Empirical Comparison of the Statistical Methods of Analyzing Intervention Effects and Correlation Analysis between Clinical Outcomes and Surrogate Composite Scores in Randomized Controlled Trials Using COMPETE III Trial Data

Empirical Comparison of the Statistical Methods of Analyzing Intervention Effects and Correlation Analysis between Clinical Outcomes and Surrogate Composite Scores in Randomized Controlled Trials Using COMPETE III Trial Data

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Abstract

Background: A better application of evidence-based available therapies and optimal patient care are suggested to have a positive association with patient outcomes for cardiovascular disease (CVD) patients. Electronic integration of care tested in the Computerization of Medical Practices for the Enhancement of Therapeutic Effectiveness (COMPETE) Π study showed that a shared electronic decision-support system to support the primary care of diabetes improved the process of care and some clinical markers of the quality of diabetes care. On the basis of COMPETE Π trial, COMPETE ΙΙΙ study showed that older adults at increased risk of cardiovascular events, if connected with their family physicians and other providers via an electronic network sharing an intensive, individualized cardiovascular tracking, advice and support program, enhanced their process of care – using a process composite score to lower their cardiovascular risk more than those in conventional care. However, results of the effect of intervention on composite process and clinical outcomes were not similar – there was no significant effect on clinical outcomes.

Objectives: Our objectives were to investigate the robustness of the results based the commonly used statistical models using COMPETE III dataset and explore the validity of the surrogate process composite score using a correlation analysis between the clinical outcomes and process composite score.

Methods: Generalized estimating equations (GEE) were used as a primary statistical model in this study. Three patient-level statistical methods (simple linear regression,

fixed-effects regression, and mixed-effects regression) and two center-level statistical approaches (center-level fixed-effects model and center-level random-effects model) were compared to reference GEE model in terms of the robustness of the results – magnitude, direction and statistical significance of the estimated effects on the change of process composite score / on-target clinical composite score. GEE was also used to investigate the correlation between the clinical outcomes and surrogate process composite scores.

Results: All six statistical models used in this study produced robust estimates of intervention effect. No significant association between cardiovascular events and on-target clinical composite score and individual component of on-target clinical composite score were found between the intervention group and control group. However, blood pressure, LDL cholesterol, and psychosocial index are significant predictors of cardiovascular events. Process composite score can both predict the cardiovascular events and clinical improvement, but the results were not statistically significant- possibly due to the small number of events. However, the process composite score was significantly associated with the on-target clinical composite score.

Conclusions: We concluded that all five analytic models yielded similar robust estimation of intervention effect comparing to the reference GEE model. The relatively smaller estimate effects in the center-level fixed-effects model suggest that the within-center variation should be considered in the analysis of multicenter RCTs. Process composite score may serve as a good predictor for CVD outcomes.

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Chapter 1 Introduction

1.1 Background

Cardiovascular disease (CVD) is the leading cause of disability and death in developed countries resulting in a tremendous burden on healthcare and community services [40, 41, 54]. While in the process of identifying new interventions to cope up with this complex pandemic, a better application of evidence-based available therapies and optimal patient care (improved management of risk factors) have been suggested to have a positive association with patient outcome in CVD patients [11, 29, 45]. However, optimal care of patients with previous CVD or cardiovascular risk factors is difficult in practical clinical settings; due to the chronic nature of most CVDs, and other factors such as limited healthcare resources, and economic considerations [7, 8, 55].

Based on the gradually adopted electronic medical records (EMRs), a computer-based decision support system (CDSS) was introduced with the aim of improving the quality of patient care and optimizes management [57]. The advantage of electronic integration of care is the ability to combine the practitioner and patient as one unit and such motivates the patients to improve their self-management with the appropriate support from the health care provider [4, 28, 33, 64]. Despite the theoretical advantage and promising results from studies [33], a lack of positive effect of computerized interventions on patient outcomes was reported [13, 14, 22]. A few factors have contributed to these controversial

reports. Firstly, the less adoption of electronic health records (the foundation of the electronic integration of care) by physicians [32] limit the possibility to design high quality randomized clinical trials (RCT) to evaluate the intervention without or less confounding bias. The variation of transition to electronic charts will also be a negative factor. Nevertheless, this uncertainty hinders the adoption of electronic integration care intervention in clinical settings to improve management of chronic diseases such as diabetes and CVDs, to have a positive impact on patient outcomes. With the rapid application of web technology in health science [4, 28, 42], advanced knowledge of the effect of performance measures on chronic disease [42], and improved statistical methods in multicenter RCT evaluation [2, 18, 23-24, 34, 47, 53, 68], it is plausible and necessary to design and properly evaluate high quality RCTs to address this uncertainty by identifying the real correlation between electronic integration of care intervention and its effects on patient and provider outcomes.

Electronic integration of care tested in the Computerization of Medical Practices for the Enhancement of Therapeutic Effectiveness (COMPETE) II study showed that a shared electronic decision-support system to support the primary care of diabetes improved the process of care and some clinical markers of the quality of diabetes care [26]. Using the knowledge from the COMPETE II trial, the COMPETE III study was designed and showed that older adults (> 55 years) are at an increased risk of cardiovascular events; if connected with their family physicians and other providers via an electronic network

sharing an intensive, individualized cardiovascular tracking, advice and support program, lowered their cardiovascular risk more than those in conventional care [27].

These two well-organized and high quality multicenter RCTs suggested positive effects of computerized interventions on patient outcomes. However, the disagreements between the effect of the intervention on process and clinical outcomes in both COMPETE II trial and COMPETE III trial [26], together with the inconsistent evidence of clinical benefits in other studies, suggests there is no definitive conclusion of the positive effect of computerized interventions on the patient's chronic condition. Electronic-health interventions used in these two trials are type of complex interventions, which are difficult to execute and evaluate since these interventions usually use process outcomes and surrogate clinical outcomes to represent patient important clinical outcomes. A clustered RCT with complex intervention and composite outcomes requires strong performance of adopted statistical models to draw proper inferences based on more accurate and precise statistical estimations. A simulation study recommended a consideration of mixed-effects models and GEE models based on their precise effect estimates regardless of the degree of clustering [12]. However, since there is a lack of definitive evidence on which statistical models perform best in multicenter RCTs with class of complex interventions, an empirical comparison of the commonly used statistical models by data from real multicenter RCTs is needed. Composite scores are very popular in studies of complex intervention on CVD management, however, the process and clinical composite scores defined in both studies were not validated and may also

contribute partly to the observed disagreement if they are not appropriately defined, furthermore, a measure of true intervention effect can only be available based on validated scales [19]. So validation of defined scale scores for a specific disease, such as CVD chronic disease or diabetes, and type of interventions is also needed.

1.2 Objectives

To better meet these statistical and methodological needs, the objectives of this project were to:

(1) compare five statistical methods, including simple linear regression, fixed-effects regression, mixed-effects regression, center-level fixed-effects model, and center-level random-effects model with generalized estimating equations (GEE), which is the primary analysis model in this study, in terms of the robustness of the results – magnitude, direction and statistical significance of the estimated effects on the change of process composite score.

(2) perform the same comparison of above six statistical models in terms of the robustness of the results – magnitude, direction and statistical significance of the estimated effects on the change of on-target clinical composite score.

(3) explore the correlation between clinical outcomes (cardiovascular events, clinical improvement composite score, on-target clinical composite score) and process composite score with GEE model.

(4) explore the correlation between cardiovascular events and on-target clinical composite score with GEE model.

1.3 Scope of the Report

Chapter 1 introduces the logic process of how the research project was initiated based on a review of COMPETE III study background and a scrutiny of its derived findings. Four objectives are set to achieve to better answer the conceived methodological and clinical related research questions.

In chapter 2, we first provide a brief introduction of COMPETE III dataset, including trial design, patients, intervention, and outcome. Second, we provide an overview of the six commonly used statistical methods in RCTs, which are compared in this project. Lastly, we describe the validation of surrogate composite scores with correlation analysis.

In chapter 3, a descriptive report of the baseline characteristics and pre-intervention outcomes is presented at the beginning, followed by the results of empirical comparison of analytical models, and ends up with results of validation checking from the perspective of a bunch of correlation analyses.

In chapter 4, the inferences from the project are discussed and limitations of the study are explained when interpreting and generalizing these findings. In the end, a future direction is proposed based on this study and previous related reports.

In chapter 5, we wrap up the key findings in this project by providing a brief description of the conclusions.

Chapter 2 Statistical Methods

2.1 Description of Data Source

2.1.1 Overview

This study is a secondary analysis of COMPETE III trial, a multi-centered RCT study of shared electronic vascular risk decision support in primary care for patients with previous cardiovascular events or cardiovascular risk factors. The primary purpose of this RCT was to determine the effect of a web-based vascular risk monitoring and advice tool in lowering cardiovascular risk in older adults compared to standard care. Some results have been published recently [27]. The trial was coordinated by St. Joseph's Healthcare, Hamilton. A total of 1,102 eligible adult patients (> 55) with previous cardiovascular events or cardiovascular risk factors, stratified by physicians, were randomly allocated (at patient level) to intervention and control groups with a 1:1 allocation ratio and block size of 6. The randomized trial lasted for 12 months. Figure 1 shows the flow diagram for the COMPETE III trial.

2.1.2 Intervention

The COMPETE III Trial intervention is a complex one which includes individualized, web-based monitoring and advice regarding eight cardiovascular prevention variables with cardiovascular tracker, support from clinical care coordinators, evidence-based patient-specific algorithms, linkage to formulary advice and prescribing support for

physicians, and linkage to community resource information for both patients and family physicians (Figure 2). The patients in control group received standard care as compared to the complex intervention delivered in the intervention group.

2.1.3 Outcomes

The primary outcome of the study is process composite score. The process composite score consisted of eight individual components of vascular tracker, including blood pressure, cholesterol, weight, smoking, diet, exercise, psychosocial, and ASA/antiplatelet use. The secondary outcomes are clinical outcomes, including on-target clinical composite score (also formed by eight individual clinical components), clinical improvement composite score, and cardiovascular events.

2.2 Statistical Analyses

2.2.1 Overview

The outcomes and baseline characteristics of selected patients are presented as mean (standard deviation) for continuous variables and count (percent) for categorical variables. The results of the analysis are reported as the estimates of intervention effect (coefficients for continuous outcomes and odds ratios [OR] for binary outcomes), corresponding 95 % confidence interval (CI), and associated *p*-values. The criterion for statistical significance was set at alpha ≤ 0.05 (2-tailed). Statistical Analysis System (SAS) version 9.1 (SAS Institute, Inc., Cary, North Carolina) and R version 2.13.1 were employed for analysis. Intention-to-treat principle was adopted in this data analysis. In

this study, we first reviewed the dataset structure of COMPETE III trial (Table 1 and Figure 1). Based on the characteristic of the target dataset and a previous simulation study [12], we compared five commonly used statistical approaches with reference GEE model in the analysis of intervention effects using COMPETE III trial data. We used 1097 individual patient data from 19 centers with previous cardiovascular events or cardiovascular risk factors. After initial examination of the targeted data, we first fit six regression models with the change of process composite score and on-target clinical composite score as continuous outcomes separately. Then we fit selected GEE model with the individual item of process and on-target clinical composite score separately. GEE models were also used to do correlation analysis between the clinical outcome variables and predictor variables.

Appendix C provides the related codes needed to fit regression models in the two statistical software packages. See Figure 3 for details of the data analysis process.

2.2.2 Computing Multiple Outcome Scores

Individual component of process composite score, process composite score, the individual component of on-target clinical composite score, and on-target clinical composite score were calculated based on the definition in COMPETE III trial protocol (Table 2). A clinical improvement composite score was calculated based on the sum of variables improved for each participant by examining the mean difference between groups. A difference of percentage of patients who improved by at least one clinical variable and by

3 or more clinical variables was calculated. An on-target clinical composite score was analyzed as the mean difference in number of variables on target within a fixed period between the intervention and control group. Each item of the composite outcomes, both for process and for clinical, was analyzed individually. The difference between groups in the change in process and the difference between groups in the proportion of patients for whom the variable was improved was evaluated for process and clinical improvement. The difference between groups in the proportion of patients who were on target for that variable was calculated for on-target score. Patients who had at least one cardiovascular event were assigned a score of 1; otherwise they were assigned a score of 0.

2.2.3 Comparing Methods to Estimate Intervention Effects

Based on a simulation study on COMPETE Π trial [12], GEE was employed as the primary statistical model used in this study to evaluate the effect of the web-based decision supporting intervention on patients CVD outcomes under the assumption of no effect by center interaction based on COMPETE ΙΙΙ trial data. Three individual patient-level analysis models (simple linear regression, fixed-effects regression, and mixed-effects regression) and two center-level analysis models (center-level fixed-effects model and center-level random-effects model) were compared to reference model (GEE) in terms of the robustness of the results – magnitude, direction and statistical significance of the estimated effects on the change of process composite score and on-target clinical composite score. All six statistical methods used in this comparison study were reviewed in detail in Table 3.

Simple Linear Regression Model

The regression equation for this statistical model is

$$Y_{ij} = \beta_0 + \beta_1 X_{ij} + \varepsilon_{ij}$$

Where,

Y_{ij}: intervention outcome of i^{th} patient in j^{th}center,

X_{ij}: intervention assignment (intervention or control),

ε_{ij}: random error assumed to follow a normal distribution $N(0, \sigma^2)$,

β_0: intercept for all centers,

β_1: effect of intervention on the mean outcome.

We fitted this general linear model in SAS via PROC GLM procedure by using the methods of ordinary least squares. The CLASS statement names the "GROUP" as a classification variable to be used in this model [43]. "MD (CENTER)" was completely ignored in this regression equation. SAS code was provided in Appendix C.

Fixed-Effects Regression Model

The equation for this regression model is

$$Y_{ij} = \beta_{0j} + \beta_1 X_{ij} + \varepsilon_{ij}$$

Where,

Y_{ij}: intervention outcome of i^{th} patient in j^{th}center,

X_{ij}: intervention assignment (intervention or control),

ε_{ij}: random error assumed to follow a normal distribution $N(0, \sigma^2)$,

β_{0j}: intercept for each center,

β_1 : the effect of intervention on the mean outcome.

Compared to the mean intercept β_0 for all participate centers in the above simple linear regression model, this model incorporates each intercept for every center [12, 46]. In this model, both group and center are fixed terms. They have the attractive feature of controlling for all stable characteristics of the individuals, whether measured or not. This is accomplished by using only within-individual variation to estimate the regression coefficients.

We fitted this regression model in SAS also via PROC GLM procedure by using ordinary least squares. This method estimates parameters by minimizing the squared difference between predicted and observed responsible variable values. In this approach, the total sum of squares is divided into two different sums of squares for effects. Comparing to simple linear regression model, "MD (CENTER)" was added as a classification variable in the CLASS statement in addition to the "GROUP" in fixed-effects regression model. All effects (fixed or random) were listed in the model statement. SAS code is provided in Appendix C.

Mixed-Effects Regression Model

The equation for this regression model is

$$Y_{ij} = \beta_0 + b_{0j} + \beta_1 X_{ij} + \varepsilon_{ij}$$

Where,

$\beta_0 + b_{0j}$: intercept that follows a normal distribution $N(\beta_0, \sigma^2{}_b)$

β_0: mean intercept,

b_{0j}: random deviation from the mean intercept for each center [6, 46].

We fitted this regression model in SAS via PROC MIXED procedure. Estimation of effects is based on generalized least squares in a Gaussian error model. This procedure uses three different principles, including maximum likelihood (ML), residual maximum likelihood (REML), and minimum variance quadratic unbiased estimation, to estimate variance components. The distribution of the error term and the random effects is required to be normal for adopting this procedure. The SAS default REML principle was used in this study. REML estimates are produced from maximizing the likelihood function of invariant to the fixed effects part. We use $\sigma^2{}_e$ denote the within-center variability, and $\sigma^2{}_b$ denote the between-center variability. Then the REML estimator of variance-covariance matrix can be expressed as

$$Var(Y_{tj}) = \sigma^2{}_e + \sigma^2{}_b \quad Cov(Y_{tj}, Y_{t'j}) = 0$$

The intra-center correlation (ICC) is:

$$ICC = \frac{\sigma^2{}_b}{\sigma^2{}_b + \sigma^2{}_e}$$

Compared to fixed-effects regression model, only the fixed effect was listed in the model statement. “MD (CENTER)” was added as a classification variable in the RANDOM statement. SAS code is provided in Appendix C.

Generalized Estimating Equations (GEE)

GEE was introduced by Liang and Zeger in 1986 [36] and has become a popular method in the analysis of correlated data, especially in the longitudinal studies and studies with cluster design. This equation models the marginal population-average intervention effect in two steps. The generalized linear model estimates are used as the starting values, and then it estimates parameters of the working correlation matrix for adjustment of the within-center dependence [62]. GEE employs quasi-likelihood to estimate regression coefficients iteratively, and a working correlation needed to approximate the within center correlation.

We assume the marginal regression model is

$$g(E[Y_{ij}|x_{ij}]) = x'_{ij}\beta$$

Where,

x_{ij} : a $p \times 1$ vector of covariates,

β : a $p \times 1$ vector of regression coefficients,

$g(.)$: the link function,

Y_{ij}: the outcome of i^{th}patient from j^{th} center.

The model for correlation is

$$V_i = \emptyset A_i^{1/2} R(\alpha) A_i^{1/2}$$

Where,

$\emptyset$: a dispersion parameter,

A: a diagonal matrix of variance functions,

$R(\alpha)$: a working correlation matrix of Y.

$\hat{\beta}$ was estimated by solving the generalized estimating equation:

$$\sum_{i=1}^{N} \frac{\partial \mu_i}{\partial \beta} V_i^{-1}(Y_i - \mu_i(\beta)) = 0$$

Where,

Y_i: a vector of outcomes,

V_i: the working correlation matrix,

μ_i: the mean of Y_i.

When a binary outcome variable is modeled using GEE, the regression coefficients were converted to ***ORs***, corresponding 95 % CIs and *p* values. The equation for the transformation is:

$$OR = \exp(\hat{\beta})$$

Where ***OR*** is the odds ratio and $\hat{\beta}$ is the prediction of regression coefficient.

We perform GEE analysis in SAS via PROC GENMOD procedure. "MD (CENTER)" and "GROUP" were added as classification variables in the CLASS statement. We specify "center" in a REPEATED statement to provide the cluster information and an exchangeable working correlation matrix was defined in this statement. SAS code is provided in Appendix C.

Center-Level Fixed-Effects Model

In our two arm, intervention and control, clinical trial, this model is reduced to a center-level inverse-variance weighted paired t-test to account for the within center correlation

[66]. The overall intervention effect is estimated by a weighted average of individual mean differences across all centers [37, 56]. The total intervention effect is estimated by inverse-variance weighting calculation as below

$$\hat{D}_{W(F)} = \frac{\sum_K d_K w_K}{\sum_K w_K} \quad d_K = \bar{Y}_{K(I)} - \bar{Y}_{K(C)} \quad w_K = \frac{1}{s^2_K} \quad s_K = se(d_K)$$

Where,

$\hat{D}_{W(F)}$: weighted intervention effect (weighted mean difference between intervention and control group) for fixed-effects models

k: the number of center

d_K: intervention effect (mean difference between intervention and control group) for K^{th} center

w_K: weight of K^{th} center

$\bar{Y}_{K(I)}$: mean outcome value of intervention group in K^{th} center

$\bar{Y}_{K(C)}$: mean outcome value of control group in K^{th} center

s_K: standard error of d_K for K^{th} center

The model was fitted by "METACONT( )" procedure in R. R code is provided in Appendix C.

Center-Level Random-Effects Model

In contrast to the center-level fixed-effects model, the center-level random-effects model factors heterogeneity of intervention effect among centers into its weighting scheme and captures within- and between-center variation of the outcome [16, 25]. In this model, the underlying true intervention effects are considered random effects, normally distributed

around a mean intervention effect with between-center variation. The calculation is as below

$$\hat{D}_{W(R)} = \frac{\sum_K d_K u_K}{\sum_K u_K} \quad d_K = \bar{Y}_{K(I)} - \bar{Y}_{K(C)} \quad u_K = \frac{1}{s^2_K + \tau^2} \quad s_K = se(d_K)$$

Where,

$\hat{D}_{W(R)}$: weighted intervention effect (weighted mean difference between intervention and control group) for fixed-effects models

k: the number of center

d_K: intervention effect (mean difference between intervention and control group) for K^{th} center

u_K: weight of K^{th} center

$\bar{Y}_{K(I)}$: mean outcome value of intervention group in K^{th} center

$\bar{Y}_{K(C)}$: mean outcome value of control group in K^{th} center

s_K: standard error of d_K for K^{th} center

τ^2: variation between centers

The model was also fitted by "METACONT( )" procedure in R. R code is provided in Appendix C.

2.2.4 Validating the Process and Clinical Composite Scores

The aim of COMPETE III trial is to determine the association between the clinical outcome and the improved composite score, or if the improvements in process will lead to improvements in clinical outcomes. To reveal a reliable association, validation of surrogate composite scores (process composite score and on-target clinical composite

score) that were used as outcome measurements, are needed. GEE regression model (based on the COMPETE III trial data structure) was employed to perform the statistical analysis to disclose these correlations. There are total four GEE regression equations, namely

$$g\left(E(Y_{ij})\right) = \beta_0 + \beta_1 X_{ij} + \beta_2 Z_{ij} + \beta_3 X_{ij} * Z_{ij}$$

Where,

Y_{ij}: cardiovascular events

clinical improvement composite score

on-target clinical composite score

X_{ij}: process composite score

on-target clinical composite score

Individual component of on-target clinical composite score

Z_{ij}: group

$X_{ij} * Z_{ij}$: interaction of process composite score and group

β_0: intercept

β_1, β_2, β_3: coefficients of X_{ij}, Z_{ij}, and $X_{ij} * Z_{ij}$

In the regression analysis, the outcomes were clinical outcomes (cardiovascular events, clinical improvement composite score, and on-target clinical composite score), and the main predictors were process composite score and on-target clinical composite/individual scores defined in the COMPETE III trial protocol, which could be calculated according to

the definition of composite score in the main trial, including blood pressure, LDL-cholesterol, weight, ASA or equivalent, smoking, physical exercise, diet, and psychosocial index. The associations between the change in process and the change in clinical outcomes were explored. The interaction terms between group and primary predictors were considered as predictors when necessary in the regression analysis.

Let Y_{ij} represent the outcome of i^{th}patient fromj^{th} center. When Y_{ij} follows Bernoulli distribution, the link function is:

$$g(\mu_{ij}) = \log\left(\frac{\mu_{ij}}{1-\mu_{ij}}\right) = x'_{ij}\beta$$

Where μ_{ij} is the mean of Y_{ij}, X_{ij} is a vector of covariates, β is the vector of regression coefficients of predictors and calculated by SAS procedure of GENMOD with REPEATED option. When a binary outcome variable is modeled using GEE, the regression coefficients were converted to ORs, corresponding 95 % CIs and *p* values.

Chapter 3 Results

3.1 Baseline Characteristics of COMPETE III Trial

A total of 1,102 patients from 49 physicians participated in COMPETE III study. Among all patients, 545 were allocated to the intervention group and 557 were randomized in the control group; 53.21 % and 53.50 % of the patients were female in the intervention and control group, respectively. The mean age in intervention group was 69.34 years with a standard deviation of 8.59 years and 68.83 years with a standard deviation of 8.81 years in control group. Patients were recruited from 18 clinical centers across Ontario, Canada. Mean follow-up period was 51.7 weeks with standard deviation 3.5 weeks for 96 % of all participants. Three deaths in the intervention group and two deaths in the control group were excluded from the statistical analysis. Other detailed baseline characteristics of participants in this study were summarized in Table 4.

3.2 Comparing Methods to Estimate Intervention Effects in COMPETE III Trial

GEE, used in reported COMPETE III study [27], was selected as a reference model to compare the robustness of estimation results with five other commonly used statistical models in the analysis of data from COMPETE III. Age, sex, and other baseline characteristics between the intervention and control group were balanced roughly equal by an individual patient-level random assignment [27].

3.2.1 Comparing Methods to Estimate Intervention Effects on Process Composite Score

This part of results was summarized in Table 5 and Figure 4. Four methods using the patient-level data (n = 1097) reached similar estimate of coefficient factor β_1, from the smallest 4.6546 (fixed-effects) to the biggest 4.7149 (simple linear regression). However, the standard error of estimated β_1 reduced from 0.2485 in simple linear regression model to 0.2304 in fixed-effects regression model, and further down to 0.23 in mixed-effects regression model. The standard error increased to 0.5313 in the GEE model when center effects were adjusted, which leaded to a wider 95 % confidence interval of 3.6312 to 5.7139, compared to a narrower 95 % confidence interval in other three patient-level data analysis methods. The intracenter correlation value was estimated 0.1324 in GEE model.

Two methods using center-level data analysis (n = 1086) got relatively smaller estimates of coefficient factor β_1, from 3.5392 in center-level fixed-effects model to 4.4114 in center-level random-effects model. The center-level fixed-effects model produced the smallest standard error (0.1809) of estimated β_1 and subsequently a narrowest confidence interval (3.1847-3.9838) among all the six regression models in this study. Of all the six models analysis, zero was not contained in the 95 % confidence interval and p values were less than 0.01, which showed a significant difference between the intervention and control groups. This significant difference between the two randomized comparable groups suggested that the active intervention significantly improved quality of

cardiovascular risk monitoring in primary care population over standard care based on the change of process composite score.

3.2.2 Estimates of Intervention Effects on Individual Component of Process Composite Score

This part of the results was summarized in Table 6 and Figure 5. The relatively smaller estimate effect in the center-level fixed-effects model in previous estimation of intervention effect on process composite scores suggested that the within-center variation should be considered in the analysis of process composite scores. Patient-level mixed-effects regression model, GEE model, and center-level random-effects model could cope with the within-center variation adjustment. Even though GEE model produced a bigger 95 % confidence interval compared to other selected models, this method was selected to estimate the intervention effect on individual component of process composite scores, due to the flexibility of accommodating both continuous outcome and categorical outcome.

The estimate of intervention effect on smoking was 0.028 with a standard error of 0.0168, which produced a 95 % confidence interval from – 0.0049 to 0.0609. Zero was contained in confidence interval and *p* value was greater than 0.05 (0.0948) suggesting that the studied intervention had little influence on the probability of the variable smoking recorded in cardiovascular tracker and composite scoring. The estimate of intervention effect on ASA or equivalent was 0.0503 (95 % confidence interval, -0.0003 to 0.1009; *p* = 0.0514) suggesting that the complex intervention had borderline significance on the

probability of the variable ASA or equivalent recorded in cardiovascular tracker and composite scoring. In terms of the remaining six component outcomes (blood pressure, LDL cholesterol, weight, psychosocial, physical exercise, diet), zero was far apart from the 95 % confidence interval and all *p* values were less than 0.01, which suggested that the experimental intervention strongly influenced the probability of all these six component outcome variables with favorable effects.

To verify the comparison of robustness based on the change of process composite score, we applied the six statistical models to one selected individual component, process blood pressure score. Indeed, we got the similar results as we got from the comparison based on the change of process composite score. The results were summarized in Table 7 and Figure 6.

3.2.3 Comparing Methods to Estimate Intervention Effects on On-Target Clinical Composite Score

This part of results was summarized in Table 8 and Figure 7. Like the estimation of intervention effect on process composite score, four approaches using the patient-level data (n = 1097) reached a similar estimate of coefficient factor β_1, from the smallest 0.0244 (fixed-effects) to the biggest 0.0309 (GEE). Among them, the estimation from simple linear regression, mixed effects regression, and GEE gave almost identical results (from 0.0302 to 0.0309). Although, the standard errors of estimated β_1 were identical in the first three models (0.0885 - 0.0889), it increased to 0.0948 in the GEE model when

center effects were adjusted, leading to a wider 95 % confidence interval of –0.1548 to 0.2166, compared to a narrower 95 % confidence interval in the other three individual patient-level data analysis methods. The intracenter correlation value was estimated to be zero in GEE model.

Two methods using center-level analysis (n = 1078) gave relatively smaller estimates of coefficient factor β_1, from –0.0017 in center-level fixed-effects model to 0.0148 in center-level random-effects model. Like the GEE model, center-level random-effects model produced the biggest standard error (0.113) of estimated β_1 and subsequently a widest confidence interval (-0.2082 to 0.2379) among all the six employed models in this study. In contrast to the estimation of intervention effects on process composite scores, of all the six-model analysis of intervention effect on on-target clinical composite score, zero was contained in the 95 % confidence interval and p values were greater than 0.05, which showed no significant difference of intervention effect between the intervention group and control group. This suggested that the active intervention did not significantly improve the quality of vascular risk monitoring in primary care population over the standard care population based on the change of on-target clinical composite score.

3.2.4 Estimates of Intervention Effects on Individual Component of On-Target Clinical Composite Score

GEE model was also used to estimate the intervention effects on individual component of on-target clinical composite score and detailed results were summarized in Table 9 and Figure 8.

Of all eight individual components recorded in vascular tracker, estimates of intervention effect on blood pressure was 0.1107 with a standard error of 0.0431, produced a 95 % confidence interval from 0.0262 to 0.1952. Zero was not contained in confidence interval and p value was close to 0.01 (p = 0.0102) suggesting that the intervention strongly influenced the probability of the individual outcome of on-target blood pressure score. The estimate of intervention effect on ASA or equivalent on-target score was 0.0503 (95 % confidence interval, -0.0003 to 0.1009; p = 0.0514), suggesting the intervention had borderline significance on the probability of the individual outcome of on-target ASA or equivalent score. In the remaining six components of outcome variables (LDL-cholesterol, smoking, weight, psychosocial, physical exercise, diet), zero was contained in 95 % confidence interval and all p values were greater than 0.05, suggesting that the experimental intervention had little influence on the probability of all these six individual component of outcome variables.

3.3 Validation Analysis for Process Composite Score and On-Target Clinical Composite Score

Total 76 events (6.9 %) from cardiovascular causes were reported in the COMPETE III trial (Table 10). There were 27 patients with a total of 34 cardiovascular events in the

intervention group and 30 patients with a total 42 cardiovascular events in the control group. The cardiovascular events rate in the intervention group (6.23 %) was slightly lower than and that in control group (7.54 %), however, there were no significant difference between these two groups. The differences in subgroups of three cardiovascular events contribute to most of the changes in total cardiovascular events between the intervention and control groups. It was hard to draw a conclusive inference by interpreting this small difference between the two groups since the event numbers are low in both groups.

3.3.1 Results of Correlation Analysis between Cardiovascular Events and On-Target Clinical Composite Score and Individual Component of On-Target Clinical Composite Score

Table 11 listed the odds ratios, 95 % confidence intervals, and *p* values for cardiovascular events from predictor variables. Both *p* values were greater than 0.05 ($p = 0.5739$ and $p = 0.7021$ respectively) if group term and interaction term between group and on-target clinical composite score were added as predictors in the regression equation, which suggested an exclusion from the final prediction equation. The odds ratio for cardiovascular events was 1.1780 (95 % confidence interval: 0.9804 – 1.4154; $p = 0.0803$) in terms of a single predictor of on-target clinical composite score. At the level of individual component of on-target clinical composite score, the odds ratio for cardiovascular events was 1.7768 (95 % confidence interval: 1.2308 – 2.5651; $p = 0.0021$) and 2.3601 (95 % confidence interval: 1.4161 – 3.9338; $p = 0.001$) in terms of

single predictor of on-target blood pressure score (Table 12) and on-target LDL cholesterol score (Table 13), respectively. One was contained in the 95 % confidence intervals and *p* values were greater than 0.05 of the odds ratio for cardiovascular events for all the remaining six individual components (BMI, psychosocial index, physical exercise, diet, ASA, and smoking) of on-target clinical composite score (Table 14-19). One interesting finding was that the odds ratio for cardiovascular events was 0.4512 (95 % confidence interval: 0.2037 – 0.9997; $p = 0.0499$) and 0.4444 (95 % confidence interval: 0.1989 – 0.9931; $p = 0.0481$) in terms of single predictor of on-target psychosocial index score when both interaction terms (interaction of group and on-target psychosocial index score) and group or only the above interaction term were added as predictors respectively. However, the odds ratio for cardiovascular events was 0.6813 (95 % confidence interval: 0.4004 – 1.1592; $p = 0.1570$) if both the interaction term and group term was removed from the left side of regression equation.

No significant differences of the association of cardiovascular events and on-target clinical composite score and on-target individual component of clinical composite score were found between the intervention group and control group. However, blood pressure, LDL cholesterol, psychosocial index were suggested to be significant predictors for cardiovascular events regardless of groups.

3.3.2 Results of Correlation Analysis between Cardiovascular Events and Process Composite Score

Table 20 listed the odds ratios, 95 % confidence intervals, and *p* values for cardiovascular events from main predictor variable (process composite score). The odds ratio for cardiovascular events was 0.8112 (95 % confidence interval: 0.7307 – 0.9007; $p < 0.0001$) in terms of process composite score when the interaction term between group and process composite score was presented as another independent predictor variable. The *p* value for the interaction term between the group and process composite score was less than 0.05 ($p = 0.0004$), which implied a disagreement of the intervention effect between the intervention group and control group. This was consistent with the report that the intervention had a significantly ($p < 0.0001$) greater improvement in mean process composite score with a difference of 4.67 (95 % confidence interval: 3.63 – 5.71) [27].

3.3.3 Results of Correlation Analysis between Clinical Improvement Composite Score and Process Composite Score

According to the main study in COMPETE III trial, the individual component of clinical outcome except ASA (prescribing ASA introduce border significant clinical improvement) had no significant difference between the intervention and control groups. Intervention also showed no significant difference on clinical composite score between randomized groups [27].

Similar result as in the above correlation analysis between the cardiovascular events and process composite scores, group (intervention) was also not a significant predictor for the clinical improvement outcome (Table 21). The coefficient for process composite score

was 0.0869 (95 % confidence interval: 0.0513 – 0.1224; $p < 0.0001$) when the interaction term of group and process composite score was added as a predictor variable at the left side of the regression equation.

3.3.4 Results of Correlation Analysis between On-Target Clinical Composite Score and Process Composite Score

The most interesting finding (Table 22) in this study was that the intervention (group) was a significant predictor for on-target clinical composite score when it, together with process composite score, was presented as an interaction term in the regression equation (as a predictor). The coefficient for process composite score was 0.1012 (95 % confidence interval: 0.0768 – 0.1255; $p < 0.0001$).

Chapter 4 Discussion

4.1 Comparison of Statistical Models in Analysis of Multicenter RCTs

Multicenter RCTs, with their advantage of generalizability of intervention for broader clinical settings, are increasingly used in the assessment of the effectiveness of interventions to improve health outcomes or prevent diseases [15]. With the advancement of statistics, new statistical techniques or methods are being gradually adopted in multicenter RCTs. Regression, with the ability to provide accurate prediction under the satisfaction of model assumptions, is perhaps one of the most frequently used and remains the central workhorse of clinical trial study. However, it is vital to apply regression models that are appropriate for analysis based on dataset structure and feasible resources. There are no concrete evaluations to support which regression model is the best approach in a particular multicenter RCTs setting, especially when center effects are considered in the statistical analysis [9, 51-52, 61, 65]. Other issues, such as randomization level, intervention type, and center numbers and size, could also influence the choice of analytical model. Four individual-level and two center-level approaches that reviewed in the methods section, are commonly used in the analysis of data from this type of clinical setting. Simulation study based on the COMPETE II structure recommended mixed-effects models and GEE models [12]. This follow up empirical study was set to map these potential methodological approaches based on COMPETE III dataset, which is similar to COMPETE II setting in terms of data structure. However, there was a much bigger

sample size (1,102 versus 512) distributed in similar center numbers (49 versus 46), which means a larger average within-center participant.

GEE was selected as the primary analysis model based on the previous studies and COMPETE III data structure. Ever since the GEE approach was introduced by Liang and Zeger [36], it has been widely used in the field of biomedical research [38]. It has a wide spectrum of applications and is available in most statistical software packages. GEE model features accommodation of both within-center and between-center relationship. It is also feasible for both continuous and categorical response variables, particularly for non-normally distributed outcomes. So, it is an efficient analysis model in a dataset with multi-types of outcome variables. For example, GEE was used by only changing the link function when the outcome in this study (for example, smoking) was a binary variable. Despite its several attractive features, previous simulation studies showed that it did not always converge when the number of patients per center was highly variable [12]. However, no convergence problems were found with GEE model in this study with an average of 22.5 patients per center (SD = 12.8). In addition, GEE model could under-estimate the intervention effect in a study with small number of centers [63]. In this study, GEE led to the conclusion that the complex intervention significantly improved patient care based on the change of process composite score (Table 5 and Figure 4; $p < 0.0001$). The proper estimate of the intervention effect in this multicenter (49 centers) RCT design agrees with a previous suggestion of a cut-off number of 40 centers to adopt GEE model [47]. However, GEE also led to the conclusion that the intervention didn't improve the

patient care based on the change of on-target clinical composite score (Table 8 and Figure 7; p = 0.7445). The disagreement between the effect of intervention on process and clinical outcome, together with an unexpected wide confidence, requires a comparison study among other possible statistical analysis models to justify the GEE selection.

Since COMPETE III is a trial only with intervention and the control groups, the effect of simple linear regression model is equal to that of a two-sample t-test [43]. This model completely ignores or assumes no influence of center. Analysis in COMPETE II trial showed that a narrower confidence interval and smaller p value would be produced despite the same intervention effect size if the center effects were ignored. However, analysis by individual patients without consideration of cluster effect might influence estimating results; though it is not a big concern in this study. Since the cluster influence can never be completely excluded in a real clinical setting with a multicenter design, this model had very little application value and was seldom used as primary analytical tool for multicenter RCTs data. However, it can serve as a useful reference when performing the comparative study among several analysis strategies.

Fixed-effects regression was initially developed to statistically control variables that cannot be observed/measured in a non-randomization research design [3]. Compared to random-effects model, fixed-effects model sacrifices efficiency in order to reduce the bias. This is useful in a non-experimental study but not in an RCT design. In an RCT, the baseline characteristics that could confound an observed association typically will be

distributed equally among the randomized groups via random assignment [60]. However, fixed-effects regression is still widely used in RCT studies when data fall into categories, such as centres in COMPETE III. In this fixed-effects regression, both the group and centre (physician) were fixed, which means a separate intercept for each centre. The model relies on within-centre action and the performance of this model will improve and will be accompanied by an increase in within-centre sample size. The average within-centre sample size (22.5) in COMPETE III trial is double to the within-centre sample size (11.1) in COMPETE II study. Theoretically, the fixed-effects model should perform better in COMPETE III trial than in COMPETE II trial if other factors are similar. The estimation (intervention effects) ratio of fixed-effects model to mixed-effects model is 0.9966 and 0.9787 in COMPETE III and COMPETE II trials, respectively, which proved this logical expectation. One potential limitation of fixed-effects models is that it cannot properly assess the effect of variables that have minor within-centre variation or in a trial with larger number of centres.

Mixed-effects regression was developed by adding the between-centre variability (random term) in addition to the within-centre variability that is provided by the fixed-effects model. In this way, it provides a compromise between ignoring data groups entirely and fitting each group with a separate model. Although this model takes between-centre variability into consideration that is more complicated, it is also more powerful since it increases the accuracy of the parameter estimation to reflect a more realistic clinical setting. Mixed-effects model produces the smallest standard error (0.23) among

all the four patient-level approaches. This model also has certain advantages in practice, such as easily converting SAS code from mixed-effects model to fixed-effects model based on the condition of the real dataset, so some statisticians even treat fixed-effects regression as a special case of mixed-effects regression model. In our study, the coefficient and standard error estimated (Table 5 and Figure 4) from both fixed-effects model and mixed-effects model were very close, and that means there is minor between-centre variability of the recruited physician in COMPETE III trial. At this point, there is no big difference between these two options, however, the mixed-effects model is deemed a more reliable model than fixed-effects model when the between-centre variation is not negligible and must be taken into account [46].

Comparing the above four models, we can see that all patient-level regression models in this study gave similar parameter estimates based on both the change of process composite score and the change of on-target clinical composite score, in terms of the magnitude, direction and statistical significance of the estimated effects. However, models with consideration of center influence can affect confidence intervals without any big changes on the estimation size of intervention as compared to models that do not consider the center effect.

Since the within-center standard deviation of intervention difference cannot be estimated from centers containing less than 2 patients per arm, a total of 1,086 patients were included for estimation of intervention effects on process composite score. About 1,078

patients were included for estimation of intervention effects on on-target clinical composite score. This kind of exclusion can make accommodation of application of the center-level models, but the reduction in sample size and subsequent compromise in the precision and power may inflate the confidence interval. From the estimation of intervention effects on process composite score (Table 5 and Figure 4), both center-level fixed-effects and center-level random-effects models underestimate intervention effects compared to patient-level models, especially in fixed-effects center level model. Since center-level random-effects model incorporates variability of intervention effect over centers, it is reasonable that center-level random-effects model performs better than center-level fixed-effects model in terms of precision at the presence of intervention by center interaction. Moreover, previous simulation results showed advantage of treating centers as random intercepts with no intervention by center interaction [12]. In reality, the center-level random-effects model was proposed to be an alternative choice for patient-level models when the sample size within every center is big [12]. Our results showed that even though the center-level random-effects model performed better compared to the center-level fixed-effects model in terms of parameter coefficients, it does inflate the standard error, especially in the estimation of intervention effects on on-target clinical composite score (Table 8 and Figure 7). Since center-level models do not take into account the patient-level covariates, so this inherent pitfall hindered the application of these models when baseline characteristics in a multicenter RCT trail were not properly balanced within experiment groups. Center-level analysis may also lead to substantially reduced statistical efficiency compared to individual-level analysis. Therefore, both

center-level fixed-effects model and center-level random-effects models are not optimal for analyzing multicenter RCTs with individual level randomization, such as COMPETE III study.

The analysis results indicate that all six models used in this study produce robust estimates of intervention effect. The relatively smaller estimate effect in the center-level fixed-effects model suggests that the within-center variation should be considered in the analysis process. There are usually several different analytical models available to choose from for analysis of RCTs data. The choice of a particular regression model may, therefore, largely depend on the nature of data, the parameter of interest, and availability of statistical software package. In the case of multicenter RCTs that use individual level randomization, complex intervention and composite outcomes, investigators should ensure that the data were analyzed with appropriate statistical approaches. This empirical comparison of analytical methods, together with previous simulation studies [12], suggests that mixed-effects model and GEE models can produce more accurate and precise estimation. GEE model is especially convenient for trials with non-normally distributed outcomes.

4.2 Validation Analysis for Surrogate Composite Scores

The data presented in Table 11 to Table 19 shows that the complex intervention delivered in this trial was not efficient enough to significantly improve the patient's important clinical outcomes in terms of reducing the risk of cardiovascular events, since no

significant difference of the association of cardiovascular events and on-target clinical composite score and on-target individual component of clinical composite score were found between the intervention group and control group. For example, the odds ratio for cardiovascular events in the intervention group was 0.9070 (95 % CI, 0.5625 to 1.4623; p = 0.6887) as compared to the control group, in the correlation analysis between the cardiovascular events and on-target clinical composite score. This was in agreement with results reported from COMPETE II and III studies [26]. However, these data were not strong enough to exclude the possible beneficial effect of the proposed complex intervention on patients in other conditional clinical settings. A better change in clinical improvement composite scores in intervention group than the control group was reported in COMPETE II study [26]. Our correlation analysis results also showed that intervention slightly increased the association between the cardiovascular events and on-target clinical composite score when group was added as a second predictor in the regression equation (odds ratio from 1.1780 to 1.1795, p = 0.0803 to p = 0.0789). Although there was only a borderline significance, the association of on-target clinical composite score and cardiovascular events was obvious. Considering the chronic nature of CVDs and the relatively small sample size, short follow-up period of COMPETE III trial, it is reasonable to assume that the minor enlargement in estimation of intervention effect may reflect a true value of the complex intervention in this study and may imply that a longer follow-up duration and/or stronger amplitude of the intervention can be translated into bigger change in cardiovascular outcomes. However, the minor increase may also be explained by a low responsiveness of the predicting model. Considering the low events

number, cardiovascular events used in the correlation analysis may not be a robust outcome variable to evaluate the intervention effect, since a subtle change in events in other clinical or community settings may lead to big impact on statistical change, say from no significant to borderline significant or even significant.

The predicting performance of on-target clinical composite score and individual component of on-target clinical composite score for the probability of cardiovascular events in this study may imply that the defined on-target clinical composite score in COMPETE III were not ideal independent variables to predict cardiovascular events. For example, compared to process composite score, on-target clinical composite score was defined narrower in range interval. This can further dilute or diminish the minor to modest intervention effect.

In addition, the composite scores used in COMPETE III were not validated in an external study and individual components of the composite scores should be examined to check for the validity [21, 44]. The analysis results (Table 6 and 9; Figure 5 and 8) indicated that equal weighting of the individual parts within composite outcomes was not a proper strategy to construct the composite score, since the complex intervention imposed effect with large variation on eight individual components of composite outcomes/score. The composition construction with even importance of individual component to patients may dilute the intervention effect by less important factors, which was consistent with other reports [21, 44, 48]. Forming an ideal on-target clinical composite score by removing the

variables of less significant influence to combine key elements is one possible strategy to increase the predicting power and accuracy, which has been recommended in COMPETE II study [26]. Another plausible approach is to change the equal weight of items in the score calculation equation to adjust item weight according to its degree of contribution to the outcome variable. For instance, although no significant difference of the association between cardiovascular events and on-target individual component of clinical composite score was found between the intervention group and control group, the result shed light on selecting key composite elements. From our data, of eight individual items of on-target clinical composite score, blood pressure and LDL cholesterol were associated with a significant increase in the risk of cardiovascular events respectively, which is consistent with other published reports [10, 35, 58, 67, 69]. Psychosocial index and ASA were also reported to be risk factors for cardiovascular disease, such as stroke [1, 50]. In this study, they were associated with a borderline significant increase in the risk of cardiovascular events when group variable was added as additional predictor. The remaining clinical components such as BMI, physical exercise, diet, and smoking were not found to be associated with the risk change of the cardiovascular events in this study. However, this was not contradictory to findings regarding these risk factors have been reported [17, 31, 49, 59] and their role in the risk of cardiovascular disease need to be further evaluated in the future. In addition, the possible correlation between the individual components of on-target clinical composite score may also compromise the validity of the defined composite score.

The complex interventions, as the one used in this study, are widely used in health research field with the advantage of effectively addressing complex situations like management of chronic disease. However, on the other side of the same coin, the low efficiency of delivering the intervention to the participants in the active intervention group may be a factor to diminish the intervention effect. As reported from other studies, delivering complex interventions are problematic. COMPETE II study reported that many clinicians noted that technical difficulties with the electronic decision support tool had a negative effect on the intervention [26]. It also found that about 86.7 % of intervention patients preferred paper tracker pages compared to the web version [27], which indicated a negative impact of the less acceptance of the integration of CDSS and EMRs.

Compared to on-target clinical composite score, process composite score was associated (odds ratio = 0.8112; $p < 0.0001$) with a significant reduction in the risk of cardiovascular events. This means that the proposed complex intervention can improve the defined process composite score, which in turn can predict the reduction of risk of cardiovascular events without significant change of on-target clinical composite score. In other words, the defined process composite score is a more robust predictor for cardiovascular events than on-target clinical composite score. Despite its attractive features over clinical outcomes, one should use process composite score with caution. For example, component of psychosocial stress involves subjective judgement that is less reliable and generalizable than clinical measurements. To cope up with this kind of influence, the number of

subjective component variables should be reduced to the minimal level for the construction of composite outcome or score.

After strong association with cardiovascular events revealed, process composite score show, as we expected, almost the same pattern of strong association with clinical improvement composite score (with a significant interaction with group). This finding is quite encouraging since the phenomena of using process composite score to predict clinical improving and clinical events not only directly confirms the hypothesis in COMPETE III trial, but also has a very useful meaning in clinical practice since measurements of process composite scores are much easier and less expensive than measurement of clinical variables.

The most interesting finding was that the use of process composite score was strongly predictive of a statistical significance for on-target clinical composite score (estimate 0.1012, 95 % confidence interval 0.0768 to 0.1225, $p < 0.0001$). This result not only proves the excellent definition of the process composite score defined in COMPETE III trial, but also indirectly infers that the defined on-target clinical composite score is on the right track for prediction and evaluation. However, as we have discussed above, the pitfalls with the surrogate composite scores alarms that further modifications are needed to improve their validity.

The disagreement of clinical and process outcome were not evidence strong enough to draw a conclusion that allowing process outcomes to act as surrogates for clinical outcomes in chronic management may be flawed. Since the on-target clinical composite score is a direct indictor of the patient important clinical outcomes, the emphasis should focus on how to improve the construction of the process composite score to better predict and reflect the clinical outcome. The association between process composite score and cardiovascular events/clinical improvement, especially by the association between the on-target clinical composite score and process composite score with a significant differentiation of experimental groups, supports this direction.

Overall, our data analysis is designed to have a conservative tendency to prevent potential over estimation of intervention effect. For example, GEE model produced a wider confidence interval compared to other statistical approaches. In addition, when computing the cardiovascular score, we assigned a score of 0 to a patient who was lost follow up. This conservative tendency doesn't change the robustness, in terms of estimate effect magnitude, direction, and significant level, of the GEE model in this project. However, it may have some effects on the evaluation of the defined surrogate composite scores when the intervention has a borderline significance. From a positive view, a conservative tendency in analysis can reduce the probability of generating type I error in the process of data analyzing. So, a comparative sensitivity analysis with other optional models (i.e. mixed-effects regression) is advised.

4.3 Limitations of the Study

It is acceptable to assume a zero intervention by center interaction when performing a regression analysis on a dataset from a multicentre RCT setting like COMPETE II and III trail [12]. However, center interactions should be considered in some multicenter RCT conditions [43]. The empirical comparison of six statistical approaches in this study was performed on continuous outcomes; it may not well extend to evaluate interventions for other type of outcomes, such as binary outcomes [2]. In addition, the inference from an empirical analysis may not hold true in other experimental settings.

The intervention has a big effect on process composite score, but no significant or only minor effect on clinical outcomes (clinical improvement composite score and cardiovascular events). The disagreement of intervention effect on process composite score and clinical outcomes dims the direct (from clinical view but not only from process view) evaluation of the intervention effect and hinders the likelihood of acceptance of this supposed promising intervention in wider clinical and community settings.

Individual components of the on-target clinical composite score were assigned equal weights. This equal assignment of weights should be viewed with caution when interpreting the regression parameters since the un-weighted composite scores were adopted with the assumption that intervention had equal effect on every individual component of the composite outcome. Our results disclosed a violation of this underlying assumption. Properly weighting each of the components is one of the strategies

recommended to cope with the drawback of composite score outcome, though the optimal methods to weigh individual component remain uncertain [20-21].

Since center is the analysis unit in two center-level models, centers were removed from analysis when the standard error for intervention difference could not be calculated. About three centers were removed when analysis based on the change of process composite score and four centers were removed when analysis based on the change of on-target clinical composite score. The resulting reduction in the sample size can potentially distort the real intervention effects given a drop of centers in a RCT setting with small number of clusters.

Extra caution should be given in interpreting the analytical results when an interaction term is added in the regression equation. For example, when we interpret the results from the correlation analysis between cardiovascular events and process composite score, we cannot draw a conclusion that group intervention has no effect on the dependent clinical outcome by a p value (greater than 0.05) for group intervention. Instead, we need to interpret the effect of group intervention in light of the interaction of process composite score and group, which suggests a no parallel effect between these two groups.

4.4 Impact of the Study and Future Direction

The consistency of empirical comparison for statistical methods in COMPETE III with the simulation study based on COMPETE II provides valuable insight into regression

model selection when analyzing data from multicenter RCTs. The analytical methods used in this study were performed under statistical assumptions, such as normal distribution for the simple linear regression. However, some of these assumptions may not always hold true in practical settings. So extension of the comparison of methods by adding Bayesian estimation approach [5] is the future direction to address additional complexities and relax statistical assumptions.

Composite scores were widely used in RCTs with its advantage to cope with lower clinical events. A further improvement of the construction of these surrogate composite scores is needed, since serving as valid outcome variables will have big impact on interpreting the treatment effects. The prediction role of process composite score on clinical outcomes calls for more research in this direction to reduce healthcare burden and promote the acceptance of e-health intervention for the management of CVDs and other chronic diseases in clinical and community settings to ultimately benefit patients.

Since delivery of complex intervention can be problematic, any improvement in delivery methods will result in the clinical benefit of intervention. Continuously developing the complex electronic-health intervention to make it more convenient and efficient in deliver is another future direction to pursue.

Chapter 5 Conclusions

All five statistical models yielded similar robust estimation of the results comparing to the reference GEE model in terms of the robustness of the results – magnitude, direction and statistical significance of the estimation of intervention effects. The relatively smaller estimate effects in the centre-level fixed-effects model suggest that the within-centre variation should be considered in the analysis of multicenter RCTs. Process composite scores may serve as an important tool to predict CVD outcomes. Any improvement on construction of these composite scores will lead to more valid evaluation of clinical intervention. The association between the clinical outcomes and complex intervention encourage a broader e-health intervention for the management of CVDs and other chronic diseases.

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Appendix A: List of Tables

Table 1. Composition Structure of COMPETE III Trial

Center ID	Family Physician	Number of Patients
01	01	15
	02	24
	03	29
	04	6
	05	14
	06	10
	07	32
	08	42
	09	6
02	01	25
03	01	30
04	01	18
	02	6
05	01	36
06	01	10
	02	2
	03	16
	04	16
	05	24
07	01	13
08	01	33
09	01	44
10	01	23
11	01	17
	02	17
	03	22
	04	16
	05	9
12	01	19
	02	44
13	01	8

14	01	34
15	01	27
16	01	46
	02	51
	03	48
	04	26
	05	13
	06	35
	07	38
	08	22
	09	34
17	01	21
	02	28
18	01	19
	02	5
	04	12
	05	12
	06	5
Total	49	1102
Average per family physician		22.49
SD		12.82

Table 2. Variables Recorded in Vascular Tracker and Composite Scoring

Vascular tracker variable	**Process target**	**Process composite score**	**Clinical target**	**On-Target clinical score**
Blood pressure	Quarterly	4	< 140/90 mmHg	1
LDL-cholesterol	Semi-annual	2	LDL < 2.5 mmol/L	1
Weight	Quarterly	4	BMI < 25 kg/m^2	1
ASA or equivalent	Annual	1	80-325 mg/day	1
Smoking	Quarterly, if smoking	4	No smoking	1
Physical exercise	Quarterly	4	≥ 4 hours/week of moderate vigorous exercise	1
Diet	Quarterly	4	≥ 4 servings of fruits and vegetables daily	1
Psychosocial Index	Quarterly	4	Low stress, no depression, good locus of control	1

This table was modified from original table 1 in the main study of COMPETE III trial (Holbrook et al., 2011)

Table 3. Pros and Cons of Statistical Methods for Comparing Analysis

Unit of Analysis	Methods Name	Pros	Cons	References
Individual patient-level	Simple linear regression	Simple to implement Equivalence to a two-sample t-test in the contest of a two group design Reduce the chance to commit a type I error compared to multiple two-sample t-tests	Fail to adjust for between-center variation or within-center correlation in the outcome measure May produce incorrect inferences due to over estimated SE for moderate to large ICC values	[43]
	Fixed-effects regression	Control confounding effects in a no-randomized controlled experiment Provide accurate estimates of the SE in the analysis of multicenter trials with large ICC value	Unable to consider random effects Produce less precise (comparing to simple linear regression model) point estimate with a design of equal center size and chance imbalance given small to moderate ICC values Not suitable for trials with minor center variation	[3, 46]

	Mixed-effects regression	Take into account of between-center variation No convergence problem Provide accurate estimates of the SE in the analysis of multicenter trials with large ICC More efficient than fixed-effects model in an unbalanced design with large number of centers	Power decrease with ICC when center size was small and the number of center was large Effects are treated as random when they are actually fixed	[6, 39, 46]
	Generalized estimating equations (GEE)	Availability in most statistical software Reflect both the within- and between-center relationship Commonly used model-based analysis for longitudinal and clustered data Accommodation for various data forms Produce accurate and precise effect estimates regardless of the degree of clustering More relax on model assumption	Need specification of working correlation structure to approximate the within center correlation Not always converge when the number of patients per center was highly variable Variance of estimated treatment effect could be underestimated when the number of centers was small The power decreased with ICC when center size was small and the number of the center was large	[12, 36, 38, 47, 62, 63]

Center-level	Center-level fixed-effects model	A form of the weighted analysis without adjustment for covariates A good choice for cluster-level randomization design	Cannot adjust for patient-level covariates in the presence of patient prognostic imbalance Generally produces larger SE and MSE, lower power than the patient-level model Large sampling variation when studies were conducted at many smaller centers May not be an optimal strategy in trials consisting of very small centers	[37, 56, 66]
	Center-level random-effects model	Capture within- and between-center variation of the outcomes A good choice for cluster-level randomization design	Cannot adjust for patient-level covariates, in the presence of patient prognostic imbalance Generally produces larger SE and MSE than the patient-level model Lower power to detect the true treatment effect due to a larger standard error that reflect s both the within-center variability and treatment by center interaction. May not be an optimal strategy in trials consisting of very small centers	[2, 16, 25]

Table 4. Baseline Characteristics and Pre-Intervention Outcomes

Variable & Outcome	Intervention (n = 545)	Control (n = 557)
Sex (n, % women)	290 (53.21)	298 (53.50)
Age (y) (mean, SD)	69.34 (8.59)	68.83 (8.81)
Height (cm) (mean, SD)	169.0 (9.80)	168.3 (9.79)
Weight (kg) (mean, SD)	78.7 (17.77)	77.5 (16.38)
Highest education completed (n, %)		
Elementary only	36 (6.61)	57 (10.23)
Secondary school only	193 (35.41)	196 (35.19)
College or university	265 (48.62)	223 (40.04)
Post-graduate school	47 (8.62)	64 (11.49)
Unknown	4 (0.73)	17 (3.05)
Living situation (n, %)		
Alone	142 (26.06)	135 (24.24)
With 1 other person	326 (59.82)	334 (59.96)
With 2 or more	77 (14.13)	78 (14.00)
Unknown	0 (0)	10 (1.80)
Internet use (n, %)		
Several times a day	113 (20.73)	111 (19.93)
Once a day	96 (17.61)	90 (16.16)
Several times a week	48 (8.81)	64 (11.49)
Once a week or less	42 (7.71)	43 (7.72)
Never	156 (28.62)	160 (28.73)
Unknown	90 (16.51)	89 (15.98)
Systolic blood pressure (mm Hg) (mean, SD)	134.31 (17.17)	133.55 (16.65)
Diastolic blood pressure (mm Hg)(mean, SD)	75.41 (10.28)	75.42 (9.39)
LDL cholesterol (mmol/L) (mean, SD)	2.60 (0.87)	2.73 (0.91)
BMI kg/m^2 (mean, SD)	27.57 (5.52)	27.21 (4.85)
ASA/equivalent (n, %)	349 (64.04)	341 (61.22)
Psychosocial Index (mean, SD)	8.66 (1.43)	8.50 (1.54)
Exercise (mean, SD)	404.18 (500.50)	363.04 (421.11)
Diet score (mean, SD)	13.14 (3.49)	13.31 (3.22)
No somker (n, %)	476 (87.34)	483 (86.71)
Previous vascular diagnoses (n, %)		
1 or more previous vascular diagnosis	150 (26.93)	159 (29.17)
Myocardial infarction	76 (13.94)	67 (12.03)
Stroke (ischemic or hemorrhagic)	50 (9.17)	46 (8.26)
Angioplasty	40 (7.34)	37 (6.64)
CABG	47 (8.62)	38 (6.82)
Peripheral vascular disease	32 (5.87)	36 (6.46)

Diabetes diagnosed	134 (24.59)	110 (19.75)
Primary Outcomes (pre-intervention) (mean, SD)		
Total process composite score	8.48 (2.61)	8.61 (2.62)
Blood pressure	2.32(1.24)	2.37(1.25)
LDL cholesterol	0.84(0.72)	0.81(0.70)
Weight	0.83(0.97)	0.81(0.97)
Smoking	3.68(0.89)	3.67(0.89)
Psychosocial Index	0.11(0.40)	0.31(0.63)
Physical exercise	0.06(0.24)	0.03(0.18)
Diet	0.01(0.10)	0.00 (0.00)
ASA or Equivalent	0.64(0.48)	0.61(0.48)
Secondary Outcomes (pre-intervention) (mean, SD)		
Total on-target clinical composite score	4.50 (1.30)	4.41 (1.36)
Blood pressure	0.36 (0.47)	0.38 (0.48)
LDL cholesterol	0.24 (0.42)	0.19 (0.39)
Weight	0.30 (0.45)	0.33 (0.46)
Smoking	0.88 (0.33)	0.87 (0.33)
Psychosocial Index	0.61 (0.48)	0.58 (0.49)
Physical exercise	0.53 (0.49)	0.49 (0.50)
Diet	0.95 (0.21)	0.96 (0.20)
ASA or Equivalent	0.64 (0.48)	0.61 (0.48)

Table 5. Estimates of Intervention Effects on Process Composite Score

Model	Sample Size	Estimate of Intervention Effects	SE	95% CI	P-Value
Simple linear regression	1097	4.7149	0.2485	4.2273 - 5.2025	<0.0001
Fixed-effects regression	1097	4.6546	0.2304	4.2026 - 5.1067	<0.0001
Mixed-effects regression	1097	4.6706	0.2300	4.2193 - 5.1220	<0.0001
Generalized estimating equations (GEE)	1097	4.6726	0.5313	3.6312 - 5.7139	<0.0001
Center-level fixed-effects model	1086	3.5392	0.1809	3.1847 - 3.8938	<0.0001
Center-level random-effects model	1086	4.4114	0.4923	3.4464 - 5.3764	<0.0001

ICC =0.1324 for GEE model

Table 6. Estimates of Intervention Effects on Individual Component of Process Composite Score

Model	Outcome	Estimate of Intervention Effects	SE	95% CI	P-Value (ICC)
Generalized estimating equations (GEE)	Blood Pressure	0.6116	0.0780	0.4588 - 0.7645	<0.0001 (0.0060)
	LDL cholesterol	0.4931	0.0472	0.4006 - 0.5856	<0.0001 (0.0203)
	Weight	0.7056	0.1184	0.4735 - 0.9377	<0.0001 (0.0648)
	Smoking	0.0280	0.0168	-0.0049- 0.0609	0.0948 (≈ 0)
	Psychosocial Index	1.0120	0.1399	0.7378 - 1.2861	<0.0001 (0.0921)
	Physical exercise	0.9059	0.1204	0.6698 -1.1419	<0.0001 (0.1805)
	Diet	0.8766	0.1319	0.6181-1.1351	<0.0001 (0.2461)
	ASA or Equivalent	0.0503	0.0258	-0.0003- 0.1009	0.0514 (0.0050)

Table 7. Estimates of Intervention Effects on Process Blood Pressure Score

Model	Sample Size	Estimate of Intervention Effects	SE	95% CI	P-Value
Simple linear regression	1097	0.6121	0.0766	0.4617 – 0.7625	<0.0001
Fixed-effects regression	1097	0.6067	0.0761	0.4574 – 0.7560	<0.0001
Mixed-effects regression	1097	0.6113	0.0762	0.4617 – 0.7609	<0.0001
Generalized estimating equations (GEE)	1097	0.6116	0.0780	0.4588 – 0.7645	<0.0001
Center-level fixed-effects model	1086	0.6087	0.0716	0.4684 – 0.7491	<0.0001
Center-level random-effects model	1086	0.6203	0.0852	0.4523 – 0.7873	<0.0001

Table 8. Estimates of Intervention Effects on On-Target Clinical Composite Score

Model	Sample Size	Estimate of Intervention Effects	SE	95% CI	P-Value
Simple linear regression	1097	0.0303	0.0885	-0.1434- 0.2039	0.7324
Fixed-effects regression	1097	0.0244	0.0889	-0.1500- 0.1988	0.7836
Mixed-effects regression	1097	0.0303	0.0885	-0.1434- 0.2040	0.7324
Generalized estimating equations (GEE)	1097	0.0309	0.0948	-0.1548- 0.2166	0.7445
Center-level Fixed-effects model	1078	-0.0017	0.0838	-0.1660-0.1627	0.9842
Center-level random-effects model	1078	0.0148	0.1138	-0.2082-0.2379	0.8964

ICC ≈ 0 for GEE model

Table 9. Estimates of Intervention Effects on Individual Component of On-Target Clinical Composite Score

Model	Outcome	Estimate of Intervention Effects	SE	95% CI	P-Value (ICC)
Generalized estimating equations (GEE)	Blood pressure	0.1107	0.0431	0.0262- 0.1952	0.0102 (≈ 0)
	LDL cholesterol	-0.0357	0.0278	-0.0902- 0.0187	0.1987 (0.0159)
	Weight	0.0148	0.0189	-0.0222- 0.0518	0.4336 (≈ 0)
	Smoking	0.0108	0.0143	-0.0171- 0.0388	0.4470 (0.0068)
	Psychosocial Index	-0.0523	0.0305	-0.1122- 0.0075	0.0863 (0.0055)
	Physical exercise	-0.0468	0.0484	-0.1416- 0.0481	0.3339 (0.0184)
	Diet	-0.0228	0.0179	-0.0579- 0.0122	0.2021 (≈ 0)
	ASA or Equivalent	0.0503	0.0258	-0.0003- 0.1009	0.0514 (0.0050)

Table 10. Cardiovascular Events in COMPETE III Trial

Intervention Group		Control Group	
Patient Code	Cardiovascular Events	Patient Code	Cardiovascular Events
101002	CAD	102020	CAD
107011	CAD	105007	CAD
108030	CAD	107012	CAD
109006	MI, CAD	201012	CAD
201011	CABG	402004	CAD
201019	Angioplasty	501001	CABG
402001	CAD, CABG	501024	PVD
501021	CAD, MI, CABG	601001	CAD
604009	Ischemic Stroke	605009	PVD
604012	Angioplasty	801023	PVD
605019	MI	801028	Angioplasty
701006	PVD	801033	Ischemic Stroke
901018	MI, Angioplasty	1001004	CAD
1101006	Ischemic Stroke	1001018	MI, Angioplasty, CAD
1401004	CAD	1101002	MI, Angioplasty
1501009	Ischemic Stroke	1104008	CAD
1601028	CAD, PVD	1202032	CAD
1602036	MI	1401002	Angioplasty
1603033	CABG	1401014	Ischemic Stroke
1604008	CAD	1601030	MI, CAD
1604018	Unstable-Angina	1602004	MI, Angioplasty
1608011	Ischemic Stroke	1602029	Angioplasty
1609011	Unstable-Angina	1603014	Ischemic Stroke
1701004	Ischemic Stroke, PVD	1607007	CABG
1701020	PVD	1607008	MI, Angioplasty, CAD
1801003	CAD	1609017	CAD
1801008	CAD	1609019	CAD, MI
		1801004	CAD
		1801013	MI, Ischemic Stroke Hemorrhagic Stroke
		1804005	MI, CAD, PVD
One events per patient: 21 Two events per patient: 5 Three events per patient: 1 Patients: 27 (4.95%) Cardiovascular events: 34 (6.23%)		One events per patient: 22 Two events per patient: 4 Three events per patient: 4 Patients: 30 (5.39%) Cardiovascular events: 42 (7.54%)	
Total patients: 57 (5.17%) Total cardiovascular events: 76 (6.90%)			

Table 11. Results of Correlation Analysis between Cardiovascular Events and On-target Clinical Composite Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-Value	ICC
Cardiovascular events	On-target clinical composite score	Clinical events = clinical-composite-diff + group + clinical-composite-diff * group				
		Clinical-composite-diff	1.1330	0.8636-1.4865	0.3676	0.0042
		Group 1 Intervention	0.8567	0.4996-1.4689	0.5739	
		Clinical-composite-diff * Group 1 Intervention	1.0802	0.7277-1.6034	0.7021	
		Clinical events = clinical-composite-diff + group				
		Clinical-composite-diff	1.1795	0.9811-1.4181	0.0789	0.0041
		Group 1 Intervention	0.9070	0.5625-1.4623	0.6887	
		Clinical events = clinical-composite-diff				
		Clinical-composite-diff	1.1780	0.9804-1.4154	0.0803	0.0040

Table 12. Results of Correlation Analysis between Cardiovascular Events and On-target Blood Pressure Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-Value	ICC
Cardiovascular events	On-target blood pressure score	Clinical events = BP-diff + group + BP-diff * group				
		BP-diff	2.1909	1.1884-4.0386	0.0120	0.0039
		Group 1 Intervention	0.9427	0.5760-1.5428	0.8144	
		BP-diff *group 1 Intervention	0.6761	0.2723-1.6787	0.3990	
		Clinical events = BP-diff + BP-diff * group				
		BP-diff	2.2293	1.2504-3.9741	0.0066	0.0038
		BP-diff *group 1 Intervention	0.6537	0.2722-1.5700	0.3416	
		Clinical events = BP-diff				
		BP-diff	1.7768	1.2308-2.5651	0.0021	0.0045

Table 13. Results of Correlation Analysis between Cardiovascular Events and On-target LDL-Cholesterol Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-Value	ICC
Cardiovascular events	On-target LDL cholesterol score	Clinical events = LDL-diff + group + LDL-diff * group				
		LDL-diff	1.6286	0.7836-3.3848	0.1914	0.0086
		Group 1 Intervention	0.6836	0.3410-1.3703	0.2836	
		LDL-diff*group 1 Intervention	2.1589	0.6521-7.1485	0.2077	
		Clinical events = LDL-diff + LDL-diff * group				
		LDL-diff	1.8801	0.8912-3.8107	0.0974	0.0078
		LDL-diff*group 1 Intervention	1.5379	0.6063-3.9013	0.3648	
		Clinical events = LDL-diff				
		LDL-diff	2.3601	1.4161-3.9338	0.0010	0.0071

Table 14. Results of Correlation Analysis between Cardiovascular Events and On-target BMI Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-Value	ICC
Cardiovascular events	On-target BMI score	Clinical events = BMI-diff + group + BMI-diff * group				
		BMI-diff	0.4504	0.1243-1.6317	0.2245	0.0049
		Group 1 Intervention	0.9363	0.5780-1.5166	0.7892	
		BMI-diff * group 1 Intervention	1.3886	0.2239-8.6124	0.7244	
		Clinical events = BMI-diff + BMI-diff * group				
		BMI-diff	0.4410	0.1193-1.6299	0.2197	0.0049
		BMI-diff * group 1 Intervention	1.4316	0.2336-8.7732	0.6981	
		Clinical events = BMI-diff				
		BMI-diff	0.5363	0.1984-1.4496	0.2194	0.0049

Table 15. Results of Correlation Analysis between Cardiovascular Events and On-target Psychosocial Index Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-Value	ICC
Cardiovascular events	On-target psychosocial index score	Clinical events = stress-diff + group + stress-diff * group				
		Stress-diff	0.4512	0.2037-0.9997	0.0499	0.0030
		Group 1 Intervention	0.9173	0.5488-1.5334	0.7419	
		Stress-diff*group 1 Intervention	2.3639	0.8120-6.8812	0.1146	
		Clinical events = stress-diff + stress-diff * group				
		Stress-diff	0.4444	0.1989-0.9931	0.0481	0.0029
		Stress-diff*group 1 Intervention	2.3762	0.8152-6.9268	0.1128	
		Clinical events = stress-diff				
		Stress-diff	0.6813	0.4004-1.1592	0.1570	0.0033

Table 16. Results of Correlation Analysis between Cardiovascular Events and On-target Physical Exercise Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-Value	ICC
Cardiovascular events	On-target physical exercise score	Clinical events = exercise-diff + group + exercise-diff * group				
		Exercise-diff	0.8447	0.5371-1.3280	0.4645	0.0036
		Group 1 Intervention	0.9039	0.5514-1.4816	0.6885	
		Exercise-diff * group 1 Intervention	0.9315	0.3703-2.3432	0.8801	
		Clinical events = exercise-diff + group				
		Exercise-diff	0.8151	0.5660-1.1736	0.2716	0.0036
		Group 1 Intervention	0.9083	0.5556-1.4848	0.7012	
		Clinical events = exercise-diff				
		Exercise-diff	0.8176	0.5678-1.1773	0.2790	0.0035

Table 17. Results of Correlation Analysis between Cardiovascular Events and On-target Diet Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-Value	ICC
Cardiovascular events	On-target diet score	Clinical events = diet-diff + group + diet-diff * group				
		Dietdiff	0.9117	0.4068-2.0436	0.8225	0.0030
		Group 1 Intervention	0.9305	0.5704-1.5180	0.7731	
		Diet-diff*group 1 Intervention	1.7512	0.4837-6.3408	0.3933	
		Clinical events = diet-diff + diet-diff * group				
		Diet-diff	0.8999	0.3997-2.0259	0.7988	0.0029
		Diet-diff*group 1 Intervention	1.7761	0.5047-6.2501	0.3709	
		Clinical events = diet-diff				
		Diet-diff	1.2312	0.6251-2.4254	0.5475	0.0029

Table 18. Results of Correlation Analysis between Cardiovascular Events and On-target ASA Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-Value	ICC
Cardiovascular events	On-target ASA score	Clinical events = ASA-diff + group + ASA-diff * group				
		ASA-diff	2.7412	0.8788-8.5506	0.0823	0.0038
		Group 1 Intervention	0.9696	0.5685-1.6533	0.9095	
		ASA-diff*group 1 Intervention	0.5101	0.1614-1.6122	0.2516	
		Clinical events = ASA-diff + group + ASA-diff * group				
		ASA-diff	2.7757	0.9524-8.0898	0.0614	0.0038
		ASA-diff*group 1 Intervention	0.4987	0.1723-1.4433	0.1994	
		Clinical events = ASA-diff				
		ASA-diff	1.8524	0.8891-3.8594	0.0997	0.0037

Table 19. Results of Correlation Analysis between Cardiovascular Events and On-target Smoking Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-Value	ICC
Cardiovascular events	On-target smoking score	Clinical events = smoker-diff + group + smoker-diff * group				
		Smoker-diff	2.3712	0.8888-6.3268	0.0846	0.0043
		Group 1 Intervention	1.0376	0.6246-1.7237	0.8867	
		Smoker-diff * Group 1 Intervention	0.1928	0.0177-2.0982	0.1765	
		Clinical events = smoker-diff + smoker-diff * group				
		Smoker-diff	2.3287	0.8799-6.1626	0.0887	0.0043
		Smoker-diff * Group 1 Intervention	0.2000	0.0204-1.9617	0.1671	
		Clinical events = smoker-diff				
		Smoker-diff	1.2963	0.5720-2.9373	0.5342	0.0039

Table 20. Results of Correlation Analysis between Cardiovascular Events and Process Composite Score

Outcome	Main predictor	Parameter	Odds ratio	95% CI	P-value	ICC
Cardiovascular events	Process composite score	Clinical events = process-composite-diff + group + Process-composite-diff * group				
		Process-composite-diff	0.7996	0.7134-0.8962	0.0001	0.0026
		Group 1 Intervention	0.8260	0.4624-1.4754	0.5183	
		Process-composite-diff * group 1 Intervention	1.2369	1.0982-1.3932	0.0005	
		Clinical events = process-composite-diff + process-composite-diff * group				
		Process-composite-diff	0.8112	0.7307-0.9007	0.0001	0.0030
		Process-composite-diff * group 1 Intervention	1.2060	1.0867-1.3386	0.0004	

Table 21. Results of Correlation Analysis between Clinical Improvement Composite Score and Process Composite Score

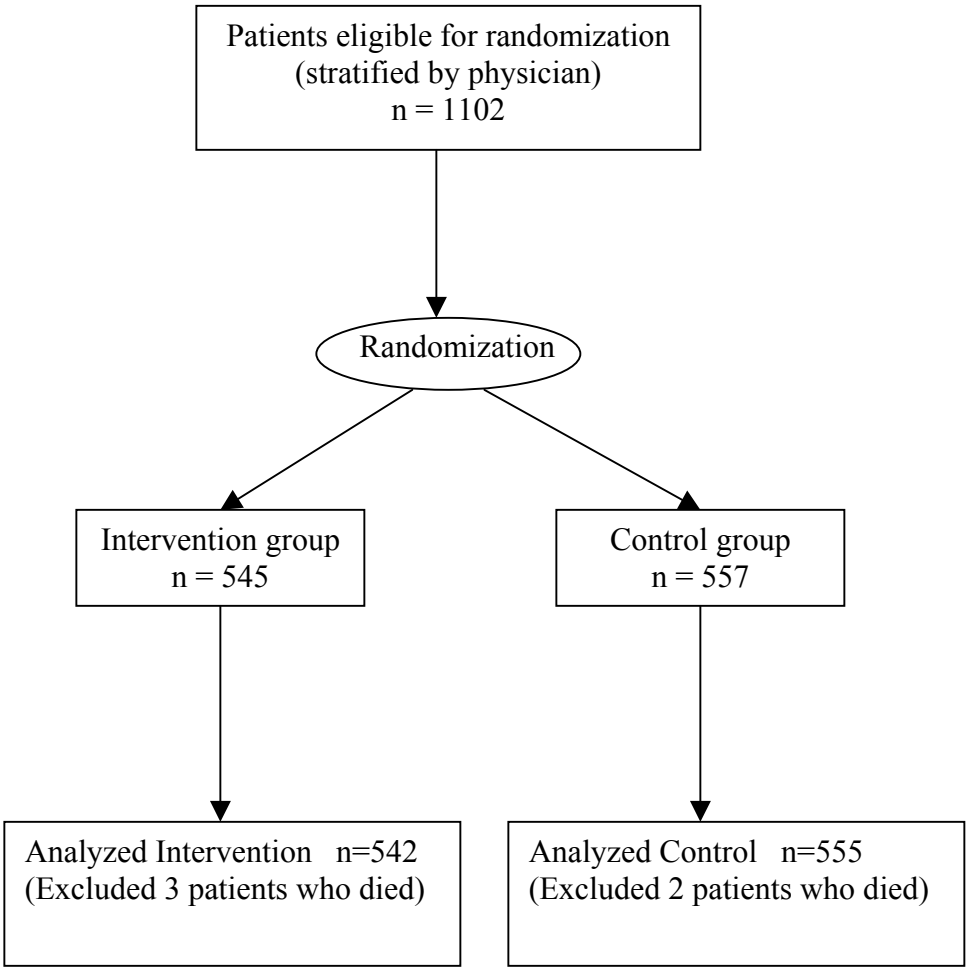
Outcome	Main predictor	Parameter	Estimate	SE	95% CI	P-Value	ICC
Clinical improvement composite score	**Process composite score**	Clinical improvement composite score = process-composite-diff + group + process-composite-diff * group					
		Process-composite-diff	0.0874	0.0171	0.0539-0.1210	0.0001	0.0167
		Group 1 Intervention	0.0138	0.1119	-0.2054-0.2331	0.9017	
		Process-composite-diff * group 1 Intervention	-0.0553	0.0211	-0.0965-0.0140	0.0087	
		Clinical improvement composite score = process-composite-diff + process-composite-diff * group					
		Process-composite-diff	0.0869	0.0181	0.0513-0.1224	0.0001	0.0166
		Process-composite-diff * group 1 Intervention	-0.0538	0.0220	-0.0968-0.0107	0.0143	

Table 22. Results of Correlation Analysis between On-target Clinical Composite Score and Process Composite Score

Outcome	Main predictor	Parameter	Estimate	SE	95% CI	P-Value	ICC
On-target clinical composite score	Process composite score	On-target clinical composite score = process-composite-diff + group + process-composite-diff * group					
		Process-composite-diff	0.1272	0.0220	0.0841-0.1703	0.0001	0.0067
		Group 1 Intervention	-0.3817	0.1237	-0.6241-0.1394	0.0020	
		Process-composite-diff*group 1 Intervention	-0.0320	0.0239	-0.0789-0.0149	0.1806	
		On-target clinical composite score = process-composite-diff + group					
		Process-composite-diff	0.1012	0.0124	0.0768-0.1255	<0.0001	0.0062
		Group 1 Intervention	-0.4385	0.1139	-0.6617-0.2153	0.0001	

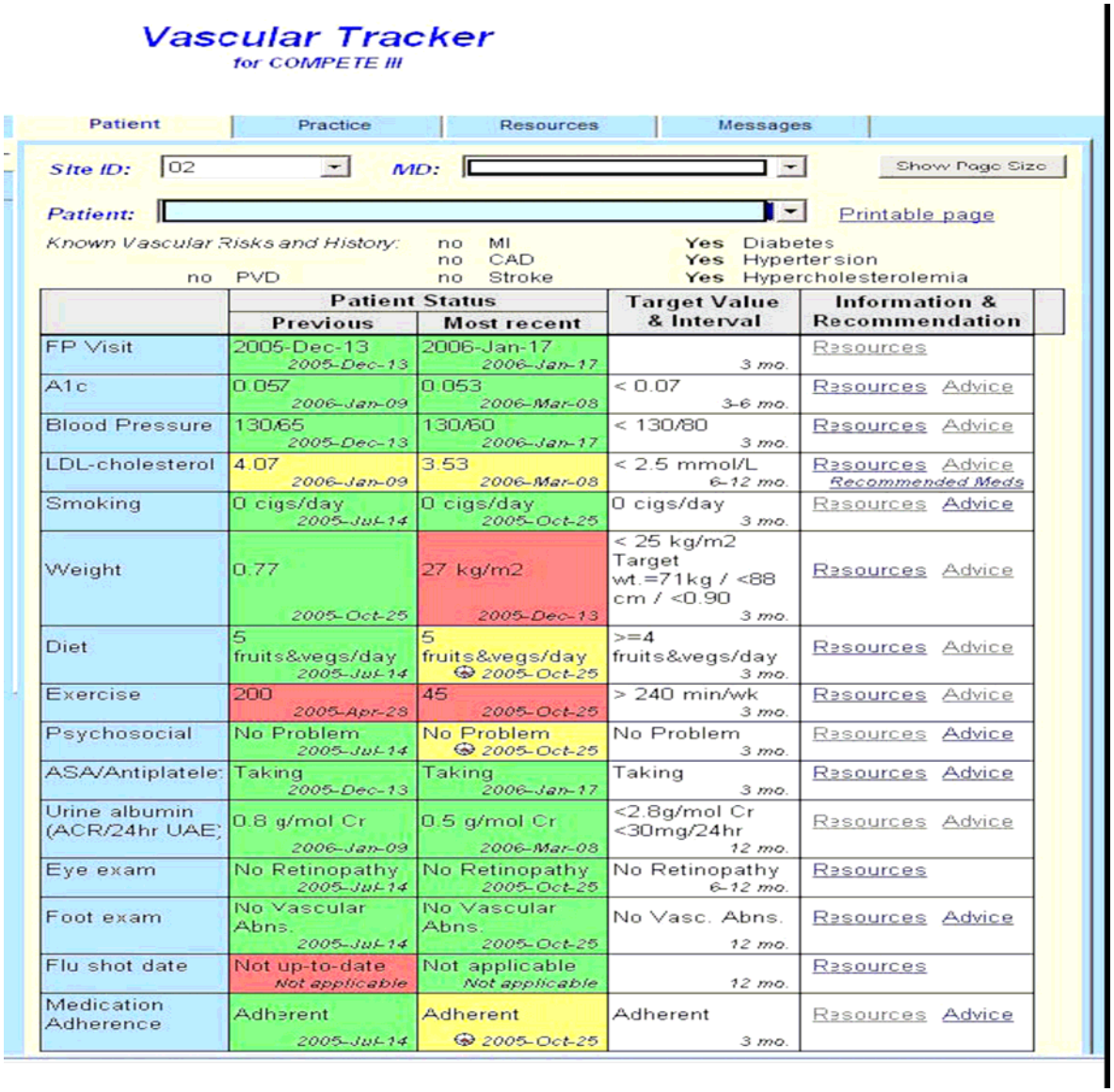
Appendix B: List of Figures

Figure 1. Flow Diagram for COMPETE III Trial



This Figure was modified from original Figure 2 in the main study of COMPETE III trial (Holbrook et al., 2011)

Figure 2. Cardiovascular Tracker for COMPETE III



Vascular Tracker
for COMPETE III

Patient | Practice | Resources | Messages

Site ID: 02 MD: Show Page Size

Patient: Printable page

Known Vascular Risks and History:

no PVD | no MI | no CAD | no Stroke | Yes Diabetes | Yes Hypertension | Yes Hypercholesterolemia

	Patient Status		Target Value & Interval	Information & Recommendation
	Previous	Most recent		
FP Visit	2005-Dec-13 *2005-Dec-13*	2006-Jan-17 *2006-Jan-17*	*3 mo.*	Resources
A1c	0.057 *2006-Jan-09*	0.053 *2006-Mar-08*	< 0.07 *3-6 mo.*	Resources Advice
Blood Pressure	130/65 *2005-Dec-13*	130/60 *2006-Jan-17*	< 130/80 *3 mo.*	Resources Advice
LDL-cholesterol	4.07 *2006-Jan-09*	3.53 *2006-Mar-08*	< 2.5 mmol/L *6-12 mo.*	Resources Advice *Recommended Meds*
Smoking	0 cigs/day *2005-Jul-14*	0 cigs/day *2005-Oct-25*	0 cigs/day *3 mo.*	Resources Advice
Weight	0.77 *2005-Oct-25*	27 kg/m2 *2005-Dec-13*	< 25 kg/m2 Target wt.=71kg / <88 cm / <0.90 *3 mo.*	Resources Advice
Diet	5 fruits&vegs/day *2005-Jul-14*	5 fruits&vegs/day *2005-Oct-25*	>=4 fruits&vegs/day *3 mo.*	Resources Advice
Exercise	200 *2005-Apr-28*	45 *2005-Oct-25*	> 240 min/wk *3 mo.*	Resources Advice
Psychosocial	No Problem *2005-Jul-14*	No Problem *2005-Oct-25*	No Problem *3 mo.*	Resources Advice
ASA/Antiplatele:	Taking *2005-Dec-13*	Taking *2006-Jan-17*	Taking *3 mo.*	Resources Advice
Urine albumin (ACR/24hr UAE)	0.8 g/mol Cr *2006-Jan-09*	0.5 g/mol Cr *2006-Mar-08*	<2.8g/mol Cr <30mg/24hr *12 mo.*	Resources Advice
Eye exam	No Retinopathy *2005-Jul-14*	No Retinopathy *2005-Oct-25*	No Retinopathy *6-12 mo.*	Resources
Foot exam	No Vascular Abns. *2005-Jul-14*	No Vascular Abns. *2005-Oct-25*	No Vasc. Abns. *12 mo.*	Resources Advice
Flu shot date	Not up-to-date *Not applicable*	Not applicable *Not applicable*	*12 mo.*	Resources
Medication Adherence	Adherent *2005-Jul-14*	Adherent *2005-Oct-25*	Adherent *3 mo.*	Resources Advice

This figure is from the main study of COMPETE III TRIAL (Holbrook et al., 2011)

Figure 3. Data Analysis Scheme

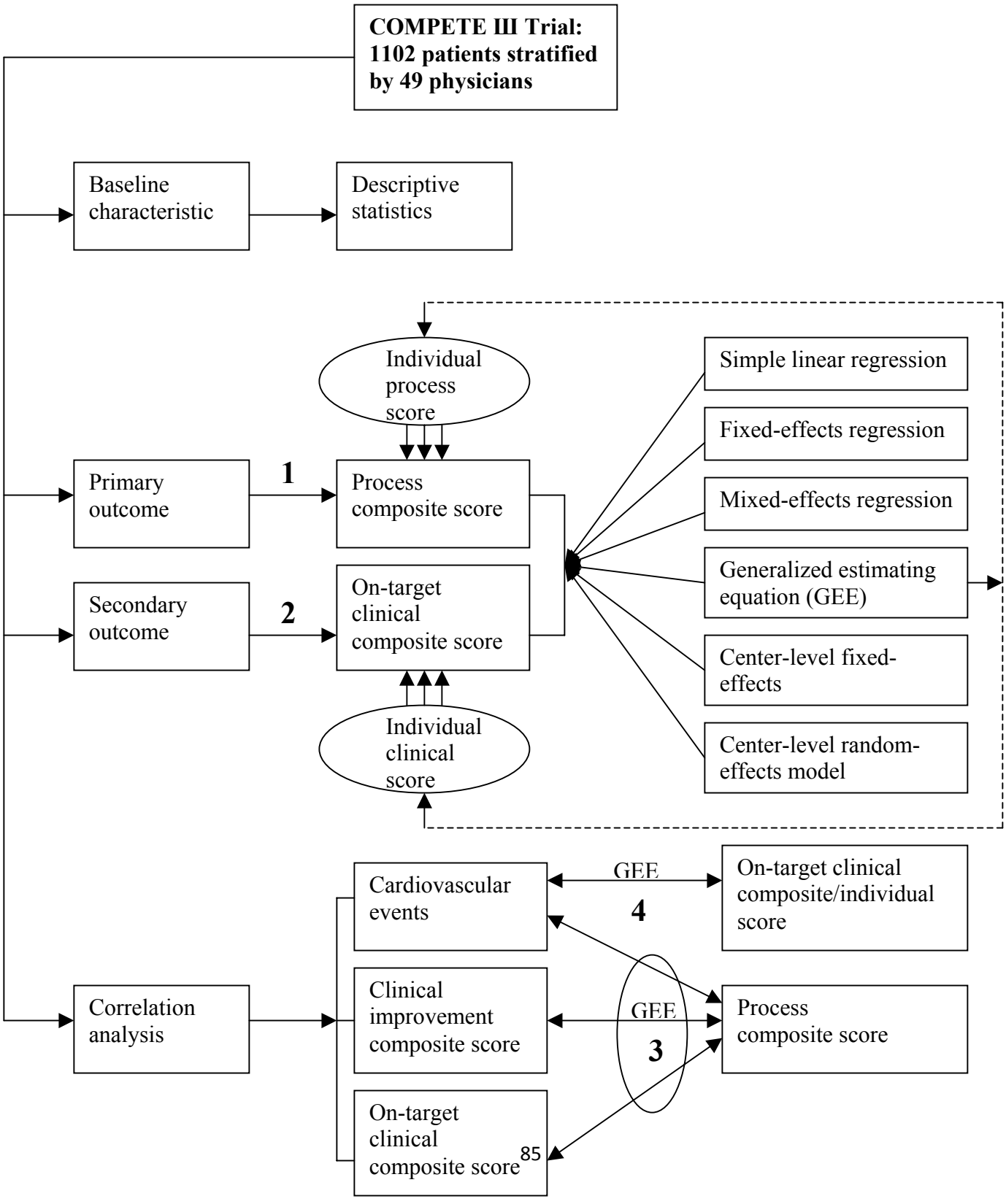


Figure 4. Impact of Intervention on Process Composite Score

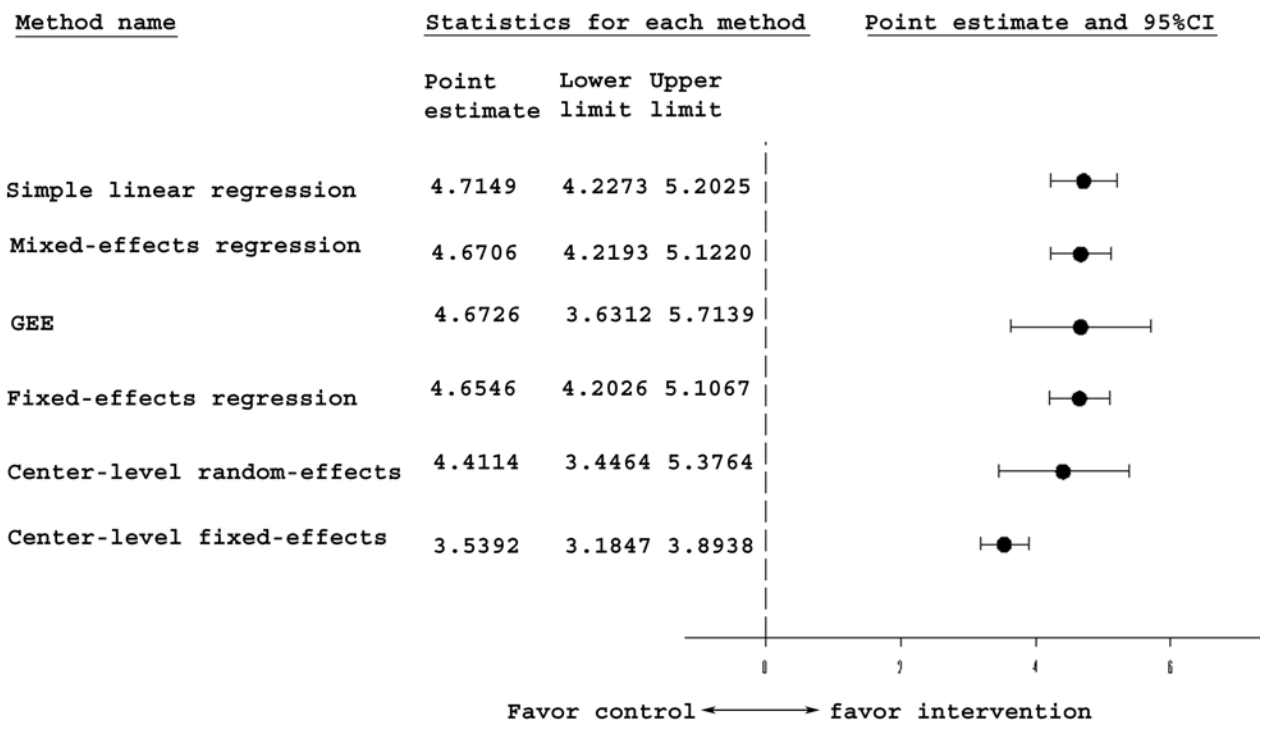


Figure 5. Impact of Intervention on Individual Component of Process Composite Score

Variable name	Statistics for each variable			Point estimate and 95% CI
	Point estimate	Lower limit	Upper limit	
Weight	0.7056	0.4735	0.9377	
Smoking	0.0280	-0.0049	0.0609	
Psychosocial	1.0120	0.7348	1.2861	
Physical exercise	0.9059	0.6698	1.1419	
LDL cholesterol	0.4931	0.4006	0.5856	
Diet	0.8766	0.6181	1.1351	
Blood pressure	0.6116	0.4588	0.7645	
ASA or equivalent	0.0503	-0.0003	0.1009	

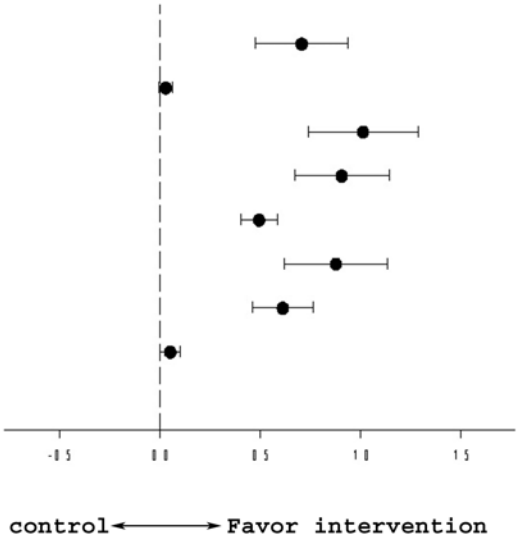


Figure 6. Impact of Intervention on Process Blood Pressure Score

Method name	Statistics for each method			Point estimate and 95%CI
	Point estimate	Lower limit	Upper limit	
Simple linear regression	0.6121	0.4617	0.7625	
Mixed-effects regression	0.6113	0.4617	0.7609	
GEE	0.6116	0.4588	0.7645	
Fixed-effects regression	0.6067	0.4574	0.7560	
Center-level random-effects	0.6203	0.4532	0.7873	
Center-level fixed-effects	0.6087	0.4684	0.7491	

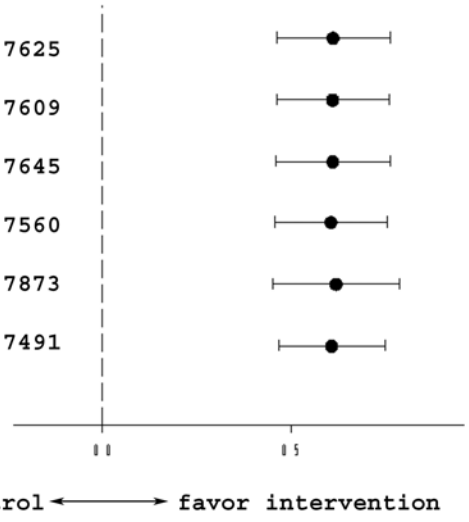


Figure 7. Impact of Intervention on On-Target Clinical Composite Score

Method name	Point estimate	Lower limit	Upper limit
Simple linear regression	0.0302	-0.1434	0.2039
Mixed-effects regression	0.0302	-0.1434	0.2040
GEE	0.0309	-0.1548	0.2166
Fixed-effects regression	0.0244	-0.1500	0.1988
Center-level random-effects	0.0148	-0.2082	0.2379
Center-level fixed-effects	-0.0016	-0.1660	0.1627

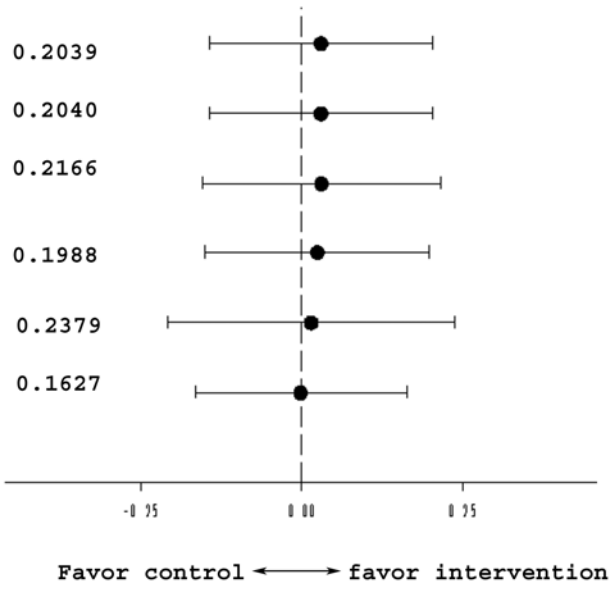
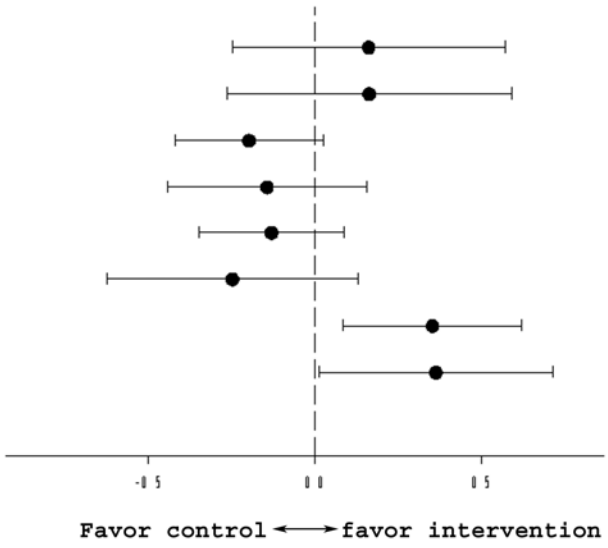


Figure 8. Impact of Intervention on Individual Component of On-Target Clinical Score

Variable name	Statistics for each variable			Point estimate and 95% CI
	Point estimate	Lower limit	Upper limit	
Weight	0.1635	-0.2462	0.5732	
Smoking	0.1654	-0.2607	0.5915	
Psychosocial	-0.1957	-0.4186	0.0272	
Physical exercise	-0.1419	-0.4393	0.1556	
LDL cholesterol	-0.1280	-0.3465	0.0905	
Diet	-0.2454	-0.6212	0.1303	
Blood pressure	0.3550	0.0866	0.6234	
ASA or equivalent	0.3653	0.0157	0.7150	



Appendix C: List of Codes

C1. Code for Data Manipulations

```
/* Code for manipulation of process individual and composite score */

%LET PATH=E:\Jian-Yi Xu\McMaster\THESIS\Thesis project\data\original data;
LIBNAME Compete3 " E:\Jian-Yi Xu\McMaster\THESIS\Thesis project\data\original
data ";
OPTIONS FMTSEARCH=(Compete3);

data compete3.process (keep=patient_cod md group process_composite_pre
process_composite_post process_composite_diff);
set Compete3.process_composite;
if process_composite_diff= . then delete;
run;

/* Compete3.process_code breaks down the patient_cod to provide site_id, md_id, and
pat_id */
data compete3.process_code;
set compete3.process;
if patient_cod < 1000000 then do;
site_id = substr (left (patient_cod), 1,1);
md_id = substr (left (patient_cod), 1,3);
pat_id = substr (left (patient_cod), 4,3);
end;
if patient_cod ge 1000000 then do;
site_id = substr (left (patient_cod), 1,2);
md_id = substr (left (patient_cod), 1,4);
pat_id = substr (left (patient_cod), 5,3);
end;

/* Converting the variables md_id and site_id from character to neumeric */
newmd_id =input (md_id, 8.0);
drop md_id;
rename newmd_id=md_id;
newsite_id =input (site_id, 8.0);
drop site_id;
rename newsite_id=site_id;
run;
proc contents data=compete3.process_code;
run;
```

```
/* Rename the compete3.process_code to compete3.process1 */
data compete3.process1;
set compete3.process_code;
run;

/* Comparing the means of two groups by t-test */
proc ttest data=compete3.process1;
class group;
var process_composite_diff;
run;

/* Comparing the means of two groups by anova */
proc anova data=compete3.process1;
class group;
model process_composite_diff = group;
run;

data compete3.process2;
set compete3.process1;
if process_composite_diff > 0;
run;
proc freq data=compete3.process2;
tables group;
run;

data compete3.process3;
set compete3.process1;
if process_composite_diff >= 3;
run;
proc freq data=compete3.process3;
tables group;
run;

data compete3.process4;
set compete3.process_composite;
if process_composite_diff= . then delete;
run;
proc freq data=compete3.process4;
tables group;
run;
proc univariate data=compete3.process4;
var process_composite_diff;
run;
```

```
proc univariate data=compete3.process4 plot;
var process_composite_diff;
run;

proc means data=compete3.process4;
class group;
var prec_sbp postc_sbp diffc_sbp
prec_ldl postc_ldl diffc_ldl
prec_weight_kg postc_weight_kg diffc_weight_kg
prec_smoking postc_smoking diffc_smoking
prec_psychosoc postc_psychosoc diffc_psychosoc
prec_exercise postc_exercise diffc_exercise
prec_diet postc_diet diffc_diet
prec_asa postc_asa diffc_asa;
run;

proc ttest data=compete3.process4;
class group;
var diffc_sbp
diffc_ldl
diffc_weight_kg
diffc_smoking
diffc_psychosoc
diffc_exercise
diffc_diet
diffc_asa;
run;

/* Converting the group from character to numerical */
data processtry;
set compete3.process4;
newgroup =input (group, 2.0);
drop group;
rename newgroup=group;
run;
proc contents data=processtry;
run;


/* Code for manipulation of on-target individual and composite score*/

%LET PATH=E:\Jian-Yi Xu\McMaster\THESIS\Thesis project\data\original data;
LIBNAME Compete3 " E:\Jian-Yi Xu\McMaster\THESIS\Thesis project\data\original
data ";
```

```
OPTIONS FMTSEARCH=(Compete3);
proc print data=Compete3.clinical_composite;
run;
proc print data=compete3.ciii_vasc_events_xu;
run;

/* Deleting five observations from analysis */
data clinical_composite1;
set compete3.clinical_composite;
if patient_cod in (103025, 201022,901038,1606007,1606018)
then delete;
run;

/* Keep variables for further processing */
data compete3.clinical_composite2 (keep=patient_cod md group
sbp_pre sbp_post
dbp_pre dbp_post
ldl_pre ldl_post
bmi_pre bmi_post
asa_pre asa_post
stress_pre stress_post
exercise_min_pre exercise_min_post
dietscore_pre dietscore_post
target_smoker_pre target_smoker_post
clinical_improvement);
set compete3.clinical_composite1;
run;

/* Converting the original data of into on-target clinical score */
data compete3.clinical_composite3;
set compete3.clinical_composite2;
newbppre=input (bppre,2.0);
if 0<sbp_pre <140 and 0<dbp_pre <90
then newbppre=1;
else newbppre=0;
drop sbp_pre dbp_pre;
rename newbppre=bppre;
newbppost=input (bppost,2.0);
if 0<sbp_post <140 and 0<dbp_post <90
then newbppost=1;
else newbppost=0;
drop sbp_post dbp_post;
rename newbppost=bppost;
newldlpre=input (ldlpre,2.0);
```

```
if 0<ldl_pre <2.5
then newldlpre=1;
else newldlpre=0;
drop ldl_pre;
rename newldlpre=ldlpre;
newldlpost=input (ldlpost,2.0);
if 0<ldl_post <2.5
then newldlpost=1;
else newldlpost=0;
drop ldl_post;
rename newldlpost=ldlpost;
newbmipre=input (bmipre,2.0);
if 0<bmi_pre <25
then newbmipre=1;
else newbmipre=0;
drop bmi_pre;
rename newbmipre=bmipre;
newbmipost=input (bmipost,2.0);
if 0<bmi_post <25
then newbmipost=1;
else newbmipost=0;
drop bmi_post;
rename newbmipost=bmipost;
newstresspre=input (stresspre,2.0);
if stress_pre >=9
then newstresspre=1;
else newstresspre=0;
drop stress_pre;
rename newstresspre=stresspre;
newstresspost=input (stresspost,2.0);
if stress_post >=9
then newstresspost=1;
else newstresspost=0;
drop stress_post;
rename newstresspost=stresspost;
newexercisepre=input (exercisepre,2.0);
if exercise_min_pre >=240
then newexercisepre=1;
else newexercisepre=0;
drop exercise_min_pre;
rename newexercisepre=exercisepre;
newexercisepost=input (exercisepost,2.0);
if exercise_min_post >=240
then newexercisepost=1;
```

```
else newexercisepost=0;
drop exercise_min_post;
rename newexercisepost=exercisepost;
newdietscorepre=input (dietscorepre,2.0);
if dietscore_pre >=8
then newdietscorepre=1;
else newdietscorepre=0;
drop dietscore_pre;
rename newdietscorepre=dietscorepre;
newdietscorepost=input (dietscorepost,2.0);
if dietscore_post >=8
then newdietscorepost=1;
else newdietscorepost=0;
drop dietscore_post;
rename newdietscorepost=dietscorepost;
newasapre =input (asapre, 2.0);
newasapre=asa_pre;
drop asa_pre;
rename newasapre=asapre;
newasapost =input (asapost, 2.0);
newasapost=asa_post;
drop asa_post;
rename newasapost=asapost;
newsmokerpre =input (smokerpre, 2.0);
newsmokerpre=target_smoker_pre;
drop target_smoker_pre;
rename newsmokerpre=smokerpre;
newsmokerpost =input (smokerpost, 2.0);
newsmokerpost=target_smoker_post;
drop target_smoker_post;
rename newsmokerpost=smokerpost;
run;

/* Transforming ASA and smoker to the same format of other variables * /
data compete3.clinical_composite4;
set compete3.clinical_composite3;
newasapre=input (asapre,2.0);
if asapre >0
then newasapre=1;
else newasapre=0;
drop asapre;
rename  newasapre=asapre;
newasapost=input (asapost,2.0);
if asapost >0
```

```
then newasapost=1;
else newasapost=0;
drop asapost;
rename  newasapost=asapost;
newsmokerpre=input (smokerpre,2.0);
if smokerpre >0
then newsmokerpre=1;
else newsmokerpre=0;
drop smokerpre;
rename  newsmokerpre=smokerpre;
newsmokerpost=input (smokerpost,2.0);
if smokerpost >0
then newsmokerpost=1;
else newsmokerpost=0;
drop smokerpost;
rename  newsmokerpost=smokerpost;
run;

/*add new variables by proper calculation statement */
data compete3.clinical_composite5;
set compete3.clinical_composite4;
bpdiff=bppost-bppre;
ldldiff=ldlpost-ldlpre;
bmidiff=bmipost-bmipre;
stressdiff=stresspost-stresspre;
exercisediff=exercisepost-exercisepre;
dietscorediff=dietscorepost-dietscorepre;
asadiff=asapost-asapre;
smokerdiff=smokerpost-smokerpre;
clinicalpre=bppre+ldlpre+bmipre+stresspre+exercisepre+
dietscorepre+asapre+smokerpre;
clinicalpost=bppost+ldlpost+bmipost+stresspost+exercisepost
+dietscorepost+asapost+smokerpost;
run;
data compete3.clinical_composite6;
set compete3.clinical_composite5;
clinicaldiff=clinicalpost-clinicalpre;
run;

proc means data=compete3.clinical_composite6;
class group;
var clinicalpre;
run;
proc means data=compete3.clinical_composite6;
```

```
class group;
var bppre;
run;
proc means data=compete3.clinical_composite6;
class group;
var ldlpre;
run;
proc means data=compete3.clinical_composite6;
class group;
var bmipre;
run;
proc means data=compete3.clinical_composite6;
class group;
var smokerpre;
run;
proc means data=compete3.clinical_composite6;
class group;
var stresspre;
run;
proc means data=compete3.clinical_composite6;
class group;
var exercisepre;
run;
proc means data=compete3.clinical_composite6;
class group;
var dietscorepre;
run;
proc means data=compete3.clinical_composite6;
class group;
var asapre;
run;


/* Code for manipulation of cardiovascular events */

data compete3.clinical_composite7;
set compete3.clinical_composite6;
length clinicalevent 8;
data compete3.clinical_composite8;
set compete3.clinical_composite7;
if patient_cod in (101002, 102020,105007,107011, 107012,108030,109006,
201011,201012,201019,
402001,402004,
501001,501021,501024,
```

```
601001,604009,604012,605009,605019,
701006,
801023,801028,801033,
901018,
1001004,1001018,
1101002,1101006,1104008,
1202032,
1401002,1401004,1401014,
1501009,
1601028,1601030,1602004,1602029,1602036,
1603014,1603033,1604008,1604018,1607007,
1607008,1608011,1609011,1609017,1609019,
1701004,1701020,
1801003,1801004,1801008,1801013,1804005)
then clinicalevent=1;
else clinicalevent=0;
run;

data compete3.clinical_composite9 (keep=patient_cod md group
bpdiff ldldiff bmidiff stressdiff
exercisediff dietscorediff asadiff smokerdiff
clinicaldiff clinicalevent
clinical_improvement);
set compete3.clinical_composite8;
run;

/* Merging process dataset and clinical dataset */
data compete3.process_composite9 (keep=patient_cod md process_composite_diff);
set compete3.process_composite;
if process_composite_diff= . then delete;
run;
data compete3.process_clinical9;
merge compete3.clinical_composite9 compete3.process_composite9;
by patient_cod;
run;
```

C2. Code for Comparison Analysis of Statistical Models

```
/* Code for process individual and composite score */

/* Simple linear regression model */
proc glm data=compete3.process4;
class group;
model process_composite_diff=group / solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group;
model diffc_sbp=group / solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group;
model diffc_ldl=group / solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group;
model diffc_weight_kg=group / solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group;
model diffc_smoking=group / solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group;
model diffc_psychosoc=group / solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group;
model diffc_exercise=group / solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group;
model diffc_diet=group / solution CLPARM;
```

```
run;
quit;
proc glm data=compete3.process4;
class group;
model diffc_asa=group / solution CLPARM;
run;
quit;

/* fixed-effects regression model */
proc glm data=compete3.process4;
class group md;
model process_composite_diff=group md /solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group md;
model diffc_sbp=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group md;
model diffc_ldl=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group md;
model diffc_weight_kg=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group md;
model diffc_smoking=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group md;
model diffc_psychosoc=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group md;
model diffc_exercise=group md/ solution CLPARM;
run;
quit;
```

```
proc glm data=compete3.process4;
class group md;
model diffc_diet=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.process4;
class group md;
model diffc_asa=group md/ solution CLPARM;
run;
quit;

/* Mixed-effects regression model */
proc mixed data=compete3.process4;
class group md;
model process_composite_diff= group /solution CL;
random md;
run;
proc mixed data=compete3.process4;
class group md;
model diffc_sbp=group / solution CL;
random md;
run;
proc mixed data=compete3.process4;
class group md;
model diffc_ldl=group / solution CL;
random md;
run;
proc mixed data=compete3.process4;
class group md;
model diffc_weight_kg=group / solution CL;
random md;
run;
proc mixed data=compete3.process4;
class group md;
model diffc_smoking=group / solution CL;
random md;
run;
proc mixed data=compete3.process4;
class group md;
model diffc_psychosoc=group / solution CL;
random md;
run;
proc mixed data=compete3.process4;
class group md;
```

```
model diffc_exercise=group / solution CL;
random md;
run;
proc mixed data=compete3.process4;
class group md;
model diffc_diet=group / solution CL;
random md;
run;
proc mixed data=compete3.process4;
class group md;
model diffc_asa=group / solution CL;
random md;
run;

/* Generalized estimating equations (GEE)*/
proc genmod data=compete3.process4;
class md group;
model process_composite_diff= group /dist=normal;
repeated subject=md /type= exch;
run;
proc genmod data=compete3.process4 descend;
class md group;
model process_composite_diff= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.process4;
class md group;
model diffc_sbp= group /link=identity dist=normal;
repeated subject=md /corr= exch corrw;
run;
proc genmod data=compete3.process4 descend;
class md group;
model diffc_sbp= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.process4;
class md group;
model diffc_ldl= group /dist=normal;
repeated subject=md /type= exch;
run;
proc genmod data=compete3.process4 descend;
class md group;
model diffc_ldl= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
```

```
run;
proc genmod data=compete3.process4;
class md group;
model diffc_weight_kg= group /dist=normal;
repeated subject=md /type= exch;
run;
proc genmod data=compete3.process4 descend;
class md group;
model diffc_weight_kg= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.process4;
class md group;
model diffc_smoking= group /dist=normal;
repeated subject=md /type= exch;
run;
proc genmod data=compete3.process4 descend;
class md group;
model diffc_smoking= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.process4;
class md group;
model diffc_psychosoc= group /dist=normal;
repeated subject=md /type= exch;
run;
proc genmod data=compete3.process4 descend;
class md group;
model diffc_psychosoc= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.process4;
class md group;
model diffc_exercise= group /dist=normal;
repeated subject=md /type= exch;
run;
proc genmod data=compete3.process4 descend;
class md group;
model diffc_exercise= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.process4;
class md group;
model diffc_diet= group /dist=normal;
```

```
repeated subject=md /type= exch;
run;
proc genmod data=compete3.process4 descend;
class md group;
model diffc_diet= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.process4;
class md group;
model diffc_asa= group /dist=normal;
repeated subject=md /type= exch;
run;
proc genmod data=compete3.process4 descend;
class md group;
model diffc_asa= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;

/* Calculating mean and sd by md and group to be used
 by two center-level regression analysis */
data compete3.process5(keep=patient_cod md group
prec_sbp postc_sbp diffc_sbp
prec_ldl postc_ldl diffc_ldl
prec_weight_kg postc_weight_kg diffc_weight_kg
prec_smoking postc_smoking diffc_smoking
prec_psychosoc postc_psychosoc diffc_psychosoc
prec_exercise postc_exercise diffc_exercise
prec_diet postc_diet diffc_diet
prec_asa postc_asa diffc_asa
process_composite_diff);
set Compete3.process_composite;
if process_composite_diff= . then delete;
run;
proc contents data=compete3.process5;
run;
proc means data=compete3.process5;
class md group;
var process_composite_diff;
run;
proc means data=compete3.process5;
class md group;
var diffc_sbp;
run;
proc means data=compete3.process5;
```

```
class md group;
var diffc_ldl;
run;
proc means data=compete3.process5;
class md group;
var diffc_weight_kg;
run;
proc means data=compete3.process5;
class md group;
var diffc_smoking;
run;
proc means data=compete3.process5;
class md group;
var diffc_psychosoc;
run;
proc means data=compete3.process5;
class md group;
var diffc_exercise;
run;
proc means data=compete3.process5;
class md group;
var diffc_diet;
run;
proc means data=compete3.process5;
class md group;
var diffc_asa;
run;

/* Center- level fixed-effects model and random-effects model(R code) */
compete<-read.csv(file= "E:\\Jian-Yi XU\\Compete\\process\\compete3.csv", header =
TRUE)
f5<-metacont(aggrdat[1:4,2], aggrdat[1:4,3],aggrdat[1:4,4],aggrdat[1:4,5],
aggrdat[1:4,6],aggrdat[1:4,7], sm="WMD")
f5$TE.fixed,f5$seTE.fixed,f5$TE.random,f5$seTE.random
f5<-metacont(n.e, mean.e, sd.e, n.c, mean.c, sd.c, data=compete, sm="MD")
<-summary(f5)
<-f5$TE.fixed;f5$seTE.fixed;f5$TE.random;f5$seTE.random


/* Codes for on-target clinical individual and composite score */

/* Simple linear regression * /
proc glm data=compete3.clinical_composite6;
class group;
```

```
model clinicaldiff=group / solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group;
model bpdiff=group / solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group;
model ldldiff=group / solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group;
model bmidiff=group / solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group;
model smokerdiff=group / solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group;
model stressdiff=group / solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group;
model exercisediff=group / solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group;
model dietscorediff=group / solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group;
model asadiff=group / solution CLPARM;
run;
quit;
```

```
/* Fixed-effects regression model */
proc glm data=compete3.clinical_composite6;
class group md;
model clinicaldiff=group md /solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group md;
model bpdiff=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group md;
model ldldiff=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group md;
model bmidiff=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group md;
model smokerdiff=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group md;
model stressdiff=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group md;
model exercisediff=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group md;
model dietscorediff=group md/ solution CLPARM;
run;
quit;
proc glm data=compete3.clinical_composite6;
class group md;
model asadiff=group md/ solution CLPARM;
```

```
run;
quit;

/* Mixed-effects regression model * /
proc mixed data=compete3.clinical_composite6;
class group md;
model clinicaldiff= group /solution CL;
random md;
run;
proc mixed data=compete3.clinical_composite6;
class group md;
model bpdiff=group / solution CL;
random md;
run;
proc mixed data=compete3.clinical_composite6;
class group md;
model ldldiff=group / solution CL;
random md;
run;
proc mixed data=compete3.clinical_composite6;
class group md;
model bmidiff=group / solution CL;
random md;
run;
proc mixed data=compete3.clinical_composite6;
class group md;
model smokerdiff=group / solution CL;
random md;
run;
proc mixed data=compete3.clinical_composite6;
class group md;
model stressdiff=group / solution CL;
random md;
run;
proc mixed data=compete3.clinical_composite6;
class group md;
model exercisediff=group / solution CL;
random md;
run;
proc mixed data=compete3.clinical_composite6;
class group md;
model dietscorediff=group / solution CL;
random md;
run;
```

```
proc mixed data=compete3.clinical_composite6;
class group md;
model asadiff=group / solution CL;
random md;
run;

/* Generalized estimating equations (GEE)* /
proc genmod data=compete3.clinical_composite6;
class md group;
model clinicaldiff= group /dist=normal;
repeated subject=md /type= exch corrw;
run;
proc genmod data=compete3.clinical_composite6;
class md group;
model bpdiff= group /dist=normal;
repeated subject=md /type= exch corrw;
run;
proc genmod data=compete3.clinical_composite6 descend;
class md group;
model bpdiff= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.clinical_composite6;
class md group;
model ldldiff= group /dist=normal;
repeated subject=md /type= exch corrw;
run;
proc genmod data=compete3.clinical_composite6 descend;
class md group;
model ldldiff= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.clinical_composite6;
class md group;
model bmidiff= group /dist=normal;
repeated subject=md /type= exch corrw;
run;
proc genmod data=compete3.clinical_composite6 descend;
class md group;
model bmidiff= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;

proc genmod data=compete3.clinical_composite6;
```

```
class md group;
model smokerdiff= group /dist=normal;
repeated subject=md /type= exch corrw;
run;
proc genmod data=compete3.clinical_composite6 descend;
class md group;
model smokerdiff= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.clinical_composite6 descend;
class md group;
model smokerdiff= group /link=logit Dist=bin;
repeated subject=md /corr=exch corrw;
run;
proc genmod data=compete3.clinical_composite6;
class md group;
model stressdiff= group /dist=normal;
repeated subject=md /type= exch corrw;
run;
proc genmod data=compete3.clinical_composite6 descend;
class md group;
model stressdiff= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.clinical_composite6;
class md group;
model exercisediff= group /dist=normal;
repeated subject=md /type= exch corrw;
run;
proc genmod data=compete3.clinical_composite6 descend;
class md group;
model exercisediff= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
proc genmod data=compete3.clinical_composite6;
class md group;
model dietscorediff= group /dist=normal;
repeated subject=md /type= exch corrw;
run;
proc genmod data=compete3.clinical_composite6 descend;
class md group;
model dietscorediff= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;
```

```
proc genmod data=compete3.clinical_composite6;
class md group;
model asadiff= group /dist=normal;
repeated subject=md /type= exch corrw;
run;
proc genmod data=compete3.clinical_composite6 descend;
class md group;
model asadiff= group /link=cumlogit  dist=mult;
repeated subject=md /corr= indep corrw;
run;

/* Calculating for two center-level regression model */
proc means data=compete3.clinical_composite6;
  class md group;
  var clinicaldiff;
run;
proc means data=compete3.clinical_composite6;
  class md group;
  var bpdiff;
run;
proc means data=compete3.clinical_composite6;
  class md group;
  var ldldiff;
run;
proc means data=compete3.clinical_composite6;
  class md group;
  var bmidiff;
run;
proc means data=compete3.clinical_composite6;
  class md group;
  var smokerdiff;
run;
proc means data=compete3.clinical_composite6;
  class md group;
  var stressdiff;
run;
proc means data=compete3.clinical_composite6;
  class md group;
  var exercisediff;
run;
proc means data=compete3.clinical_composite6;
  class md group;
  var dietscorediff;
run;
```

```
proc means data=compete3.clinical_composite6;
  class md group;
  var asadiff;
run;

/* Center- level fixed-effects model and random-effects model(R code) */
compete<-read.csv(file= "E:\\Jian-Yi XU\\Compete\\clinical\\compete3.csv", header =
TRUE)
f5<-metacont(aggrdat[1:4,2], aggrdat[1:4,3],aggrdat[1:4,4],aggrdat[1:4,5],
aggrdat[1:4,6],aggrdat[1:4,7], sm="WMD")
f5$TE.fixed,f5$seTE.fixed,f5$TE.random,f5$seTE.random
f5<-metacont(n.e, mean.e, sd.e, n.c, mean.c, sd.c, data=compete, sm="MD")
<-summary(f5)
<-f5$TE.fixed;f5$seTE.fixed;f5$TE.random;f5$seTE.random
```

C3. Code for Correlation Analysis between the Clinical Outcomes and Surrogate Composite Scores

```
/* Clinical events correlation with clinicaldiff */
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = clinicaldiff group clinicaldiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = clinicaldiff group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md;
model clinicalevent = clinicaldiff /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;

proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = bpdiff group bpdiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = bpdiff bpdiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md;
model clinicalevent = bpdiff/link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;

proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = ldldiff group ldldiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
```

```
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = ldldiff ldldiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md;
model clinicalevent = ldldiff/link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;

proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = bmidiff group bmidiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = bmidiff bmidiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md;
model clinicalevent = bmidiff/link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;

proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = stressdiff group stressdiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = stressdiff stressdiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md;
model clinicalevent = stressdiff/link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;

proc genmod data=compete3.process_clinical9 descend;
```

```
class md group;
model clinicalevent = exercisediff group exercisediff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = exercisediff group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md;
model clinicalevent = exercisediff/link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;

proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = dietscorediff group dietscorediff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = dietscorediff dietscorediff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md;
model clinicalevent = dietscorediff/link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;

proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = asadiff group asadiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent =  asadiff asadiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md;
model clinicalevent =  asadiff/link=logit Dist=bin;
```

```
repeated subject=md/corr=exch corrw;
run;

proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = smokerdiff group smokerdiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md group;
model clinicalevent = smokerdiff smokerdiff*group /link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9 descend;
class md;
model clinicalevent = smokerdiff/link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;

/* Clinical events correlation with process_composite_diff */
proc genmod data=compete3.process_clinical9;
class md group;
model clinicalevent = process_composite_diff group process_composite_diff*group
/link=logit Dist=bin;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9;
class md group;
model clinicalevent = process_composite_diff process_composite_diff*group /link=logit
Dist=bin;
repeated subject=md/corr=exch corrw;
run;

/* Clinical-improvement composite score correlation with process_composite_diff */
proc genmod data=compete3.process_clinical9;
class md group;
model clinical_improvement = process_composite_diff group
process_composite_diff*group /dist=nor link=identity;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9;
class md group;
model clinical_improvement = process_composite_diff process_composite_diff*group
/dist=nor link=identity;
```

```
repeated subject=md/corr=exch corrw;
run;

/* On-target clinical composite score correlation with process_composite_diff */
proc genmod data=compete3.process_clinical9;
class md group;
model clinicaldiff = process_composite_diff group process_composite_diff*group
/dist=nor link=identity;
repeated subject=md/corr=exch corrw;
run;
proc genmod data=compete3.process_clinical9;
class md group;
model clinicaldiff = process_composite_diff group /dist=nor link=identity;
repeated subject=md/corr=exch corrw;
run;
```

C4. Code for Forest Plots

```
data test;
input method $ 1-30 lower_limit estimate upper_limit;
datalines;
Simple linear regression          4.2273  4.7149  5.2025
Fixed-effects regression          4.2026  4.6546  5.1067
Mixed-effects regression          4.2193  4.6706  5.1220
GEE                               3.6312  4.6726  5.7139
Center-level fixed-effects        3.1847  3.5392  3.8938
Center-level random-effects       3.4464  4.4114  5.3764
;
run;
length function style color $8;
retain xsys ysys '2' when 'a';
set test;
function='move'; xsys='2'; ysys='2'; yc=method; x=lower_limit; color='black'; output;
function='draw'; x=upper_limit; color='black'; size=1; output;
function='move';xsys='2'; ysys='2';yc=method; x=lower_limit; color='black'; output;
function='draw';x=lower_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=lower_limit; y=-2; size=1;output;
function='move';xsys='2'; ysys='2'; yc=method; x=upper_limit; color='black'; output;
function='draw';x=upper_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=upper_limit; y=-2; size=1; output;
run;
axis1 label=none
minor=none
offset=(5,5);
axis2 order=(-2 to 8 by 2)
label=('Mean')
minor=none;
symbol1 interpol=none color=black value=dot height=1.5;
proc gplot data=test;
plot method*estimate / annotate=anno
nolegend
vaxis=axis1
haxis=axis2
href = 0
lhref = 2;
run;
quit;

data test;
```

```
input method $ 1-30 lower_limit estimate upper_limit;
datalines;
Weight                  0.4735   0.7056     0.9377
Smoking                -0.0049   0.0280     0.0609
Psychosocial            0.7388   1.0120     1.2861
Physical exercise       0.6698   0.9059     1.1419
LDL-cholesterol         0.4006   0.4931     0.5856
Diet                    0.6181   0.8766     1.1351
Blood pressure          0.4588   0.6116     0.7645
ASA                    -0.0003   0.0503     0.1009
;
run;
data anno;
length function style color $8;
retain xsys ysys '2' when 'a';
set test;
function='move'; xsys='2'; ysys='2'; yc=method; x=lower_limit; color='black'; output;
function='draw'; x=upper_limit; color='black'; size=1; output;
function='move';xsys='2'; ysys='2';yc=method; x=lower_limit; color='black'; output;
function='draw';x=lower_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=lower_limit; y=-2; size=1;output;
function='move';xsys='2'; ysys='2'; yc=method; x=upper_limit; color='black'; output;
function='draw';x=upper_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=upper_limit; y=-2; size=1; output;
run;
axis1 label=none
minor=none
offset=(5,5);
axis2 order=(-0.5 to 0.5 by 0.25)
label=('Mean')
minor=none;
symbol1 interpol=none color=black value=dot height=1.5;
proc gplot data=test;
plot method*estimate / annotate=anno
nolegend
vaxis=axis1
haxis=axis2
href = 0
lhref = 2;
run;
quit;


goptions reset=all cback=white border htitle=12pt htext=10pt;
```

```
data test;
input method $ 1-30 lower_limit estimate upper_limit;
datalines;
Simple linear regression          0.4617  0.6121  0.7625
Fixed-effects regression          0.4574  0.6067  0.7560
Mixed-effects regression          0.4617  0.6113  0.7609
GEE                               0.4588  0.6116  0.7645
Center-level fixed-effects        0.4684  0.6087  0.7491
Center-level random-effects       0.4532  0.6203  0.7873
;
run;
data anno;
length function style color $8;
retain xsys ysys '2' when 'a';
set test;
function='move'; xsys='2'; ysys='2'; yc=method; x=lower_limit; color='black'; output;
function='draw'; x=upper_limit; color='black'; size=1; output;
function='move';xsys='2'; ysys='2';yc=method; x=lower_limit; color='black'; output;
function='draw';x=lower_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=lower_limit; y=-2; size=1;output;
function='move';xsys='2'; ysys='2'; yc=method; x=upper_limit; color='black'; output;
function='draw';x=upper_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=upper_limit; y=-2; size=1; output;
run;
axis1 label=none
minor=none
offset=(5,5);
axis2 order=(-2 to 8 by 2)
label=('Mean')
minor=none;
symbol1 interpol=none color=black value=dot height=1.5;
proc gplot data=test;
plot method*estimate / annotate=anno
nolegend
vaxis=axis1
haxis=axis2
href = 0
lhref = 2;
run;
quit;

data test;
input method $ 1-30 lower_limit estimate upper_limit;
```

```
datalines;
Simple linear regression          -0.14341   0.03027   0.20396
Fixed-effects regression          -0.15002   0.02442   0.19887
Mixed-effects regression          -0.1434    0.03028   0.2040
GEE                               -0.1548    0.0309    0.2166
Center-level fixed-effects        -0.1660   -0.00166   0.1627
Center-level random-effects       -0.2082    0.01482   0.2379
;
run;
data anno;
length function style color $8;
retain xsys ysys '2' when 'a';
set test;
function='move'; xsys='2'; ysys='2'; yc=method; x=lower_limit; color='black'; output;
function='draw'; x=upper_limit; color='black'; size=1; output;
function='move';xsys='2'; ysys='2';yc=method; x=lower_limit; color='black'; output;
function='draw';x=lower_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=lower_limit; y=-2; size=1;output;
function='move';xsys='2'; ysys='2'; yc=method; x=upper_limit; color='black'; output;
function='draw';x=upper_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=upper_limit; y=-2; size=1; output;
run;
axis1 label=none
minor=none
offset=(5,5);
axis2 order=(-0.5 to 0.5 by 0.25)
label=('Mean')
minor=none;
symbol1 interpol=none color=black value=dot height=1.5;
proc gplot data=test;
plot method*estimate / annotate=anno
nolegend
vaxis=axis1
haxis=axis2
href = 0
lhref = 2;
run;
quit;

data test;
input method $ 1-30 lower_limit estimate upper_limit;
datalines;
Weight                          -0.2462   0.1635    0.5732
Smoking                         -0.2607   0.1654    0.5915
```

```
Psychosocial              -0.4186   -0.1957   0.0272
Physical exercise         -0.4393   -0.1419   0.1556
LDL-cholesterol           -0.3465   -0.1280   0.0905
Diet                      -0.6212   -0.2454   0.1303
Blood pressure             0.0866    0.3550   0.6234
ASA                        0.0157    0.3653   0.7150
;
run;
data anno;
length function style color $8;
retain xsys ysys '2' when 'a';
set test;
function='move'; xsys='2'; ysys='2'; yc=method; x=lower_limit; color='black'; output;
function='draw'; x=upper_limit; color='black'; size=1; output;
function='move';xsys='2'; ysys='2';yc=method; x=lower_limit; color='black'; output;
function='draw';x=lower_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=lower_limit; y=-2; size=1;output;
function='move';xsys='2'; ysys='2'; yc=method; x=upper_limit; color='black'; output;
function='draw';x=upper_limit; ysys='9'; y=+1; size=1; output;
function='draw';x=upper_limit; y=-2; size=1; output;
run;
axis1 label=none
minor=none
offset=(5,5);
axis2 order=(-0.5 to 0.5 by 0.25)
label=('Mean')
minor=none;
symbol1 interpol=none color=black value=dot height=1.5;
proc gplot data=test;
plot method*estimate / annotate=anno
nolegend
vaxis=axis1
haxis=axis2
href = 0
lhref = 2;
run;
quit;
```