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A Multivariate Distance-based Analytic Framework for Microbial Interdependence Association Test in Longitudinal Study

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Abstract

Human microbiome is the collection of microbes living in and on the various parts of our body. The microbes living on our body in nature do not live alone. They act as integrated microbial community with massive competing and cooperating and contribute to our human health in a very important way. Most current analyses focus on examining microbial differences at a single time point, which do not adequately capture the dynamic nature of the microbiome data. With the advent of high-throughput sequencing and analytical tools, we are able to probe the interdependent relationship among microbial species through longitudinal study. Here we propose a multivariate distance-based test to evaluate the association between key phenotypic variables and microbial interdependence utilizing the repeatedly measured microbiome data. Extensive simulations were performed to evaluate the validity and efficiency of the proposed method. We also demonstrate the utility of the proposed test using a well-designed longitudinal murine experiment and a longitudinal human study. The proposed methodology has been implemented in the freely distributed open-source R package and Python code.

Keywords

longitudinal data; MANOVA; microbial interdependence; nonparametric test

Introduction

The human body harbors a huge and complex microbial ecosystem, called the human microbiome. Within a microbial community, a vast number of species do not exist in isolation but instead form complex ecological interaction webs [Faust et al., 2012]. Some

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Web Resources

The methods/approaches (NMIT) described in this paper are implemented for the R computing environment. Further information on the software package, NMIT, as well as the python code can be found at <https://sites.google.com/site/huilinli09/software>.

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microbial species may compete for space and resources, and some may have mutualistic interactions involving exchange of metabolic products with mutual benefit. However such microbial interrelationship is not static and it can be changed by many factors such like diet, drugs, and the environment etc. For example, antibiotic-altered murine microbiota show differences in dynamic colonization patterns compared to that from untreated controls; such altered patterns can be linked to developmental differences [Cox et al., 2014]. Considering the shifts in microbial community structure have been recently associated with human diseases including inflammatory bowel disease, diabetes mellitus, obesity and cancer etc. [Larsen et al., 2010; Turnbaugh et al., 2006, 2009; Wu et al., 2010], it is of great interest to study and develop statistical methods to compare microbial interdependence structures between groups and check its association with a continuous marker.

Compared with a cross-sectional study, which can only detect the relative location (i.e. distance) differences in microbial abundances between groups at a specific time, a longitudinal study provides the opportunity to identify differences in microbial interdependent relationships between groups over time. Such analysis is essential to study interdependence between species and to further understand the biological mechanisms underlying responses to environmental factors and diseases. However, most longitudinal microbiome studies employ static [Cho et al., 2012; Cox et al., 2014; Nobel et al., 2015; Wu et al., 2016], rather than dynamic analytical techniques. To compare changing trends of microbial structure between groups at each time point, the data are first displayed using a principal coordinate analysis (PCoA) plot. Then a distance-based method, permutation MANOVA [Anderson, 2001; McArdle & Anderson, 2001; Tang et.al 2016] is usually adopted to evaluate the association between the overall microbiome composition and the outcome of interest at each time point. However, those analyses do not adequately capture the dynamic nature of data by ignoring inherent ordering and other temporal dependencies.

Recently, with the need in studying the health relevant temporal dynamics of host-associated microbial communities (the microbiota) [Buffie et al., 2012; Cho et al., 2012; Cox et al., 2014], several new statistical methods have been proposed. Bucci et al., [2016] proposed a suite of Bayesian algorithm for inferring dynamical systems models from time-series data and predicting temporal behaviors. Xia et al. [2013] developed a theoretical approach to approximate the statistical significances of local similarity analysis of biological time series data. Trosvik et al. [2015] inferred the biotic interaction using time series regression model based on simple linear regression or generalized additive model in analyzing human gastrointestinal microbiota time series data. However, those methods are all working on the high frequent time series of microbial data and are subject to the irregular sampling times and complicated modeling and implementation. Chen and Li [2016] proposed a two-part mixed effects Beta regression model to identify taxa that are associated with phenotypes. Although this method deals with the longitudinal data which have less frequent sampling time points, similar to the aforementioned methods, they focus on the temporal pattern of single bacteria species and never intend on studying the interdependence of the microbial species.

In this paper, we propose a novel method to test how interdependence of microbial species within a community might differ between groups over time, or how these might be

associated by continuous environmental factors, such as a drug or diet. Our method is simple and powerful based on a multivariate distance-based non-parametric test. It has two major steps: firstly, we capture the individual microbial dependencies over time by performing pair-wise correlation analysis within each subject using the longitudinal microbial measurements. Then, we test whether the correlation structure is different between groups or associated with an interested outcome or not using permutation MANOVA [Anderson, 2001; McArdle & Anderson, 2001; Tang et.al 2016]. Network analysis is used to visualize microbial dependency in different groups, and a heatmap is used to visualize the results of the temporal correlation structure differences between groups.

The paper is organized as follows. In the Method Section, we describe the data structure and the proposed test. In the Results Section, we illustrate the performance of the test by real data examples and simulations. Discussion Section provides conclusions for the paper. Technical details and more simulation results are in the supplemental materials.

Method

For simplicity, we illustrate our method in a simplified longitudinal study design, i.e. the repeated microbial observations are made at the same time points for all subjects. However our method can be directly extended to more complicated observational studies with unbalanced study design and missing observations for some subjects. In a study, suppose we have obtained the relative abundance of N subjects for K taxa over J time points. For the i^{th} subject at time j , let $\mathbf{Y}_{ij} = (y_{ij1}, \dots, y_{ijK})^T$ denote the relative abundances of K taxa. Let $\mathbf{X}_i = (x_{i1}, \dots, x_{ip})$ denote p covariates collected for subject i . These covariates could be binary outcome (e.g. disease status, gender or case-control group indicator), or disease-associated quantitative variables (e.g. age, BMI, blood pressure or biomarker measurement). Our goal is to test the association between the temporal microbial interdependence profiles and the covariates of interest.

We propose to first capture the interdependence profile for each subject by a $K \times K$ pair-wised taxa correlation matrix for each subject. Specifically, we let $\mathbf{U}_i = \{u_{i;k,k'}\}_{k,k'=1}^K$ denote the $K \times K$ temporal correlation matrix of subject i . Here the element $u_{i;k,k'}$ is the temporal correlation between taxa k and k' . Note that since the interdependence correlation matrix is calculated based on the repeated microbiome measurements within each subject, it is not affected by the different time points across subjects or missing observations for some subjects. In the second step, we calculate the distance matrix $\mathbf{D} = \{d_{ii'}\}_{i,i'=1}^N$ which measures the temporal correlation distance between subjects i and i' . We then compare these distances among subjects in the same group with those in the different groups using permutation MANOVA to infer the group difference in term of microbial interdependence profile.

The core part of the proposed test is to construct the correlation matrix for each subject to summarize their microbial interdependent correlation structures using the repeatedly measured microbiome data. We evaluate the following three correlation methods within the test frame proposed here, while considering the unique microbiome data structure. They are

1) Pearson correlation, 2) Kendall's rank correlation, and 3) maximal information coefficient (MIC) [Reshef et al., 2011].

Pearson correlation is widely used to evaluate the linear association between two random variables. Considering the spurious correlation with compositional data [Pearson, 1896; Ranganatha and Borges, 2011], the following centered log ratio (clr) transformation suggested by Aitchison [Aitchison, 2003] is usually implemented first in order to remove the possible compositional effect:

$$\text{clr}(z) = (\ln \frac{z_1}{g(z)}, \dots, \ln \frac{z_K}{g(z)}),$$

where $z = (z_1, \dots, z_K)$ denotes a vector of relative abundance for K taxa and

$g(z) = (\prod_{k=1}^K z_k)^{1/K}$ is the geometric mean of z . However, we do not suggest this transformation in the proposed test, because the correlation is calculated between any pair of taxa using the microbiome measurements at the multiple time points within each subject. The geometric mean function in the above transformation varies across different time points and doing the transformation at each time point independently will contaminate the original correlation. The spurious correlation concern is originated in the ecology studies, in which the dimension of the data is relatively low. However, in the microbiome studies, the number of taxa is usually large. Since when the diversity of the samples is large, the compositional effect such as the spurious correlation is mild [Fridman and Alm 2012], we suggest using the original abundance data to calculate the interspecies correlations.

Considering the possibility of the nonlinear association among microbial species, the non-parametric Kendall's rank correlation based on rank instead of value is another candidate. The third correlation method is the recently developed maximal information coefficient (MIC) method [Reshef et al., 2011] which measures how much information two random variables share. This correlation method is claimed to be able to capture both linear and nonlinear associations between two continuous variables. Although several microbiome studies have used MIC to capture the correlations between taxa [Cho and Blaser, 2012; Maurice et al., 2013; Pinto et al., 2014], it was only used in cross-sectional studies. Here we use MIC to construct a temporal microbial correlation network.

There are many ways to calculate the distance of two correlation matrices. For example, the

Frobenius norm defined as $d_{ii} = K^{-1} \sqrt{\sum_{k=1}^K \sum_{k'=1}^K (u_{i;k,k'} - u_{i';k,k'})^2}$ is one commonly used distance. The other distance metrics considered in our simulations are listed in the supplemental material. With any predetermined distance metric, the permutation MANOVA test is used to evaluate whether the distances between subjects within groups are shorter than the distances between subjects across groups. Specifically let $X = (X_1, \dots, X_N)^T$ be the $N \times p$ covariate matrix, then the projection matrix $H = X(X^T X)^{-1} X^T$ and the centroid matrix $G = (I - 11^T/n)A(1 - 11^T/n)$, in which A is the adjacent matrix of D defined as

$A = \{a_{ii}\} = \{-d_{ii}^2/2\}$, $i=1, \dots, N$, I is an $N \times N$ identity matrix and $\mathbf{1}$ is an N by 1 vector with all elements being 1. The pseudo-F statistics can be constructed as

$$F = \frac{\text{tr}(HGH)}{\text{tr}[(I - H)G(I - H)]}.$$

Here $\text{tr}(\cdot)$ is the trace of a matrix. Given the difficulty to investigate the null distribution of the pseudo-F statistics, permutation strategy is usually used to assess the statistical significance (the detailed permutation strategy is provided in supplemental material). This test has been widely adopted in the metagenomics community to analyze single time microbial location differences and in the genetic literature as well [Reiss, et al., 2010]. Here we provide a framework to apply it to capture the overall microbial interdependence group differences over time. Because the proposed test provides a nonparametric group comparison for microbial interdependence, we term our proposed test as the Non-parametric Microbial Interdependence Test (NMIT). In Figure 3, we illustrate the detailed structured instruction on how to implement NMIT using a real example.

Results

We first illustrate our proposed method using two real longitudinal microbiome studies: the longitudinal murine study and early childhood antibiotics and the microbiome (ECAM) study in the Real Data Analyses subsection. Then based on the parameters estimated in the longitudinal murine study, we conducted a comprehensive simulation study to further evaluate the performance of our method. The simulation method and the results are presented in the Simulation subsection.

Real Data Analyses

Longitudinal Murine Study—Cox et al. [2014] conducted a longitudinal murine study to examine the effect of low-dose penicillin (LDP) on the relationships that involve gut microbiota structure and metabolic phenotypes. Here, we re-examine a small portion of its studies to address whether the microbial structure in the LDP treated group presents a different microbial interdependence profile from that in the control group. In this study, cecal microbiota collected from conventional control or from LDP-treated mice was transferred to two groups of germ-free mice, respectively. Fecal samples were collected from 7 control microbiota-recipient mice and 8 LDP microbiota-recipient mice at days 2, 6, 9, 14, 21, 28, and 34 after the transfer. The microbial populations were analyzed on the basis of the 16S rRNA gene V4 region sequences using the Illumina MiSeq platform. We denote those two groups of mice as Control and LDP respectively in the following text. Originally, there are 342 genus level taxa, but our analysis focuses on 34 prevalent taxa with relative abundance $>0.1\%$ in $\geq 20\%$ of all samples (across 15 mice over 7 time points).

The mean relative abundances of the major genus-level taxa in Control and LDP groups over time are presented in Figure 1. Visually we can observe the different dynamic changes of the gut microbial community between two groups. In the original analyses [Cox et al., 2014], the different microbial structures between the groups were explored using PCoA at

individual time points, which could only confirm the group differences in the microbiome profiles at each time point. We hypothesize that prior antibiotic exposure (in the LDP microbiota) disturbed the microbial interdependence structure following the transfer and colonization of the new hosts. In Figure 2 we present the group microbial interdependence relationship in Control and LDP groups separately using the correlation networks. For each subject, the pair-wised correlation matrix on 34 selected major taxa is first calculated. Then in the networks, each taxon $i=1, \dots, 34$ is a node. If the absolute correlation between any two taxa is greater than 0.6 in at least 50% subjects within the group, the two nodes are connected by an edge. From the figure, we can see Control group has more correlated temporal interdependent structure than LDP group. Whereas there is a prominent cluster of *Bacteroidetes* (light blue nodes) in LDP group, Control group has prominent clusters at *Oscillospira*, *Ruminococcus* and *Lachnospiraceae*. Those correlation differences indicate that prior antibiotic treatment disturbs the microbial interdependence profile. Note that the network comparison in Figure 2 is only for visual illustration purpose and our hypothesis testing framework does not rely on how to build the networks. The definition of hub and the choice of threshold do not affect the test performance we proposed here.

In order to test these differences statistically, we implement the NMIT test on this study and present its analysis flowchart in Figure 3. In Step 1, relative abundances are obtained at the subject level and 34 selected dominant taxa are retained in this example after filtering (relative abundance $>0.1\%$ in $>20\%$ of all samples). In Step 2, for each subject, the Kendall rank correlations between any pair of taxa are computed. The results of this step are 15 correlation matrices. The third step is to calculate the distance between any two correlation matrices in Step 2 based on the Frobenius norm. The heatmap shows that the within-group distances are smaller than the between-group distances. In the fourth step, permutation MANOVA is used to test how well prior antibiotic disruption explains the distances between subjects obtained in step 3. The conclusion is that microbial interdependence profiles over the studied period are statistically different between Control and LDP group with $p = 0.004$. We also performed the proposed test based on the Pearson and MIC methods, and the p -values were 0.001 and 0.003 respectively.

Early Childhood Antibiotics and the Microbiome (ECAM) Study—We also applied the proposed test to a more complex human study. In this study, we longitudinally monitored the microbiome profiles of 42 children since their birth [Bokulich et.al 2016]. The infant stool samples were collected at each visit during the first year of life. Among 42 children, twenty-four of them were vaginally delivered and eighteen of them were cesarean-delivered.

We asked whether the microbial interdependence is different during babies' first year life between two delivery modes while adjusting their gender, diet type (breast feeding or on formula), mother ever used antibiotics status during the pregnancy and baby ever used antibiotics during the first year. In this longitudinal data set, each child had multiple stool samples collected during this period. In total, 505 stool samples had been collected; the average number of stool samples for each child was 12 and the minimal number of samples was 7. We observed 498 different taxa at the genus level and we retained 23 major taxa, which have their relative abundance $>0.1\%$ in $>15\%$ of the total samples. In the heatmap of the correlation distance matrix (Figure 4), we used The Kendall's method to calculate the

temporal correlation matrix for each sample and the Frobenius norm to evaluate the distance between any two correlation matrices. The distances within the vaginal-born and cesarean-delivered groups are smaller than the distance between two groups. Following the procedures described in Figure 3, the p-values for comparing the group difference related to the microbial interdependence for this study after adjusting the aforementioned covariates based on Kendall, Pearson and MIC correlation methods are <0.001 , <0.001 and <0.001 respectively. Thus we concluded that the delivery type did perturb the microbial interdependence in early childhood.

Simulation Studies—We designed a simulation study in mimicking the longitudinal murine example to evaluate the performance of our proposed method with three correlation measures: the Pearson's method, Kendall's rank method, and MIC. For the type I error simulation, we considered scenarios with and without confounding effects. For the power simulation, we focused on evaluating the performance of different correlation methods and distance metrics in the proposed analytic framework using the binary outcome. The ability to incorporate multiple covariates and to adjust the confounding covariates of our proposed test is fulfilled by the permutation MANOVA test utilized in the Step 4 of Figure 3. This test has been widely adopted in the metagenomics community to analyze single time microbial location differences and in the genetic literature as well. The property of this test has been very well studied [Anderson, 2001; McArdle and Anderson, 2001; Tang et.al 2016]. Thus, here we just focus on conducting the power simulation to show the validity of the proposed analysis framework on testing the association between microbial interdependence and interested covariates over time.

For the type I error evaluation, the temporal OTU tables for each subject were simulated based on the longitudinal murine data Cox et al. [2014]. Specifically, we first estimated the connection probability matrix, denoted as p_0 , of Control group in the murine data [Cox et al. 2014]. The specific values of p_0 is given in the supplement material. The connection probability between the k^{th} and k'^{th} taxa in Control group is calculated as the percentage of their absolute temporal correlation, denoted as $|u_{i;k,k'}|$, being larger than 0.6 among all

subjects in Control group, i.e. $p_{0;k,k'} = \sum_{i=1}^{N_0} I(|u_{i;k,k'}| > 0.6) / N_0$, where N_0 is the number of subjects in Control group. The network of Control group can be constructed by having an edge between k^{th} and k'^{th} taxa if $p_{0;k,k'}$ was larger than 0.5. Each individual temporal correlation network is generated by randomly adding and deleting $n_e = 10$ edges from the Control group network. From the i^{th} individual network, the temporal variance-covariance matrix $\sum_{0i}$ for subject i can be constructed as described in the supplemental material. We then simulated the temporal OTU tables for the i^{th} individual by the NORMal-To Anything (NORTA) procedure [Cario & Nelson, 1997] from the multivariate normal distribution with zero mean vector and correlation matrix $\sum_{0i}$. Next, for each taxon we converted the simulated continuous value into counts by matching the quantile between the standard normal distribution and the zero-inflated negative binomial distribution with parameters estimated from the longitudinal murine study [Cox et al. 2014] by using maximum likelihood method.

We considered three scenarios to evaluate the Type I error for different correlation methods.

1) Binary outcome. A binary outcome was independently generated from a Bernoulli distribution with probability of success being 0.5; 2) Continuous outcome. A continuous outcome was independently generated from a standard normal distribution. 3) Binary outcome with a continuous confounder. We took the largest eigenvalue of the temporal variance-covariance matrix for each subject, then standardized it to zero mean and unit variance and denoted it as the confounder variable Z . We further simulated the binary outcome with probability $\exp(0.5Z)/(1+\exp(0.5Z))$. It is clear that the confounding covariate is associated with the microbial interdependency. We replicated the simulation procedures 5,000 times to evaluate the type I error at a significance level of 0.05.

For the power evaluation, we estimated the connection probability matrices of Control and LDP groups in the longitudinal murine data, denoted as p_0 and p_1 (the specific values for both matrices can be found in the supplementary file). We set the connection probability matrices in the simulated control and case groups as $\tilde{p}_0=p_0$ and $\tilde{p}_1=(1-\lambda)p_0+\lambda p_1$, respectively. Here, the parameter λ (a number between 0 and 1) was used to control the dissimilarity of the connection networks between case and control groups. In the simulation studies, we varied λ from 0 to 1 by 0.05. When λ was 0, the control and case groups shared the same connection network which led to the simulated data under the null hypothesis. A nonzero λ led to a set of simulated data under the alternative hypothesis with larger λ implying a higher degree of dissimilarity between two groups. From $\tilde{p}_0$ and $\tilde{p}_1$, we

constructed the temporal variance-covariance matrix $\sum_{0i}$ and $\sum_{1j}$ for each subject in the control and case groups (details are provided in the supplemental materials) respectively. We then simulated the temporal OTU tables for each individual by the NORMal-To Anything (NORTA) procedure as we did for Type I error evaluation. We replicated the simulation procedures 1,000 times to evaluate the power with different values of λ .

Using the above procedure, we generated $p=34$ taxa at $J=8, 12$ or 16 longitudinal time points for $n=14, 20$ or 26 subjects. The significance level α was set to 0.05. For the scenarios without confounder effects, the permutation MANOVA test was performed on the distance matrix. For the scenario with confounder effects, the PERMANOVA-S test was performed [Tang et.al 2016].

The empirical type I errors are reported in Table 1. NMIT maintains the nominal type I error in all the considered scenarios. For the power evaluation, Figure 5 illustrates the simulation results with λ changing from 0 to 1. When $\lambda>0$, comparing Pearson, Kendall and MIC methods, MIC presents a consistent power insufficiency compared to the other two methods. While Kendall and Pearson are always comparable and both pick up the increasing power gain as λ approaches to 1, Kendall shows a slight power edge over Pearson method for the medium λ values between 0.25 and 0.75. In the Supplemental material, we additionally reported the simulation results for the comparison on the different distance norms, including the Frobenius, Maximum, Infinity and Spectral norms. As shown in Figure S1, Frobenius norm outperformed the other distance norms in most cases.

Discussion

Next generation sequencing and longitudinal study design have enabled the study of microbiome structure and dynamics to great depth. Microbial association network has been built for human microbiome community to infer the complex ongoing microbial interactions [Faust and Raes, 2012]. However, it is of importance in formally answering the questions such as: How much of the microbial interdependence similarity exhibited by a group of individuals can be explained by their treatment group, disease status or any ancillary information? Or rather, is it the case that individuals with a trait or elevated values of a particular phenotype have similar microbial interdependence network which is unlikely to have arisen by chance? In this paper, we proposed an association methodology to address those questions. There is currently no established statistical rigorous method to capture such dynamic nature of the microbiome data. With longitudinally observed microbiome observations, we proposed to use temporal correlations to evaluate the interdependence between microbiome taxa and then use the permutation MANOVA test to evaluate the group difference. The proposed method can apply to both balanced and unbalanced longitudinal study with multiple covariate adjustment. Through extensive simulations and real data analysis, we showed the feasibility of detecting microbial temporal correlation group differences using the proposed method NMIT.

In this paper, we considered three correlation methods. In the simulations and real data analyses, the Kendall method outperforms the Pearson method slightly, while those two methods have overall comparable performance. Comparing to those two methods, MIC has less satisfying power, which may due to the small sample size [Heller, Heller and Gorfine, 2013] and moderate effect size we implemented in the simulation setting. However, in the practice the correlation methods should not be restricted to those three methods. If other correlation method suits the studied microbial correlation better, one can easily include it into the proposed framework to perform NMIT test.

The current procedure of NMIT cannot handle time-varying covariate. It is worth further investigation on how to evaluate the association between time-varying covariates and microbial interdependence.

Finally, we would like to stress that the proposed test is the first step towards conducting a dynamic analysis of a longitudinal microbiome study. It provides an overall assessment of the group difference in term of the interdependent relationship among taxa. It sheds the light for the next step—specific key taxa identification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Average relative abundance of 10 selected major taxa over time in Control and LDP groups in the longitudinal murine experiment. Colors represent different types of taxa.

Figure 2. Estimated microbial interdependence networks for 34 selected major taxa (genus level) in Control (left panel) and LDP (right panel) groups in the longitudinal murine example. Nodes are colored by their phylum levels. An edge indicates that the correlation between the connected taxa is greater than 0.6 in at least 50% subjects within the respective groups.

permutation MANOVA is used to test how well prior antibiotic disruption explains the distances between subjects obtained in Step 3. The conclusion is that the microbial interdependence profiles over the studied period are statistically different between Control and LDP group with $p < 0.001$.

Figure 4.

Heatmap of the Frobenius distance between temporal correlation matrices in ECAM data.

Temporal correlation matrices are calculated by the Kendall's rank correlation method over 23 selected major taxa.

Figure 5.

Power comparison for MINT with three correlation methods when the number of subjects $N=7, 10, 13$ and the number of longitudinal observations $J=8, 12, 16$ based on the Frobenius norm.

Empirical type I error of NMIT for the number of longitudinal observation J=8, 12, and 16, and the number of subjects N=7, 10 and 13 with the Frobenius distance

Table 1

Correlation Methods	J=8			J=12			J=16		
	N=7	N=10	N=13	N=7	N=10	N=13	N=7	N=10	N=13
Scenario 1. Binary Outcome									
Kendall	0.055	0.051	0.050	0.051	0.051	0.051	0.053	0.044	0.044
Pearson	0.051	0.049	0.051	0.048	0.049	0.052	0.050	0.051	0.050
MIC	0.047	0.050	0.053	0.043	0.043	0.052	0.046	0.047	0.046
Scenario 2. Continuous Outcome									
Kendall	0.050	0.055	0.051	0.049	0.051	0.047	0.055	0.047	0.047
Pearson	0.046	0.050	0.051	0.051	0.050	0.048	0.046	0.047	0.046
MIC	0.051	0.048	0.053	0.048	0.048	0.042	0.049	0.047	0.051
Scenario 3. Binary Outcome with a Continuous Confounder									
Kendall	0.060	0.052	0.048	0.061	0.055	0.049	0.055	0.049	0.049
Pearson	0.059	0.049	0.048	0.062	0.051	0.046	0.065	0.051	0.051
MIC	0.054	0.044	0.059	0.066	0.052	0.044	0.058	0.047	0.053