On Transportability of Parameters and Estimation of Risks associated with Metabolic Syndrome

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***Abstract*—Recently, some studies emphasize the potential problems in using estimated parameter values in an independent study for analysis of the primary study, and introduce the concept of "transportability." As far as we know, however, a mathematical definition and statistical considerations of the transportability have not been fully developed. This paper defines the transportability of a regression model, presents a sufficient condition, describes a necessary assumption, and examines the transportability of the regression model with real data. The motivation of the study comes from the fact that we have to wait for the results of an over ten-year cohort study being conducted at the Radiation Effects Research Foundation to know the epidemiological significance of waist circumference (WC) in the definition of the metabolic syndrome (MS). We considered that it would be possible to estimate the risk associated with WC if an unbiased estimate of WC for each subject ten years earlier could be obtained based on the transportability arguments. Implementing this idea with the cohort database administered by the Radiation Effect Research Foundation, we obtained the relative risk of death from MS-related causes. The results indicated that the risk of death was smaller for a larger WC, which contradicted the suggestion that the risk of death should be higher for a larger WC. The implications of our results are discussed.**

***Index Terms*— Transportability, Survival Analysis, Retrospective Cohort Study, Metabolic Syndrome.**

I. Introduction

The validity of the diagnostic criteria for Metabolic Syndrome (MS) has been questioned since the syndrome was introduced [1]–[3]. To verify the criteria validity, the best strategy would be a cohort study. However, waist circumference (WC), which is necessary for the diagnosis of MS, was introduced to health examinations only recently. If a current regression model of WC could be transported to an earlier sample, a cohort study using estimates of WC would be possible. On the other hand, [4] emphasize the potential dangers in using estimated parameter values in an independent-study for analysis of the primary study, and introduce the concept of "transportability." Transportability means "not only the model but also the relevant parameter estimates can be transported without bias." Therefore, we define the transportability of a regression model, propose a sufficient condition for the transportability from a mathematical point of view. Using data from the Radiation Effect Research Foundation (RERF), we examined whether the proposed condition could be statistically confirmed in a real dataset. A transported estimate of WC was then obtained for each examinee for a period ten years earlier in the RERF sample and was used as a covariate in a Cox proportional hazards model to estimate an association between WC and the risk of MS-related causes of death.

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II. Transportability of a Regression Model

We assume a population Γ_1 of elements $(y, \mathbf{x})$ that follow a regression model

$$y = \alpha + \beta^{\mathrm{T}}\mathbf{x} + \varepsilon,\ \varepsilon \sim N(0, \sigma^2) \tag{1}$$

where y is a response variable, $\mathbf{x} = (x_1, ..., x_p)$ is a vector of explanatory variables, β is a vector of regression coefficients, and ε is a normal random variable with mean 0 and variance σ^2. Let $S = \{(y_1, \mathbf{x}_1), ..., (y_m, \mathbf{x}_m)\}$ be a random sample of Γ_1 and

$$\hat{y} = \hat{\alpha} + \hat{\beta}^{\mathrm{T}}\mathbf{x} \tag{2}$$

be a sample regression equation associated with S.

We also consider a similar but distinct population Γ_1^* of elements $(y^*, \mathbf{x}^*)$ that follow a regression model

$$y^* = \alpha^* + \beta^{*\mathrm{T}}\mathbf{x}^* + \varepsilon^*,\ \varepsilon^* \sim N(0, \sigma^{*2}) \tag{1*}$$

Let $S^* = \{(y_1^*, \mathbf{x}_1^*), ..., (y_{m^*}^*, \mathbf{x}_{m^*}^*)\}$ be a random sample of Γ_1^* and

$$\hat{y}^* = \hat{\alpha}^* + \hat{\beta}^{*\mathrm{T}}\mathbf{x}^* \qquad (2^*)$$

be a sample regression equation associated with S^*. Let us put $\Delta = \alpha - \alpha^*$.

Definition (Transportability)

When $\beta = \beta^*$ holds, (2) is termed as transportable to Γ_1^* and $\hat{\alpha} + \hat{\beta}^{\mathrm{T}}\mathbf{x}^*$ is a transported estimate of y^* for given $\mathbf{x}^*$ in Γ_1^*. Conversely, (2^*) is transportable to Γ_1 and $\hat{\alpha}^* + \hat{\beta}^{*\mathrm{T}}\mathbf{x}$ is a transported estimate of y for given $\mathbf{x}$ in Γ_1.

When $\beta = \beta^*$ and the sample size *m* is large, $\hat{\beta}^{\mathrm{T}}\mathbf{x}^*$ should be approximately equal to $\beta^{*\mathrm{T}}\mathbf{x}^*$ and therefore $y^* - (\hat{\alpha} + \hat{\beta}^{\mathrm{T}}\mathbf{x}^*)$ should be approximately distributed as $N(\Delta, \sigma^{*2})$.

The bias Δ does not affect relative risks between different values of y^* in terms of the Cox regression model in this study.

Proposition (A sufficient condition for Transportability)

When Γ_1 and Γ_1^* are both multivariate normal distributions, β and β^* are determined by the variance matrix of Γ_1 and that of Γ_1^*, respectively [5]. In other words, the equality of the variance matrices of the multivariate normal distributions is a sufficient condition for the transportability. Furthermore, since σ^2 in (1) is also determined by the variance matrix of Γ_1 [5], the equality of the variance matrices leads to not only the transportability but also $\sigma^2 = \sigma^{*2}$.

To apply the Proposition with y unavailable, we need a certain practical assumption. Let $\mathbf{x}^* = (x_1^*, ..., x_p^*)$ denote a vector of p test results and y^* an unknown WC value for an examinee ten years earlier.

Definition (*y*-Homogeneity)

Let Γ_0 denote the marginal distribution of $\mathbf{x}$ in Γ_1 and Γ_0^* that of $\mathbf{x}^*$ in Γ_1^*. We consider the following two conditions:

(A) Γ_0, Γ_0^*, and Γ_1 are all multivariate normal distributions and the variance matrices of Γ_0 and Γ_0^* are mutually equal.

(B) Γ_1^* is a multivariate normal distribution and the variance matrices of Γ_1 and Γ_1^* are mutually equal.

We say *y*-Homogeneity holds from Γ_1 to Γ_1^* if (B) follows from (A).

To extrapolate estimates, we must make an assumption about relationships between variables beyond the limit of the observations [6]. The assumption *y*-Homogeneity implies that if the relationships among the components of $\mathbf{x}^*$ ten years earlier still hold now among $\mathbf{x}$ and the relationship between y and $\mathbf{x}$ is normal now, then the latter relationships also hold between y^* and $\mathbf{x}^*$ ten years earlier. Since WC was not measured ten years ago, the direct verification of the WC-Homogeneity is difficult. Instead, Weight-Homogeneity will be investigated in detail and the results will be extrapolated with medical considerations to WC-Homogeneity.

In statistical applications, the equality of the variance matrix between Γ_1 and Γ_1^* is examined by hypothesis testing using samples, therefore, even if the null hypothesis of the equality is not rejected, it does not ensure the mathematical equality. The results of the tests depend on their sample sizes, as well. Furthermore, since the magnitude of the errors in the transported estimates also depends on the sample size, it should be confirmed that the sample size is large enough for transported estimates to be sufficiently accurate for use in risk analysis.

III. Dataset

A total of 3,374 men in Nagasaki have received biennial health examinations since 1958 as part of a follow-up program associated with the Radiation Effects Research Foundation (RERF), formally the Atomic Bomb Casualty Commission. A detailed description of that program has been published elsewhere [7], [8]. The examination records for 667 men who were younger than 75 years old, similar to the Framingham study [9], with valid height and weight measurements in 1994-96 (the 19th examination period), and 323 men satisfying the same condition in 2004-06 (the 24th examination period), were analyzed in the present study. The examination items included: height, weight, temperature, systolic blood pressure (SBP), diastolic blood pressure (DBP), asparate aminotransferase (AST), alanine aminotransferase (ALT), glucose (GLU), alkaline phosphatase (ALP), cholinesterase (ChE), serum urea (UA), triglyceride (TG), total cholesterol (T-Cho), albumin (Alb), iron (Fe), high-density lipoprotein (HDL-Cho), white blood cell counts (WBC), red blood cell counts (RBC), thymol turbidity test (TTT), hemoglobin (Hb), hematocrit (Ht), and platelet count (PLT). Waist circumference (WC) has been measured only since 2004. Further, BMI (body mass index) for all participants was calculated from height and weight.

In Japan, MS was defined, among men with a WC in excess of 85 cm and women with a WC in excess of 90 cm, and having 2 or more components from among the following; 1) Dyslipidemia: triglycerides ≥ 150 mg/dl and/or HDL cholesterol < 40 mg/dl

2) Hypertension: blood pressure ≥ 130/85 mmHg
3) Impaired glucose tolerance: fasting plasma glucose ≥ 110 mg/dl.
In this study, those with at least two of these three criteria will be referred to as "Semi-MS."

IV. Analysis of Data

A. Verification of Transportability of a Regression Model

Using the RERF cohort database and Weight which is strongly associated with WC, we first examined whether the conditions (A) and (B) for Weight-Homogeneity in the Definition holds as well as whether the transportability of Weight holds between the current sample and the sample ten years earlier. Based on the results, we considered the transportability of WC. The Henze-Zirkler test and the Bartlett test were used to test the multivariate normality and the equality of two variance matrices, respectively. The stepwise variable selection methods were applied to obtain linear regression equations for each Weight and WC. Analyses are performed with SAS 9.1.

B. The Risk of Death using Transported Estimates

We first constructed a linear regression equation for WC on the current sample. Secondly, the assumption for WC-Homogeneity was examined with the selected variables. Then, a transported estimate of WC was obtained for each examinee in the sample ten years earlier. Finally, we applied the Cox regression model using the transported estimate of *WC*, *SemiMS* (1 for Semi-MS, 0 for otherwise) and *Age* as covariates:

$$ln\lambda\left[t \mid ln(WC), SemiMS\right] = ln\lambda_0(t) + \beta_1 ln(WC) + \beta_2 SemiMS + \beta_3 ln(WC) \times SemiMS + \beta_4 Age$$

where $\lambda_0(t)$ is an unspecified baseline hazard, × denotes interaction and β's are regression coefficients to estimate. Hereafter, the difference $ln\lambda\left[t \mid ln(WC), SemiMS\right] - ln\lambda_0(t)$ will be denoted by $ln(RR)$, since it is normally understood as a *log* relative risk.

The follow-up period is ten years and the endpoint is MS-related death. To treat non-linearity of WC in relative risk functions, the following piecewise linear functions [10] were employed:

$$< Age - C_1 >= \max(Age - C_1, 0), C_1 = 50, 55, 60, 65, 70$$
$$< ln(WC) - lnC_2 >= \max\{ln(WC) - lnC_2, 0\},$$
$$C_2 = 70, 75, 80, 85, 90, 95$$

where *ln* denotes log-transformation. Interactions between selected variables will also be employed.

V. Results

A. Normalization

Since the variables are all continuous, Box-Cox transformation [11] was applied to normalize each variable. Normality was tested using the skewness, kurtosis, and Shapiro-Wilk tests. We excluded extreme measurements and some variables that were difficult to transform to normal. The basic statistics of the variables remained for statistical analyses are shown in Table 1.

Table 1. Results of Normalization

	Current			Ten years previous		
	Mean	SD	N	Mean	SD	N
Height	163.67	5.800	317	163.35	5.917	667
ln(Weight)	4.12	0.166	317	4.09	0.160	667
ln(SBP)	4.85	0.136	317	4.87	0.145	667
ChE	1.01	0.176	303	0.99	0.185	602
UA	5.56	1.293	313	5.95	1.325	615
T-Cho	197.63	33.157	314	192.02	33.343	620
ln(HDL-Cho)	3.91	0.253	312	3.95	0.275	614
RBC	458.90	43.205	309	466.38	42.043	609
Hb^2	210.73	36.384	306	213.56	36.144	609
$PLT^{1/2}$	4.39	0.509	307	4.45	0.578	609
ln(WC)	4.43	0.108	317	-	-	-
BMI	3.13	0.140	317	3.11	0.136	667

B. Transportability of the Regression Model for Weight and WC

We first examined the transportability of Weight which is strongly correlated with WC (r=0.88, n=323) in the current sample. The regression equation for Weight on the current sample is as follows:

$$Weight = 1.01 + 0.014 \times Height + 0.18 \times SBP + 0.20 \times ChE + 0.013 \times UA - 0.14 \times HDL + 0.00054 \times RBC \quad (7)$$

We applied the tests described in Section II to examine the conditions (A) and (B) of Weight-Homogeneity using the selected six variables to obtain the results shown in Table 2. First, the multivariate normality for each of Γ_0, Γ_0^*, Γ_1, and Γ_1^* is not rejected (p=0.5182, 0.8066, 0.4761, and 0.8509, respectively). Then, the equality of variance matrices of Γ_0 and Γ_0^* in (A) and that of Γ_1 and Γ_1^* in (B) are tested to find out each of them is not rejected (p=0.3645, p=0.4490, respectively). The results are not against the hypothesis that Weight-Homogeneity holds.

The regression equation for Weight using the six variables on the sample ten years earlier becomes:

$$Weight = 1.49 + 0.013 \times Height + 0.071 \times SBP + 0.22 \times ChE + 0.0067 \times UA - 0.11 \times HDL + 0.00049 \times RBC \quad (8)$$

The average of the residuals from (7) in the current sample and from (8) in the sample ten years earlier were both 0.00

and SD's were 0.115 and 0.114, respectively. The results clearly demonstrate the transportability of (7) to the sample ten years earlier.

In this study, we verified the transportability of Weight which is strongly correlated with WC. Since WC is considered to represent the amount of "fat" and Weight is "fat and muscle," if the relationship between WC and Weight ten years earlier was different from that in the current sample, it should be caused by the change in the amount of muscle. Since the sample consists of 48-75 years old persons, the case seems unlikely. Therefore we assumed that the relationship between WC and Weight has not changed significantly. These considerations lead us to the *WC*-Homogeneity.

TABLE 2. THE RESULTS OF THE TEST FOR THE *WEIGHT*-HOMOGENEITY

(A) HENZE-ZIRKLER TEST

sample	T	n	p
Current(**x**)	-0.65	296	0.5182
Ten years previous(**x**)	0.24	582	0.8066
Current(y, **x**)	0.71	296	0.4761
Ten years previous(y, **x**)	0.19	582	0.8509

(B) BARTLETT TEST

sample	X^2	n_1	n_2	p
Current(**x**) Ten years previous(**x**)	22.62	296	582	0.3645
Current(y, **x**) Ten years previous(y, **x**)	28.29	296	582	0.4490

C. Analysis of the Risk of Death using Transported Estimates

The regression equation for WC on the current sample is as follows:

$$WC = 1.60 + 0.0041 \times Height + 0.035 \times SBP + 0.00017 \times Hb + 0.63 \times BMI$$

with the coefficient of determination R^2=0.81 and SD=0.047 · As presented in Table 3, neither the normality of the test for each of Γ_0, Γ_0^*, and Γ_1 (p=0.2418, 0.3467, and 0.2802, respectively) nor the condition (A) of WC-Homogeneity is rejected (p=0.6542).

TABLE 3. RESULTS OF THE TEST FOR THE ASSUMPTIONS OF *WC*-HOMOGENEITY

(A) HENZE-ZIRKLER TEST

sample	T	n	p
Current(**x**)	1.17	306	0.2418
Ten years previous(**x**)	0.94	609	0.3467
Current(y, **x**)	1.08	306	0.2802
Ten years previous(y, **x**)	-	-	-

(B) BARTLETT TEST

sample	X^2	n_1	n_2	p
Current(**x**) Ten years previous(**x**)	7.74	306	609	0.6542
Current(y, **x**) Ten years previous(y, **x**)	-	-	-	-

Since the condition (A) is not statistically rejected, we assume it. Thus, it follows from the WC-Homogeneity assumption that the regression equation for WC on the current sample is transportable to the sample ten years earlier. Thus, we obtained a transported estimate of WC for each of 608 examinees in the sample ten years earlier. The mean and SD of the estimates are 4.42 and 0.094, respectively.

They were followed-up until June 2008 and their survival experiences were analyzed in terms of a Cox proportional hazards model as specified in Section IV.

The final results for MS-related causes of death are shown in Table 4 and illustrated in Fig. 1, where $ln(WC)^*$ is $ln(WC)$ minus 4.49 for stabilization of estimates.

At first, we obtained the following results:

$$ln(RR) = 53.13 \times SemiMS - 11.82 \times SemiMS \times ln(WC) + 0.13 < Age - 60 >$$

Since 53.13 is simply an intercept of the regression line when $SemiMS = 1$, we modified it to the following expression

$$ln(RR) = -11.82 \{ SemiMS \times (ln(WC) - 4.49) \} + 0.13 < Age - 60 >$$

Both equations are mathematically equivalent to each other.

The results indicate that, for those with Semi-MS, the larger the WC, the smaller the risk of MS-related death.

TABLE 4. MS-RELATED CAUSES OF DEATHS (NUMBER OF THE ENDPOINTS OBSERVED IS 37)

	Estimate	SE	p
<Age - 60>	0.13	0.040	0.001
SemiMS·ln(WC)*	-11.82	2.000	<.0001

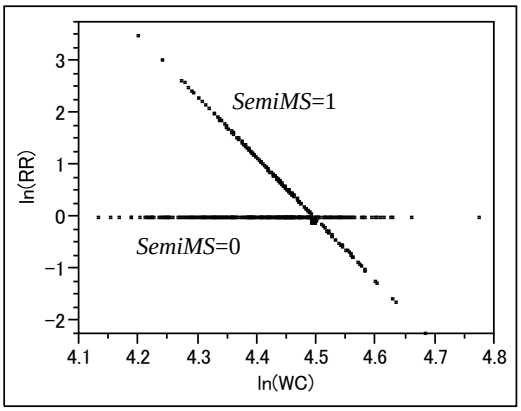

Fig 1. *ln(RR)* as a function of *ln(WC)* obtained from the proportional hazards model with the transported estimate of *ln(WC)* and *Age* as covariates and MS-related causes of deaths as the endpoint.

VI. MODEL FITNESS

We examined the fitness of the proportional hazards model obtained in the previous section as follows.

1) The subjects were classified into three groups depending on the estimates of *ln*(*RR*) so that the number of endpoints observed are approximately equal among the

groups. The cutpoints are 0.8 and 1.8 and the sample sizes (the number of endpoints observed) are 382 (9), 168 (15) and 58 (13), respectively.

2) The Kaplan-Meier survival curve S(t) was obtained for each group.
3) Finally log{−logS(t)}, or the log cumulative hazard, at the end of the study period was plotted in Fig.2.

Except for the early stage where a small number of deaths were accumulated, the three graphs show relationships approximately parallel to each other, indicating that the proportional hazards model describes the data well.

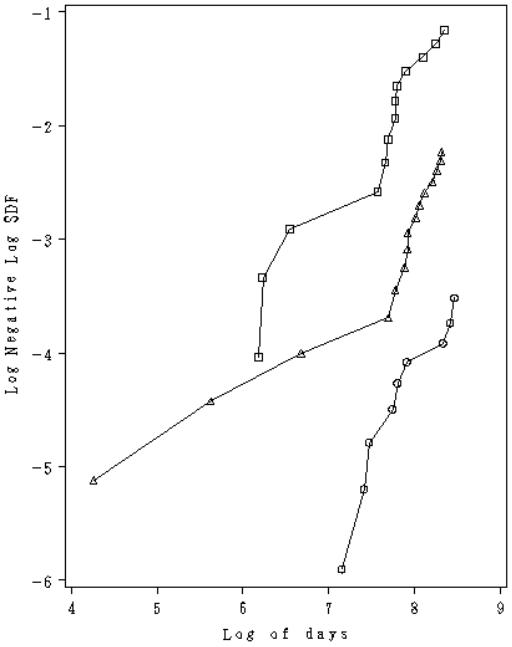

Fig 2. log-log plot for the three groups classified according to the estimated *ln(RR)*.

VII. Discussion and Conclusion

We formally define the "transportability" introduced by [4] and propose a sufficient condition for it and confirmed the feasibility of the condition with RERF follow-up data for ten years. The RERF sample from A-bomb survivors is somewhat unusual in that the subjects have been covered with free comprehensive health examinations, free medical treatment, and health insurance by the Japanese Government. Those conditions seem to contribute to a high participation rate to the health examinations and keeping their health conditions.

We used the transported estimates of WC as a covariate in the proportional hazards model to study the risk of MS-related death associated with WC. Since the transported estimates are inevitably subject to measurement errors, the estimated regression coefficients may be biased. However, we assume them to be negligible, since [12] reveal that the error is of Berkson-type and [13] indicate that the effects of Berkson-type measurement errors on the estimation of regression coefficients in the proportional hazards model is negligible.

As for the risk of MS-related death for those with Semi-MS, our results indicate that the larger the WC, the smaller the risk. That unexpected result might be due to the fact that each Semi-MS subject had at least two of these three conditions: dyslipidemia, hypertension, and impaired glucose tolerance; in other words, most of Semi-MS subjects may have been already ill at the time the baseline examinations. This consideration suggests that it is necessary to exclude those who died of any cause within five years after the baseline examinations [14] to unbiasedly estimate the risk of death associated with WC.

The unexpected results also apparently contradict the assumption used in the definition of MS that the larger the *WC*, the higher the risk of death. Possible causes of these contradictory findings were either that the definition of MS was not correct or the data used in the analysis were biased. To obtain reliable information to investigate the problem, a larger and longer cohort study should be conducted.

Another possible explanation for the contradictory findings may lie in a similarly observed phenomenon called the "obesity paradox [15]." Obesity is a major factor increasing the risk of all types of heart disease, however once diagnosed with heart disease, obese patients do better, thus improving prognosis. Furthermore, there is solid evidence to suggest that being overweight or obese may improve survival, not just in heart failure, but also in diseases like hypertension, coronary artery disease, and peripheral artery disease [16]. Thus, it will be interesting to examine whether the transported estimates of WC really decrease as MS-related diseases progress in Semi-MS subjects.

Finally, we emphasize that the key factor for a successful application of the definition of transportability and a sufficient condition for it, as discussed in Section II, is the normalization of measurements. To fully exploit the property of the multivariate normality, the definition was confirmed to be proper for dealing with the RERF cohort database that consisted of health examination results. Therefore, it would be interesting to apply the transportability theory to other cohort databases, such as the Framingham study.

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