\beta}'_4 l(0)\big]$. By substituting the individual value

of $l(0)$ in this formula, we obtain $\widehat{\Pr}\big(Y_{1,\bar{S}_0}(t)|l(0)\big)$ and $\widehat{\Pr}\big(Y_{0,\bar{S}_0}(t)|l(0)\big)$ for each

individual. Thus, we can estimate the marginal probability $\widehat{\Pr}\big(Y_{1,\bar{S}_0}(t)\big)$ and

$\widehat{\Pr}\big(Y_{0,\bar{S}_0}(t)\big)$ from the average of $\widehat{\Pr}\big(Y_{1,\bar{S}_0}(t)|l(0)\big)$ and $\widehat{\Pr}\big(Y_{0,\bar{S}_0}(t)|l(0)\big)$,

respectively, for the entire population. If the intervention Z is set to the value z and

intermediate S is set to that corresponding to control treatment, the incidence

probability by the end of the trial can be estimated as $\widehat{\Pr}(Y_{z,\bar{S}_0}) = 1 - \prod_{k=0}^{5}\{1 -$

$\widehat{\Pr}(Y_{z,\bar{S}_0}(k))\}$. The estimated average natural direct effect is $\widehat{\Pr}(Y_{1,\bar{S}_0}) - \widehat{\Pr}(Y_{0,\bar{S}_0})$, and

the average natural indirect effect = average total effect − average natural direct effect,

as defined above. The re-sampling-based CIs for each estimate of the natural direct and

indirect effects were calculated on the basis of the normal approximations with 500

bootstrap samples and their standard deviations [25]. The CI of the total effect is

constructed on the basis of the normal approximation (*i.e.*, $1.96 \times$ standard error of

the risk difference). All statistical analyses were conducted using SAS ver. 9.2.

Results

Table 1 shows the baseline characteristics, concomitant therapies, and average

systolic blood pressure and diastolic blood pressure during the follow-up and the

number of cardiovascular, cerebrovascular, and cardiac events. Of the 4703 patients in

the intention-to treat population in the CASE-J trial, 150 patients never underwent

systolic blood pressure measurements before they were censored or experienced

cardiovascular events during follow-up; therefore, they were excluded from the analysis.

As shown in Table 1, the patients excluded from the analysis had higher baseline

systolic and diastolic blood pressures than the remaining 4,553 patients analyzed and

did not receive antihypertensive drugs at the baseline, but there were no statistical

significant differences in the other baseline variables between the groups. During

follow-up, concomitant antihypertensive drugs were more often taken in the candesartan

arm than in the amlodipine arm. The mean achieved systolic and diastolic blood

pressures in the candesartan arm were higher by 1.7 and 1.0 mmHg, respectively, than

those in the amlodipine arm (Table 1). Figure 3 shows the time course of the changes in

systolic blood pressure in the candesartan and amlodipine arms. The achieved systolic

blood pressure gradually decreased with the follow-up time.

Table 2 shows the results of the associations between the baseline

characteristics and the achieved systolic blood pressure through the linear regression

model with repeated measurements. These parameter estimates are the causal

parameters estimated in the first marginal structural model explained above. Several

baseline variables, also considered strong risk factors for cardiovascular events, were

found to be strongly associated with the achieved systolic blood pressure. In this

analysis, the systolic blood pressure in the candesartan arm was 1.9 mmHg higher than

that in the amlodipine arm ($P < 0.001$). There was no association between the treatment

arm and time at which the decreased systolic blood pressure was observed (data not

shown).

Table 3 presents the average total effect; two estimates of the counterfactual

incidence probabilities; their difference (*i.e.*, average natural direct effect); and the

average natural indirect effects for cardiovascular, cerebrovascular, and cardiac events.

The first row in Table 3 presents the estimated average total effect represented as a risk

difference between the candesartan and amlodipine arms. No significant differences

were observed in the average total effect between the candesartan and amlodipine arms

with regard to the cardiovascular, cerebrovascular, and cardiac events. To explain this

simply, in Table 3, $\widehat{\Pr}\left(Y_{1,\bar{s}_0}\right)$, is the incidence probability obtained when the entire

population received candesartan but with the achieved systolic blood pressure set to what it would have been had the entire population received amlodipine. On the other hand, $\widehat{\Pr}\left(Y_{0,\bar{S}_0}\right)$ is the incidence probability obtained when the entire population received amlodipine but with the achieved systolic blood pressure set to what it would have been had the entire population received amlodipine. The fourth and fifth rows show the corresponding average natural direct and indirect effects. With regard to cardiovascular events, the average natural direct effect was –1.14% (95% bootstrap CI = –3.12 to 0.84) and average natural indirect effect was 1.05% (95% bootstrap CI = –0.33 to 2.43). These point estimates of the direct and indirect effects were in the opposite direction, and this is reflected in there being no difference in the average total effect (risk difference = –0.10; 95% CI = –1.44 to 1.25). For the cerebrovascular events, the achieved blood pressure differences between the candesartan and amlodipine arms during the follow-up had negative effects (average natural indirect effect = 0.25%; 95% bootstrap CI = –0.61 to 1.11). Further, candesartan influenced the cerebrovascular events negatively compared to amlodipine when the achieved systolic blood pressure was set to what it would have been had the entire population in the candesartan arm received amlodipine (average natural direct effect = 0.23%; 95% bootstrap CI = –1.04 to 1.50). Although the 95% CIs were quite large, the average natural direct and indirect

effects contributed to the total effect (risk difference = 0.48; 95% CI= −0.39 to 1.35) to

an equal degree.

Discussion

In this paper, we have described a method for estimation of average natural

direct and indirect effects by fitting the marginal structural model, and we have

evaluated the contribution of the average natural direct and indirect effects to the

average total effect in the CASE-J trial. To our knowledge, this is the first application of

the average natural direct and indirect effects to real RCT data. Although the 95% CIs

are wide and no strong effects are seen in this analysis, we can suggest that there are

some small blood pressure-independent effects from candesartan on cardiovascular and

cardiac events but not cerebrovascular events. Moreover, 3 outcomes in the CASE-J

trial show that the contributions of blood pressure-independent and dependent effects

were similar in cardiovascular and cardiac events but different in cerebrovascular events.

These results are also consistent with the previous findings of the Blood Pressure

Lowering Treatment Trialists' Collaboration [26].

There are some merits of using average natural effects compared to average

controlled effects. First, the average total effect can be decomposed into natural direct

and indirect effects, and we can evaluate the proportion of direct effects (or indirect

effects) in the total effect. This can be naturally considered as one measure for the

evaluation of a surrogate endpoint (*e.g.*, the ratio of the absolute values of the average

natural direct and indirect effects or the ratio of the indirect effect and the sum of the

absolute value of the natural direct and indirect effects). This concept is similar to that

of Freedman et al. [2] or Taylor et al. [27], and it could be considered a different

approach from the classical validation approach [28]. Secondly, when the intermediate

variable is continuous and since it is well known that the lower the systolic blood

pressure the better, it is difficult to interpret the results of the controlled direct effect if

we simply "set" the intermediate to a certain value (*e.g.*, 140 mmHg in the CASE-J trial

data). This especially holds for some patients whose systolic blood pressure can actually

be controlled below a certain value, and it is not difficult to interpret if we use the

average natural effects.

However, there are several conditions for identification of average natural

direct and indirect effects. One of the most difficult conditions is the conditional

independency between 2 potential variables as $Y_{z,s} \coprod S_0 | X$. Petersen et al. proposed the

less restrictive condition $E(Y_{1,s} - Y_{0,s} | S_0, X) = E(Y_{1,s} - Y_{0,s} | X)$. However, in either

case, we can never simultaneously observe $Y_{z,s}$ and S_0 in an individual; therefore, it is

difficult (or almost impossible) to verify this assumption from data [9]. Recently,

VanderWeele proposed a sensitivity analysis for unmeasured confounders in order to

estimate the controlled and natural effects [29]. This simple formula is especially useful when the specific confounder is not measured, and its influence on the results can be presumed. In addition, several techniques for the sensitivity analysis for unmeasured confounders and model misspecification have been proposed in the context of the estimation of total or joint effects [30-32]. Another approach using bounds might be utilized more fully at the time of evaluating the direct or indirect effects, even though the ranges of bounds are generally wide [33-35]. In an RCT, the causal graph given in Figure 2 is more reasonable than epidemiological data if non-compliance for the use of the allocated drugs is negligible, because we can control the treatment schedule and data collection. We measured many variables in the CASE-J trial data that correspond to either systolic blood pressure (intermediate) or cardiovascular events (outcome). Thus, we considered that the conditional independency between 2 potential variables is satisfied as far as this is practically presumed.

In conclusion, we considered direct effects with repeated measurements in the longitudinal setting and estimated the average natural direct and indirect effects through the achieved systolic blood pressure in the CASE-J trial. This first application of estimating the average natural effects in an RCT can be useful for obtaining an in-depth understanding of the results and further development of similar interventions.

Acknowledgements

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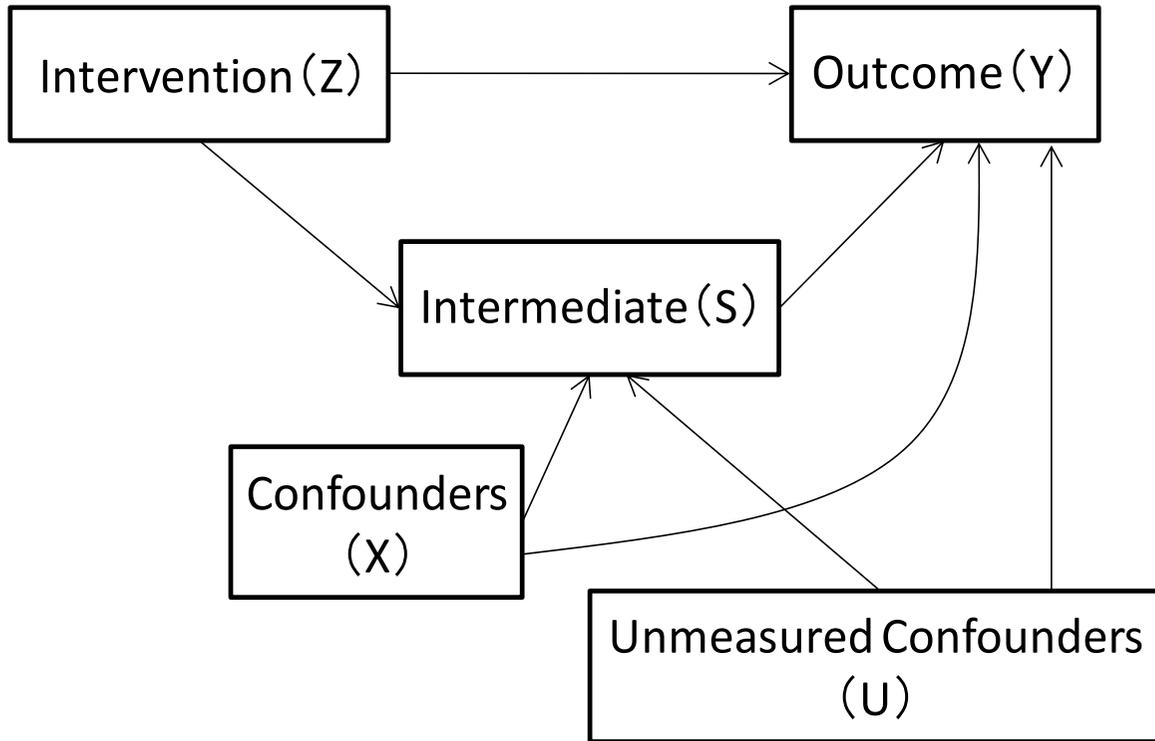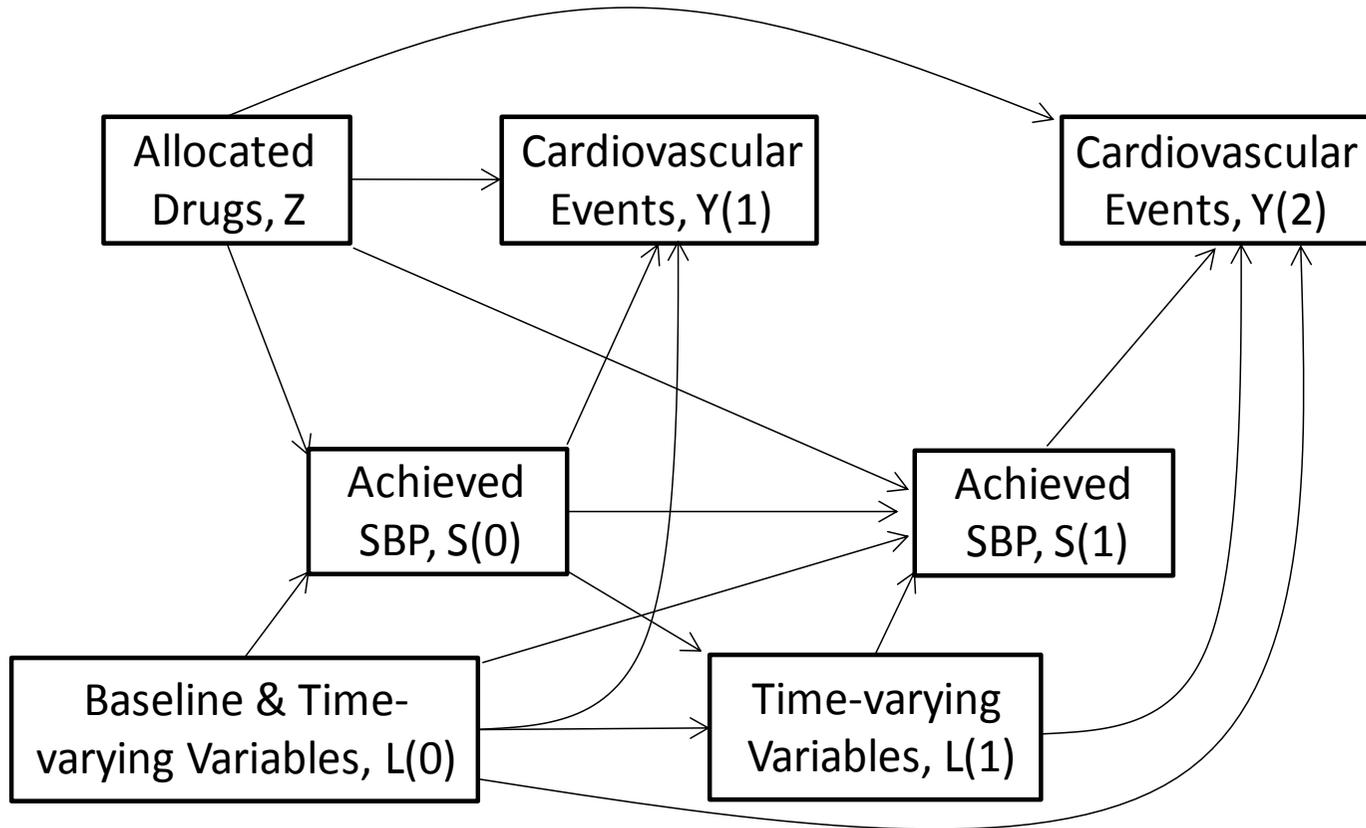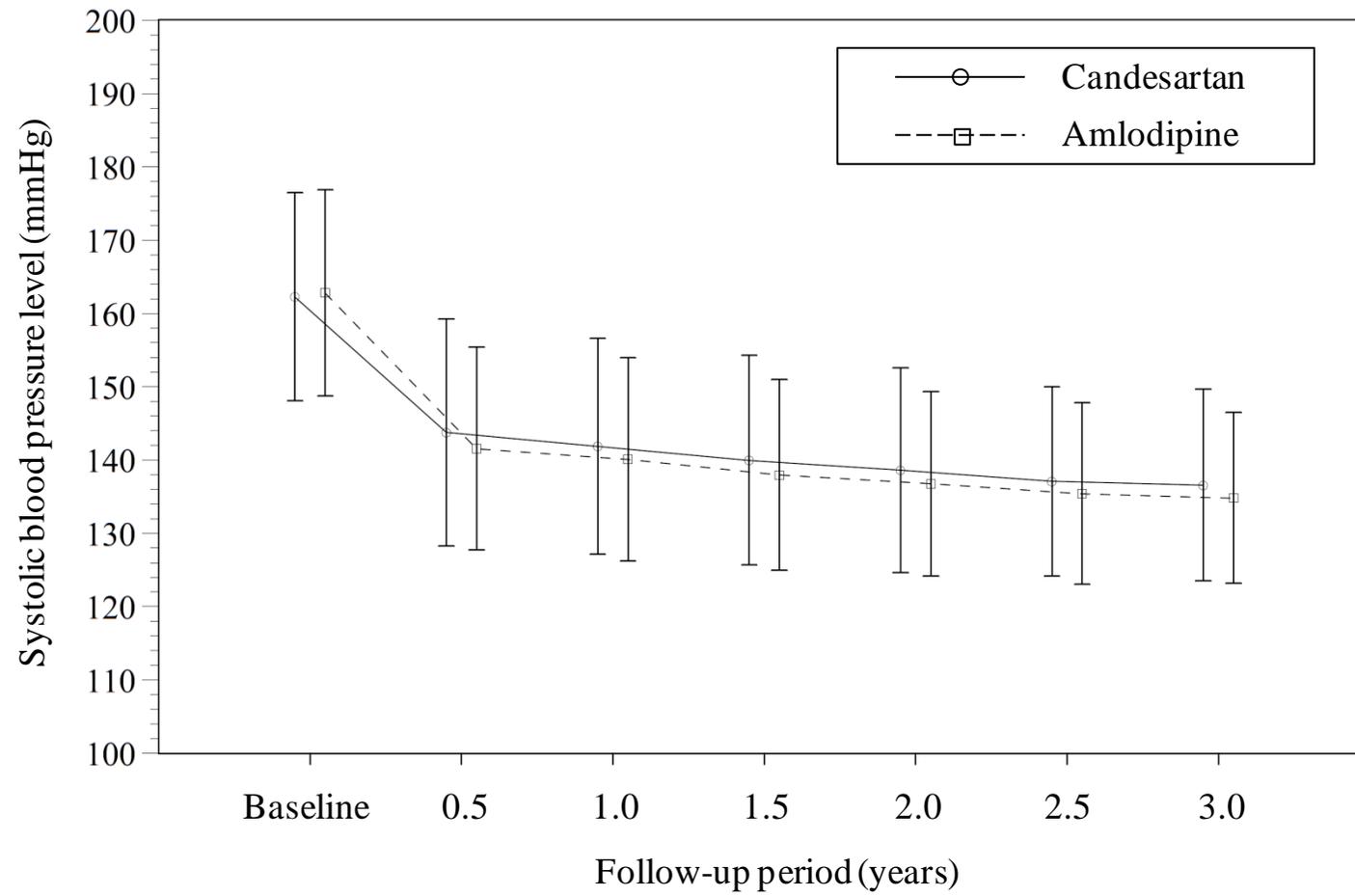**Figure 1. Directed acyclic graph of an ideal randomized clinical trial**

Figure 2. Directed acyclic graph of the CASE-J trial

Figure 3. Time course of changes in systolic blood pressure in each comparative arm during the CASE-J trial

Table 1. Patient characteristics at baseline and during follow-up

	Included in the analysis			Excluded from the analysis		
	Candesartan (N = 2,278)	Amlodipine (N = 2,275)	*P* value	Candesartan (N = 76)	Amlodipine (N = 74)	*P* value
Age (years) (SD)	63.8 (10.4)	64.1 (10.5)	0.554	63.3 (12.5)	63.4 (13.4)	0.967
BMI (kg/m^2) (SD)	24.6 (3.7)	24.5 (3.6)	0.220	25.0 (4.2)	24.2 (4.5)	0.276
Female gender (%)	1055 (46.3)	981 (43.1)	0.030	37 (48.7)	33 (44.6)	0.616
Severe hypertension (%)	435 (19.1)	464 (20.4)	0.271	19 (25.0)	29 (39.2)	0.063
Pre-existing diabetes (%)	976 (42.8)	982 (43.2)	0.827	35 (46.1)	25 (33.8)	0.125
Cerebrovascular history (%)	243 (10.7)	221 (9.7)	0.288	5 (6.6)	4 (5.4)	0.762
Left ventricular hypertrophy (%)	769 (33.8)	789 (34.7)	0.511	30 (39.5)	24 (32.4)	0.369
Ischemic heart disease (%)	291 (12.8)	296 (13.0)	0.812	7 (9.2)	2 (2.7)	0.093
Renal dysfunction (%)	562 (24.7)	528 (23.2)	0.248	10 (13.2)	15 (20.3)	0.243
Vascular disease (%)	29 (1.3)	23 (1.0)	0.405	0 (0.0)	1 (1.4)	-
Antihypertensive drug use (%)	1573 (69.1)	1527 (67.1)	0.162	39 (51.3)	26 (35.1)	0.309
Current smoking or history (%)	677 (29.7)	766 (33.7)	0.004	28 (36.8)	27 (36.5)	0.964
Alcohol consumption (%)	1078 (47.3)	1084 (47.7)	0.826	37 (48.7)	36 (48.7)	0.997
Hyperlipidemia (%)	1042 (45.7)	986 (43.3)	0.103	26 (34.2)	24 (32.4)	0.817
SBP (mmHg) (SD)	162.4 (14.2)	163.0 (14.1)	0.152	165.9 (13.6)	170.7 (14.7)	0.039

DBP (mmHg) (SD)	91.5 (11.0)	91.7 (11.3)	0.489	93.3 (12.2)	95.1 (11.7)	0.350
ACEI use during follow-up (%)	41 (1.8)	70 (3.1)	0.005	-	-	-
Diuretic use during follow-up (%)	550 (24.1)	308 (13.5)	<0.001	-	-	-
β blocker use during follow-up (%)	508 (22.3)	311 (16.8)	<0.001	-	-	-
α or αβ blocker use during follow-up (%)	674 (29.6)	481 (21.1)	<0.001	-	-	-
Anti-hyperlipidemic drug use during follow-up (%)	1017 (44.6)	996 (43.8)	0.557	-	-	-
Anti-diabetic drug use during follow-up (%)	844 (37.1)	868 (38.2)	0.442	-	-	-
Mean SBP during follow-up (mmHg) (SD)	139.9 (10.8)	138.2 (10.1)	<0.001	-	-	-
Mean DBP during follow-up (mmHg) (SD)	79.9 (7.6)	78.9 (7.3)	<0.001	-	-	-
Primary CV events (%)	128 (5.6)	130 (5.7)	0.889	6 (7.9)	4 (5.4)	0.541
Cerebrovascular events (%)	58 (2.5)	47 (2.1)	0.281	3 (4.0)	3 (4.1)	0.973
Cardiac events (%)	42 (1.8)	47 (2.1)	0.588	1 (1.3)	0 (0.0)	0.322

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, ACEI = angiotensin-converting enzyme inhibitor, CV = cardiovascular, SD = standard deviation

Table 2. Association between the baseline variables and the achieved SBP during the CASE-J trial

	Increase in achieved SBP per unit	95% CI	*P* value
Candesartan (vs. amlodipine)	1.91	(1.37, 2.46)	<0.001
Age at baseline (per 10 years)	0.29	(−0.01, 0.59)	0.056
BMI (per 5 kg/m^2)	0.85	(0.44, 1.26)	<0.001
Female (vs. male)	0.23	(−0.50, 0.97)	0.530
Pre-existing diabetes	2.11	(1.44, 2.78)	<0.001
Cerebrovascular history	−0.66	(−1.59, 0.27)	0.166
Left ventricular hypertrophy	0.48	(−0.15, 1.12)	0.136
Ischemic heart disease	−1.94	(−2.76, −1.11)	<0.001
Renal dysfunction	1.18	(0.52, 1.83)	0.001
Antihypertensive drug use	2.59	(1.96, 3.22)	<0.001
Current smoking or history	0.36	(−0.31, 1.04)	0.293
Alcohol consumption	1.19	(0.50, 1.88)	0.001
Hyperlipidemia	0.01	(−0.56, 0.59)	0.971
SBP at baseline (per 10 mmHg)	2.05	(1.80, 2.30)	<0.001
DBP at baseline (per 5 mmHg)	−0.30	(−0.45, −0.15)	<0.001

Table 3. Parameter estimates of the natural direct and indirect effects for each event

Estimated causal quantities	CV events		Cerebrovascular events		Cardiac events	
	Estimates	95% CI†	Estimates	95% CI†	Estimates	95% CI†
Total effect (%)*	−0.10	(−1.44, 1.25)	0.48	(−0.39, 1.35)	−0.22	(−1.02, 0.58)
$\widehat{\Pr}\left(Y_{0,\bar{s}_0}\right)$ (%)	6.78	(5.23, 8.33)	2.30	(1.43, 3.16)	2.49	(1.31, 3.68)
$\widehat{\Pr}\left(Y_{1,\bar{s}_0}\right)$ (%)	5.64	(4.29, 6.98)	2.53	(1.50, 3.55)	1.80	(1.08, 2.52)
Natural direct effect (%)	−1.14	(−3.12, 0.84)	0.23	(−1.04, 1.50)	−0.69	(−1.87, 0.49)
Natural indirect effect (%)	1.05	(−0.33, 2.43)	0.25	(−0.61, 1.11)	0.47	(−0.27, 1.21)

CI = confidence interval

* Total effect was the risk difference between the candesartan arm and the amlodipine arm estimated on the basis of the intention-to-treat principle.

†95% CI is calculated using the bootstrap method except in the case of total effect.