2013•2014
FACULTY OF SCIENCES
Master of Statistics

Master's thesis
Identification of potential targets controlling the inflammatory response after cardiac surgery

Promotor :
dr. Tatsiana KHAMIAKOVA

Transnational University Limburg is a unique collaboration of two universities in two countries:
the University of Hasselt and Maastricht University.

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Universiteit Hasselt | Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Universiteit Hasselt | Campus Diepenbeek | Agoralaan Gebouw D | BE-3590 Diepenbeek

Kouam Kamani
Thesis presented in fulfillment of the requirements for the degree of Master of Statistics

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TO

My Dad Michel, my Mum Anne, my brothers, sister and nephew; Nelson, Wilson, Vidal, Corletta and Quincell

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ABSTRACT

Inflammation is a complex biological response of an organism to harmful stimuli, such as pathogens, damaged cells, or irritants. The systemic inflammatory response to cardiac surgery is common and can lead to severe postoperative morbidity and mortality. Due to the limited knowledge on the diagnosis, understanding and control of the inflammatory response, more and more attention is being paid to changes in glycan structures. This paper presents the use of the joint modeling approach using random-effects in the selection of potential biomarkers (glycans) of inflammatory response. The random-effects approach using linear mixed models is applied on the levels of ten plasma N-linked glycans (GP7 – GP16) that were analyzed on 109 patients who underwent cardiac surgery. Due to computational issues, pairwise bivariate models were fitted in place of a joint linear mixed model. This study revealed that the age and hypertensive medication of a patient were associated with GP15. Sex and rheumatic disease medications were associated with GP13. Further, it suggested GP12 (log-transformed) as a potential biomarker of the inflammatory response. However, additional investigation is needed to get more evidence on the potential of GP12.

Keywords: *Glycans, inflammatory response, biomarker, linear mixed model, joint modeling, random effects*

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1. Introduction

Cardiac surgery has been routinely performed using cardiopulmonary bypass (CPB) ever since its clinical introduction during the 1950s. CPB is, however, associated with an intense inflammatory response because of conversion to laminar flow, blood contact with the artificial bypass surface, cold cardiac ischaemia and hypothermia.[1] The systemic inflammatory response to cardiac surgery is common, and resultant impairment of multiple organ function is generally mild or subclinical due to physiological reserve within organ systems.[2] Even uncomplicated cardiac surgery with CPB in low-risk patients produces a clinical spectrum from simple pyrexia, leukocytosis, tachycardia, hypotension and excessive fluid accumulation in the interstitum, to subtle signs of multiple organ injury, manifest as a slight creatinine rise on the first day post-operatively, pulmonary oedema, mild confusion or ileus.[3]

Inflammation is a complex biological response of an organism to harmful stimuli, such as pathogens, damaged cells, or irritants. This protective attempt to remove injurious stimuli and to initiate the process of healing is a part of almost all pathological conditions[4]. The inflammatory reaction after cardiac surgery can intensify to a systemic inflammatory response syndrome (SIRS) associated with serious morbidity and mortality.[1] The SIRS refers to the concept of a whole-body inflammatory response to cardiac surgery that manifests in the first 24 hours post-operatively.[2] SIRS after cardiac surgery can lead to severe postoperative morbidity[5,6] and mortality.[6] Although its peri- and postoperative management has significantly improved over the past few decades, SIRS still remains a life-threatening complication of cardiac surgery.[1] Despite significant efforts invested in studying it, our knowledge on how to diagnose, understand and control inflammatory response, is still very limited.[7] Every inflammatory process is accompanied by numerous changes at the site of inflammation as well as many systemic physiological and biochemical changes[8], but in the past two decades more and more attention is being paid to changes in glycosylation[9,10].

Glycosylation is the most diverse post-translational protein modification that provides numerous elaborate ways to modulate protein function[13-15]. Many diseases are associated with changes in glycan structures.[16] The clinical relevance of glycosylation has become the focus of considerable research, as the role of glycosylation in the development, regulation and progression of disease is, slowly but surely, being unveiled.[12] Glycan structures on proteins

have an important influence on their half-life and function[17,18] and are often reported to be changed in many pathological conditions.[11]

These alterations can be very specific, and studies of serum protein glycosylation offer a good basis for diagnosis and prognosis of many diseases.[7] Glycans can therefore serve as potential biomarkers of the inflammatory response; biomarkers can determine the risk of developing a disease, serve as tools for initial diagnosis and staging diseases, as well as monitor disease progression and the effect of medication[19]. The main goal of this master project is to identify potential biomarkers (glycans) of inflammatory response adjusting for the clinical covariates and variation within subjects. Under healthy conditions, plasma glycans are stable in an individual which implies that glycosylation is under significant genetic control. Changes observed in glycan profiles are therefore consequences of environmental influences and physiologic responses and therefore have a significant diagnostic potential.[20]

The data in this project consist of the levels of ten glycans that were analysed in each of 109 individuals prior to surgery and on day 1 and 3 after surgery. The age, gender, the medications given and the blood parameters levels of these individuals were also recorded. These data were collected in order to follow intra individual changes of total plasma glycans during the early course of systemic inflammation caused by cardiac surgery. Due to the continuous and repeated nature of the outcomes, linear mixed models were considered to carry out this goal. The ten outcomes are modeled independently to begin with. But being measured at the same time and collected from the same individual, the analysed levels of glycans are correlated. The use of a model that captures these correlations is therefore expected. Hence, a joint modeling approach was also considered. An added value of joint modeling is that inferences can be drawn about the association between outcomes as well. Modeling the responses jointly is thus appealing to draw overall inferences using all responses and to capture the association among the responses.[21]

Section 2 introduced the data on the glycan levels collected prior to and after surgery. The different modeling approaches using linear mixed models are detailed in Section 3. Section 4 presents the results of the different fits and section 5 contains the discussion and conclusion.

2. DATA

This was a multivariate longitudinal observational study; different responses on the same patient were measured repeatedly over time. The data was collected on 109 patients (aged between 21 and 89 years) that underwent cardiac surgery. The levels of 10 glycans taken from plasma samples of each patient have been analysed prior to surgery and on the first and third day after surgery. Glycans are compounds which consist of a large number of monosaccharides linked by means of a covalent bond that joins a sugar molecule to another group. These plasma glycans are called N-linked plasma glycans and are measured in glucose units (GU). N-Linked glycans are attached in the endoplasmic reticulum to the nitrogen (N) in the side chain of asparagine in an Asn-X-Ser or Asn-X-Thr sequence, where X is any amino acid except proline. Age, gender and medications taken by a patient which have been shown to also produce anti-inflammatory effects[22] were recorded. Also, blood parameters which generally reflect the inflammatory response namely, leukocytes, thrombocytes, creatinine and C-reactive protein (CRP)[2,7,22,23] were collected. Table 1 gives a brief description of the variables involved.

Table 1: *Brief description of the data set variables*

Variables	Description
Response Variables	
GP7, GP8, GP9, GP10, GP11, GP12, GP13, GP14, GP15, GP16	Ten different glycans structures collected from the plasma of each patient as explained in section 2.1. These variables are continuous.
Explanatory Variables	
ID	Identification number of the patient
Age	Age of the patient
Sex	Gender of the patient coded as 0 for female and 1 for male
Day	Day 0 prior to surgery, day 1 and 3; one day and 3 days after surgery
Hyperlipidemia	Indicates if a medication was given to the patient to regulate hyperlipidemia
Hypertension	Indicates the intake or not by the patient of an hypertensive medication
Rheumatic disease	Indicates the intake or not by the patient of a rheumatic medication

Chronic renal insufficiency	Indicates the intake or not by the patient of a drug to help regulate his/her kidney function
Dialysis	Indicates if yes or no, the dialysis was performed on the patient
Beta blockers	Indicates the intake or not of beta blockers by the patient for the management of his/her cardiac arrhythmias
ACE inhibitors	Indicates the intake or not by the patient of ACE inhibitors
Diuretic	Indicates the intake or not by the patient of medication to help with the production of urine
Statins	Indicates the intake or not of a drug by the patient to help lower his/her cholesterol levels
Amiodarone	Indicates the intake or not by the patient of an amiodarone
Blood parameters	
Leucocytes 1 , 3	Leucocytes levels ($\times 10^9$/L) collected on the patient day 1 and day 3
Thrombocytes 1 , 3	Thrombocytes levels ($\times 10^9$/L) collected on the patient day 1 and day 3
C-reactive protein 1, 3 (CRP)	CRP levels collected on the patient on day 1 and day 3
Creatinine 3	Creatinine levels on day 3
Max CRP	Maximum value of the CRP 0, 1, and 3 levels

For the measurement of the response variables, Hydrophilic Interaction High Performance Liquid Chromatography was chosen which separates the plasma glycome into 16 groups labeled as GP1 through GP16. [11,24] Only GP7 – GP16 were used for this study. For detailed information on their structures, the reading of Gornik et al. (2009) is advisable.

3. STATISTICAL METHODOLOGY

3.1. Exploratory Data Analysis (EDA)

This was done to detect underlying patterns necessary for the statistical modeling. To gain insight, descriptive statistics (mean, standard deviation), individual and mean profiles were used.

3.2. Joint modeling: Linear Mixed Models (LMM)

Since the outcomes - glycan levels measured each at three time-points – are correlated within patients, linear mixed models (LMM) were built. Let Y_{ij} denote the jth measurement for the ith patient, $i= 1,...,N$, $j=1,...,n_i$, and let $\mathbf{Y_i}$ denote the vector of all measurements for the ith patient, that is, $\mathbf{Y_i}' = (Y_{i1},...,Y_{in_i})$. Linear mixed models assume that the n_i-dimensional vector satisfies

$$\mathbf{Y_i} \mid \mathbf{b_i} = N(X_i\beta + Z_i\mathbf{b_i}, \Sigma_i), \text{ with } \mathbf{b_i} \sim N(0, D) \text{ and } \mathbf{\varepsilon_i} \sim N(0, \Sigma_i) \tag{1}$$

where X_i and Z_i are ($n_i \times p$) and ($n_i \times q$) dimensional matrices of known covariates, β is a p-dimensional vector of regression parameters called fixed effects, b_i is the q-vector containing the random effects and ε_i an n_i-vector of residual components with $b_1,...,b_N, \varepsilon_1,...,\varepsilon_N$, are independent,. Finally D is a ($q \times q$) covariance matrix with (i, j) element $d_{ij}=d_{ji}$ and Σ_i is a ($n_i \times n_i$) covariance matrix which depends on i only through its dimension n_i, that is the set of unknown parameters in Σ_i will not depend upon i. The assumption for conditional independence then reduces $\Sigma_i = \sigma^2 I_{n_i}$. Marginally, $\mathbf{Y_i}$ follows a normal distribution with mean $X_i\beta$ and covariance matrix $V_i = Z_i D Z_i' + \Sigma_i$.[25,26]

3.2.1. Univariate Linear Mixed Models

The levels of each glycan were modeled by equation (2), age and sex of the patient and *MEDI* - matrix of medication parameters used in the analysis as the explanatory variables (fixed effects), patient and categorized day as the random effects. The need to treat day as a categorical variable arise from the unequal spacing of the time points and from the non-linearity of the patient profiles. In some of the models, the glycan levels were log-transformed to account for the skewness in their distribution.

$$Y_{kij} = \beta_{k0} + b_{k1i} + \beta_{k1}day1 + \beta_{k2}day3 + \beta_{k3}age + \beta_{k4}sex + \beta_{kd}MEDI + b_{k2i}day1 + b_{k3i}day3 + \varepsilon_{kij} \quad (2)$$

in which Y_{kij} denotes the jth measurement of the glycan k for the ith patient, the vectors $(\beta_{k0}, \beta_{k1}, \beta_{k2}, \beta_{k3}, \beta_{k4})'$ and β_{kd} of fixed effects represent the average evolution of the level of the k glycan, $day1 = \begin{cases} 1, \text{ if day} = 1 \\ 0 \text{ otherwise} \end{cases}$ and $day3 = \begin{cases} 1, \text{ if day} = 3 \\ 0 \text{ otherwise} \end{cases}$, the vector $\mathbf{b_i} = (b_{k1i}, b_{k2i})'$ of random effects describes how the profile of the ith patient deviates from the average profile and ε_{kij} is the random error for the level of the kth glycan.

The purpose of fitting these univariate LMM models was to test for the difference between the glycan levels prior to surgery (day 0) and day 1, day 0 and day 3. The study interest being on the changes that occurred after the surgery, the differences tested were needed in order to identify those glycans that depict changes after day 1 as potential targets of the inflammatory response after cardiac surgery.

Each of these ten univariate analyses accounts for the intra-individual variability but they do not account for the correlation between plasma glycans. Further, the univariate models address the question about the change of the levels of glycans with time, adjusting for the clinical covariates however do not provide means to answer how the glycans-specific evolutions are related to each other. To take into account the correlation between the glycans, joint modeling was considered.

3.2.2. Joint Linear Mixed Model

Several modeling approaches are described in literature for specifying a joint distribution[21,27,28,29]. All of them opt for directly specifying the joint distribution for all outcomes via a mixed model, by specification of the marginal distributions, conditional on correlated random effects[30]. Due to its flexibility[27], several authors have paid attention in their recent publications to the random-effects approach for the joint modeling of multivariate longitudinal profiles. Joint modeling allows the use of highly unbalanced data and is applicable in situations where linear, nonlinear, or generalized linear mixed models are used to describe the evolution of the specific outcome processes. Further additional correlation structures in the data, such as a longitudinal data structure, can be modeled within the same framework.[28]

3.2.2.1. Multivariate Linear Mixed Model (MLMM)

In the joint (multivariate) linear mixed model, the levels of glycans are modeled independently using linear mixed models and these models will be joined by specifying a common distribution for their random effects[27]. More precisely, the ten linear mixed models of section 3.2.1 will be fitted by imposing a joint multivariate distribution on their model-specific random effects and in doing so, associating the different plasma glycan levels[27]. Joining the equations in (2), we obtain

$$\begin{cases} Y_{1,ij} = \beta_{1,0} + b_{1,1i} + \beta_{1,1}day1 + \beta_{1,2}day3 + \beta_{1,3}age + \beta_{1,4}sex + \beta_{1,d}MEDI + b_{1,2i}day1 + b_{1,3i}day3 + \varepsilon_{1,ij} & \text{GP7} \\ Y_{2,ij} = \beta_{2,0} + b_{2,1i} + \beta_{2,1}day1 + \beta_{2,2}day3 + \beta_{2,3}age + \beta_{2,4}sex + \beta_{2,d}MEDI + b_{2,2i}day1 + b_{2,3i}day3 + \varepsilon_{2,ij} & \text{GP8} \\ \quad. & \quad\vdots \quad\vdots \\ Y_{10,ij} = \beta_{10,0} + b_{10,1i} + \beta_{10,1}day1 + \beta_{10,2}day3 + \beta_{10,3}age + \beta_{10,4}sex + \beta_{10,d}MEDI + b_{10,2i}day1 + b_{10,3i}day3 + \varepsilon_{10,ij} & \text{GP16} \end{cases}$$

$$\text{with } \mathbf{b_i} = \begin{pmatrix} b_{11i} \\ b_{21i} \\ \vdots \\ b_{10,1i} \\ b_{12i} \\ b_{22i} \\ \vdots \\ b_{10,2i} \end{pmatrix}' \sim N \left\{ \begin{pmatrix} 0 \\ 0 \\ \vdots \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{b_{11}}^2 & \sigma_{b_{11}b_{21}} & \cdots & \sigma_{b_{11}b_{10,1}} & \sigma_{b_{11}b_{12}} & \sigma_{b_{11}b_{22}} & \cdots & \sigma_{b_{11}b_{10,2}} \\ & \sigma_{b_{21}}^2 & \cdots & \sigma_{b_{21}b_{10,1}} & \sigma_{b_{21}b_{12}} & \sigma_{b_{21}b_{22}} & \cdots & \sigma_{b_{21}b_{10,2}} \\ & & \ddots & & \vdots & \vdots & \vdots & \vdots \\ & & & \sigma_{b_{10,1}}^2 & \sigma_{b_{10,1}b_{12}} & \sigma_{b_{10,1}b_{22}} & \cdots & \sigma_{b_{10,1}b_{10,2}} \\ & & & & \sigma_{b_{12}}^2 & \sigma_{b_{12}b_{22}} & \cdots & \sigma_{b_{12}b_{10,2}} \\ & & & & & \ddots & & \vdots \\ & & & & & & & \sigma_{b_{10,2}}^2 \end{pmatrix} \right\} \quad (3).$$

The joint model displayed in (3) is considered to a linear mixed model similar to (2). The parameters of (3) are defined in 3.2.1 and conditionally on the random effects, the responses $\mathbf{Y}_{1i}, \mathbf{Y}_{2i}, ..., \mathbf{Y}_{10i}$ are assumed to be independent. Let $\mathbf{\Theta}^*$ be the vector containing all fixed effects and covariance parameters, $l_i\left(\theta^* \mid \mathbf{Y}_{1i}, \mathbf{Y}_{2i}, ..., \mathbf{Y}_{10i}\right)$ then refers to the log-likelihood contribution of subject i to the MLMM of equation (3). This MLMM can be fitted by standard statistical software such as R[31] and SAS[32].

3.2.2.2. Pairwise Bivariate Models

The marginal density of equation (2) can be calculated analytically. However it is not the case for equation (3), generalized and non-linear mixed models. A dimensionality reduction was proposed as a solution to the computational problems which arise as the dimension of the vector of random effects $\mathbf{b_i}$ in the joint model increases[26,29]. This reduction involves fitting each of the $k(k-1)/2$ (*i.e.*45 in this case) pairwise bivariate models instead of maximizing the likelihood of the MLMM displayed by equation (3). Assuming the MLMM in equation

(3) is correct, all pairwise models are correct. In addition to solving the computational issues, this pairwise estimation method yields unbiased estimates and valid standard errors in a maximum likelihood (ML) framework.

More precisely, instead of maximizing $l_i\left(\Theta^* \mid \mathbf{Y}_{1i}, \mathbf{Y}_{2i}, ..., \mathbf{Y}_{10i}\right)$, log-likelihoods of the form $\sum_{i=1}^{N} l_{rsi}(Y_{ri}, Y_{si} \mid \Theta_{r,s})$ will be maximized separately with *r=1,...,9, s=r+1,...,10* and N the total number of subjects. $\mathbf{\Theta}_{r,s}$ represents the vector of all parameters in the bivariate LMM corresponding to the pair *(r, s)*. Let $\mathbf{\Theta}$ be the stacked vector combining all pair-specific parameter vectors $\mathbf{\Theta}_{r,s}$. Note that, $\mathbf{\Theta}^*$ and $\mathbf{\Theta}$ are not equivalent.

Some parameters in $\mathbf{\Theta}^*$ will have a single counterpart in $\mathbf{\Theta}$ whereas other elements in $\mathbf{\Theta}^*$ will have multiple counterparts in $\mathbf{\Theta}$. Relative to the latter case, all corresponding pair-specific ML estimates in Θ are averaged to obtained a single estimate. These averages are still asymptotically normally distributed. However, the standard errors of the estimates obtained by averaging cannot be obtained in a similar way. Indeed, the pair-specific estimates exhibit a variability which needs to be taken into account. Further, the correlation (overlapping information) that arises from the two pairwise models with a common outcome has to be accounted for in the sampling variability of the combined estimates Θ^*. To obtain the estimates for the standard errors, ideas from the pseudo-likelihood framework are borrowed. The estimates for the elements in $\mathbf{\Theta}$ are obtained by maximizing each likelihood separately. Fitting all possible pairwise models is equivalent to maximizing a function of the form $rsl_i(\Theta) = l(Y_1, Y_2 \mid \Theta_{1,2}) + l(Y_1, Y_3 \mid \Theta_{1,3}) + ... + l(Y_{k-1}, Y_k \mid \Theta_{k-1,k})$. The latter function is a pseudo-likelihood function and the pairwise approach fits within the pseudo-likelihood framework. Hence, an asymptotic multivariate normal distribution for Θ can be derived and is given by $\sqrt{N}(\Theta - \Theta) \sim MVN(0, J^{-1}KJ^{-1})$ where *J* is a block-diagonal matrix with diagonal blocks J_{pp} and where *K* is a symmetric matrix containing blocks K_{pq}, given by

$$J_{pp} = -\frac{1}{N}\sum_{i=1}^{N} E\left(\frac{\partial^2 l_{pi}}{\partial \theta_p \partial \theta_q^{'}}\right) \quad \text{and} \quad K_{pq} = -\frac{1}{N}\sum_{i=1}^{N} E\left(\frac{\partial l_{pi}}{\partial \theta_p}\frac{\partial l_{qi}}{\partial \theta_q^{'}}\right), p,q=1,...,P \text{ and } P = k(k-1)/2.$$ A

SAS macro written by Fieuws[33] for the implementation of (3) combining the results of the pairwise bivariate models is presented in Appendix 5. To combine the results of these pairwise models, estimates for the parameters in Θ^* are calculated by taking averages over all

pairs. This is obtained by equating Θ^* to $A\Theta$ with Θ^* following a multivariate normal distribution with mean $\mathbf{\Theta}^*$ and covariance $A\sum(\Theta)A^{'}$. A is a matrix containing the appropriate coefficients for the averages calculation and $\sum(\Theta)$ equals $J^{-1}KJ^{-1}$.[26] In this study, interest was on the estimates of these bivariate models since this approach is advantageous whenever the full multivariate mixed model is too time-consuming as it is in this case.

These pairwise bivariate models will help us determine whether or not the glycans evolutions are associated since the association between Y_{rij} and Y_{sij} is captured via the bivariate normal random effects[21]. Fieuws and Verbeke (2004) derive this correlation to be

$$Corr(Y_{rij}, Y_{sij}) = \frac{\sigma_{b_{r1}b_{s1}} + t\sigma_{b_{r1}b_{s2}} + t\sigma_{b_{r2}b_{s1}} + t^2\sigma_{b_{r2}b_{s2}}}{\sqrt{\sigma_{b_{r1}}^2 + 2t\sigma_{b_{r1}b_{r2}} + t^2\sigma_{b_{r2}}^2 + \sigma_{b_{r2}}^2}\sqrt{\sigma_{b_{s1}}^2 + 2t\sigma_{b_{s1}b_{s2}} + t^2\sigma_{b_{s2}}^2 + \sigma_{b_{s2}}^2}} .$$ Hence,

for any time point t (t=0, 1 and 3 in this study), we can obtain the correlation between two responses. These models will also allow to select potential biomarkers of the inflammatory response after cardiac surgery by looking at the association of the glycan levels with the blood parameters. In case of a bivariate random intercept model, that is, when

$$D = \begin{bmatrix} \sigma_{b_{r1}}^2 & \sigma_{b_{r1}b_{s1}} \\ \sigma_{b_{s1}b_{r1}} & \sigma_{b_{s1}}^2 \end{bmatrix}$$ we have that $Corr(Y_{rij}, Y_{sij}) = \frac{\sigma_{b_{r1}b_{s1}}}{\sqrt{\sigma_{b_{r1}}^2 + \sigma_{\varepsilon_r}^2}\sqrt{\sigma_{b_{s1}}^2 + \sigma_{\varepsilon_s}^2}}$.[21,26,29]

3.3. Software Used

R version 2.14.3 and SAS version 9.3 were used to carry out all statistical analysis and a p-value <0.05 was considered statistically significant. Pinhiero and Bates (2000) give details on the fit of linear mixed models in R while Thiébaut et al. (2002) illustrate with the help of examples the bivariate joint linear mixed models in SAS.

4. RESULTS

4.1. Exploratory Data Analysis

Two datasets were available for this study. The first dataset called meta contained the information (phenotypic variables) such as age, sex, medication parameters as well as blood parameters of the patients and the second dataset called plasma included the day (0, 1 and 3) and the levels of plasma N-linked glycans.

The observations of 3 patients were not collected in both datasets. This may be due to their retrieval from the study before the collection of data started. In general, 7% of the observations were missing in the meta dataset. In particular, C_reactive protein (CRP) at day 1 had 65 missing values. Furthermore, the levels of thrombocytes, CRP and leukocytes were not registered for day 0 and day 1. The plasma glycan dataset was balanced with 294 observations. Apart from the 3 patients stated above, 10% of the observations were missing in this dataset. The reason for this was that all observations were discarded if at least at one time point (day), the data collectors failed to analyzed the levels of the plasma glycans of a patient. After joining both datasets and checking the plausible missingness mechanism of the data which was found to be missing completely at random, these patients were deleted from the final dataset and thus we remained with 291 observations obtained from 97 patients. Hence N = 97 patients were used to answer the study objective.

Of the resulting 97 patients, 26 (26.80%) were females and 71 (73.20%) males. The mean age was found to be 64.61 years. 55.67% of these patients were given medication for hyperlipidemia, 78.35% for hypertension while 87 and 85 patients were not administered medication for rheumatic disease and chronic renal insufficiency, respectively. The number of patients with diuretic was balanced that is, 45 patients took the substance and 45 did not while 5.16% of these patients had missing values. Dialysis was performed on only one patient while we ignore if it was performed or not on 7 others. Beta blockers were administered to 67 patients for the management of their cardiac arrhythmias while they weren't for 25 patients. This resulted in 5 patients for which we ignore their beta blockers intake. The same number of patients had missing values with respect to amiodarone while 9.27% of them took the latter medication. ACE inhibitors were administered to 60.82% of the patients and 61.86% took statins.

Patient H11 was observed to have thrombocytes level at day 3, 1124 $\times 10^9$/L, exceeding the normal range. Table 2 gives a brief summary of the blood parameters.

Table 2: *Mean and standard deviation of the blood parameters*

	Day 1			Day 3				
	Leucocytes	**thrombocytes**	**CRP[2]**	**Leucocytes**	**thrombocytes**	**CRP**	**Creatinine**	**maxCRP**
Mean	11.72	127.54	35.31	10.35	157.74	148.53	131.58	153.79
SD[1]	3.50	47.90	19.86	3.01	119.33	58.02	93.66	59.20

[1]Standard deviation, [2]C_reactive protein

A look at the glycans' levels revealed that some of them had a skewed distribution, and there was a need to approximate these distributions to the normal and therefore render them adequate for the fit of the linear mixed models. The log-transformation was used in this effect (Figure 1A in Appendix 1). Since measurements were taken repeatedly, we expect each of the glycans levels within patients to be correlated and measurements within patients to be more similar than between patients. This is observed in individual profile plots (Figure 1). Indeed, from Figure 1, much between-patient variability is observed for all plasma glycans while there is little within-patient variability: more precisely, at day 0, that is prior to surgery, there is high variability in the intercepts for all plasma glycans and the patients seem to evolve in a similar way (indicating not much variability in the slopes) with the exception of some patients.

1. GP7 levels   **2. Log-transformed GP8 levels**
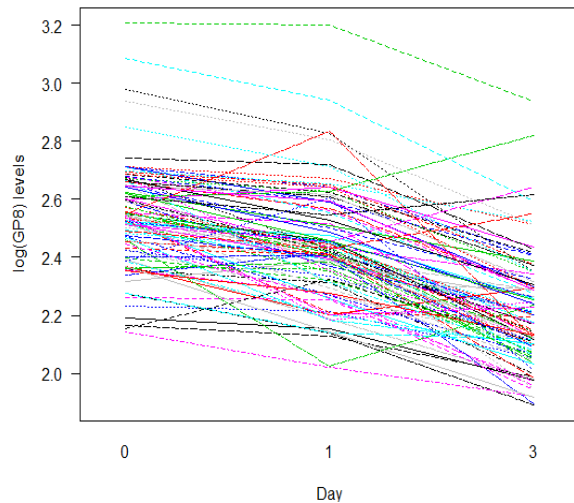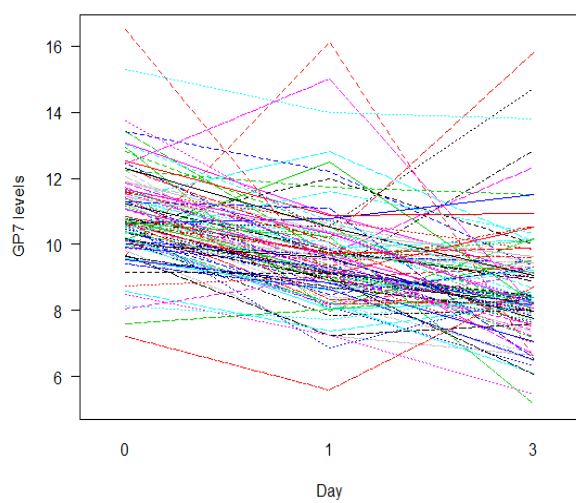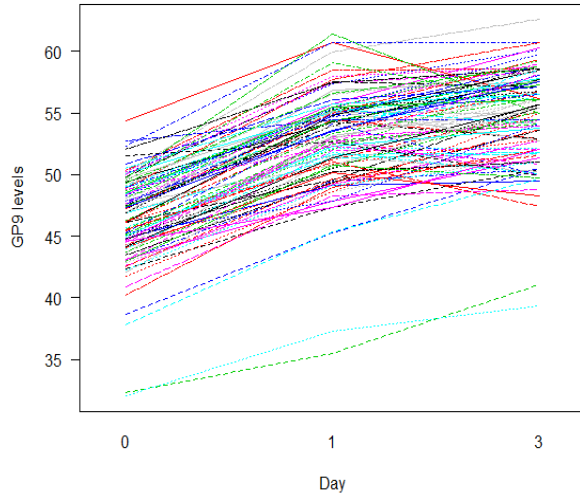
3. GP9 levels
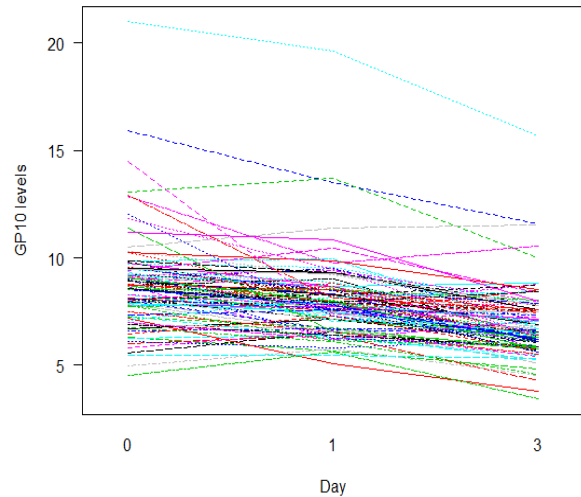
4. GP10 levels
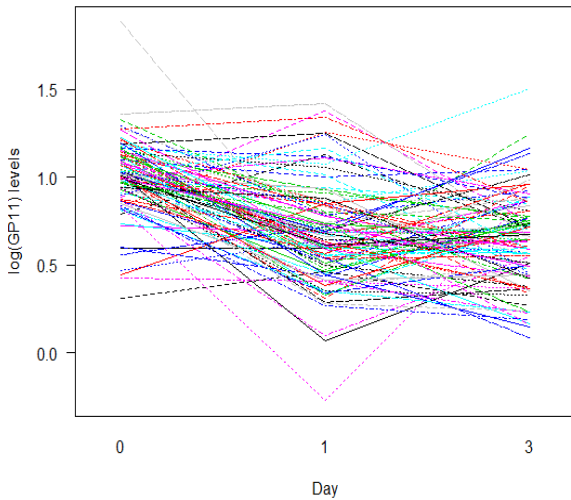
5. Log-transformed GP11 levels
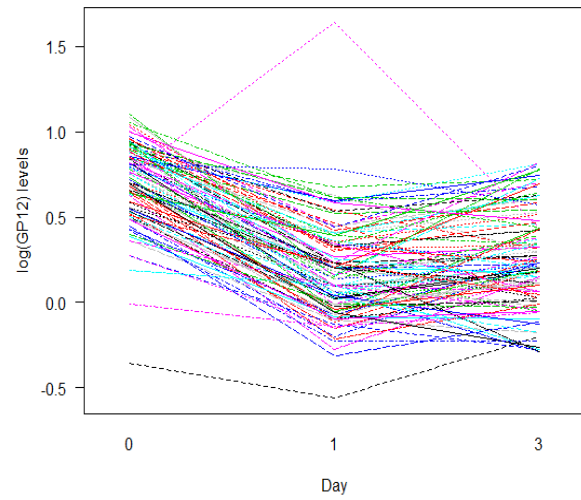
6. Log-transformed GP12 levels
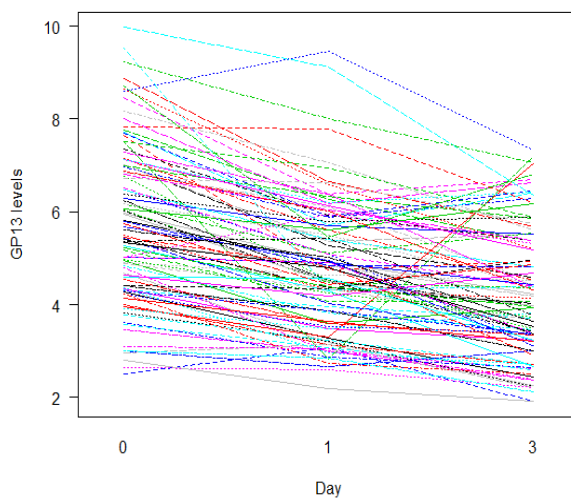
7. GP13 levels
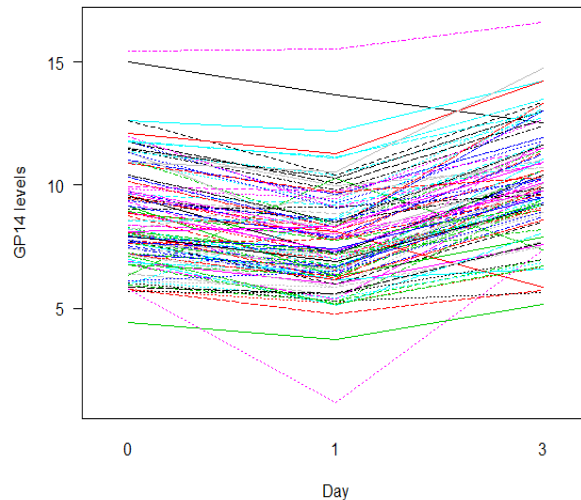
8. GP14 levels
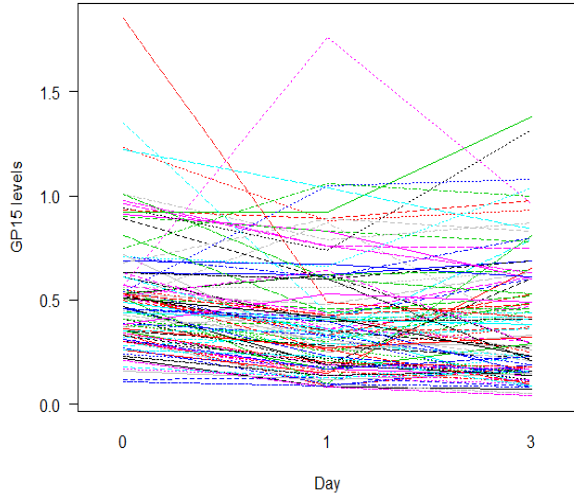
9. GP15 levels
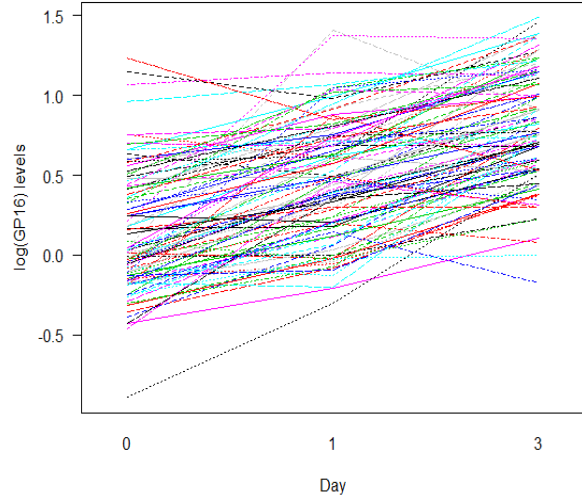
10. Log-transformed GP16 levels

Figure 1: *Individual profile plots of GP7 (1), GP9 (3), GP10 (4), GP13 (7), GP14 (8), GP15 (9), and log-transformed GP8 (2), GP11 (5), GP12 (6) and GP16 (10) by day of follow-up*

Figure 1 shows some patients behaving differently from the average population. This is the case for GP10 (Figure 2) where IDs 51, 20 and 27 are seen to be out of the profile bundle.
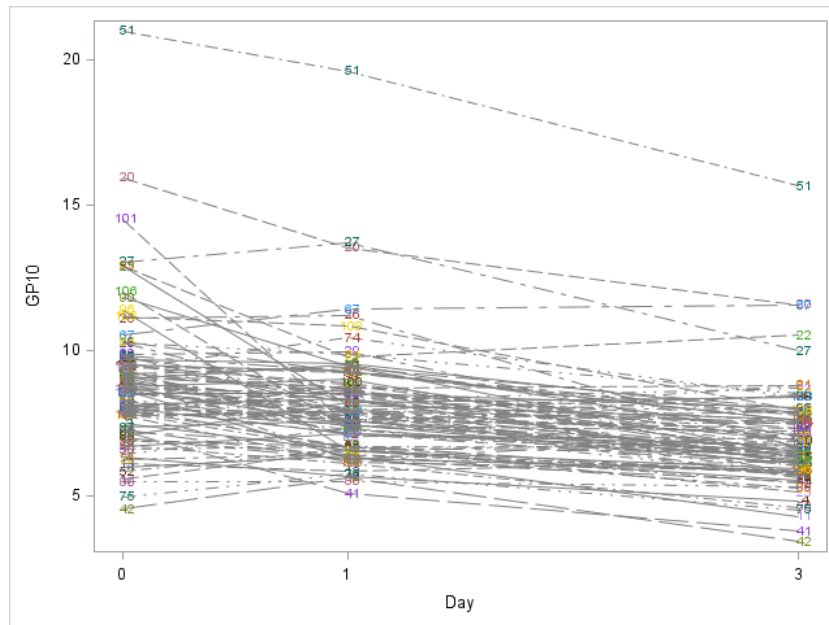
Figure 2: *Individual profile plot of GP10 showing potential outliers.*

Further, a glance at the mean and standard deviation plots of the glycans levels per time of follow-up (Figure 1B, Appendix 1) tells us that is a difference between day 1 and day 0 on one hand, and day 3 and day 0 on the other, for all glycans levels. Also, while most of the glycans levels show a complete decrease or increase (GP16 – log-transformed – shows a steady increase) for both day 1 and day 3, GP14 levels decrease after day 0 and later on, after

day 1, increase. The marginal correlation between log(GP8) and GP9 levels is negative (-0.72) . Also, a positive correlation (0.77) between GP13 and GP15 levels and almost none between GP7 and GP15 are observed. A scatter plot matrix of these glycans is displayed in the Appendix 1, Figure 1C.

4.2. Univariate Linear Mixed Models

Random intercepts and slopes models were fitted for each of the 10 glycans. The mixture of Chi-square test was used to test whether both random effects were needed[25]. The hypotheses tested were H_0: the random intercept and H_a: random intercept + random time slope. For all the models, the test failed to reject the null hypothesis (results not shown). This finding confirmed our EDA which suggested that the patients started with different levels for the glycans but they evolve in a similar way after day 0. Since the aim of the study required modeling the glycans while adjusting for the covariates and variation within patients, a model selection procedure was not carried out. But it is worth noticing that, except for day 1 and day 3 which were significant (p-value < .0001) in all the models (except GP16), hypertension and age were significant in the model for GP15. It was also significant for GP13 along side with the sex of the patient and his/her of rheumatic medication. These results can be seen in Table 3 which gives a summary of those models which had more than one statistical significant variable different from day1, day3 and the intercept. The variance structures of these models were investigated using the anova function for lme as illustrated by Pinheiro and Bates (2000)[34].

Table 3: *Linear mixed model estimates for glycans levels with more than one statistically significant covariates: both models have an independence structure for their random effects.*

Effects	Par[1].	GP13 - Independence			GP15 - Independence		
		Estimate	S.E[2]	p-value	Estimate	S.E	p-value
Intercept	β_0	6.1263	0.4621	**<0.0001***	0.4849	0.0999	**<0.0001**
day1	β_1	-0.9992	0.1083	**<0.0001**	-0.1136	0.0270	**<0.0001**
day3	β_2	-1.5158	0.1083	**<0.0001**	-0.1112	0.0270	**0.0001**
Age[3]	β_3	-0.0269	0.0119	**0.0269**	-0.0054	0.0026	**0.0398**
Sex	β_4	-1.1990	0.2922	**0.0001**	-0.1187	0.0630	0.0635
Hyperlipidemia	β_5	0.3463	0.2881	0.2334	0.0162	0.0621	0.7952
Hypertension	β_6	1.0017	0.3693	**0.0084**	0.1722	0.0796	**0.0339**
Rheumatic[4]	β_7	-1.1900	0.5361	**0.0296**	-0.1969	0.1155	0.0927
Chronic renal[5]	β_8	-1.0738	0.7737	0.1694	-0.1422	0.1668	0.3966

Dialysis	β_9	-1.6482	1.3977	0.2422	-0.1476	0.3013	0.6256
Beta blockers	β_{10}	0.0373	0.3430	0.9136	-0.0012	0.0739	0.9875
ACE inhibitors	β_{11}	-0.4367	0.3295	0.1892	-0.0201	0.0710	0.7783
Statins	β_{12}	0.0704	0.3173	0.8250	0.0424	0.0684	0.5369
Amiodarone	β_{13}	-0.2574	0.4998	0.6080	-0.0804	0.1077	0.4577
Diuretic	β_{14}	-0.2801	0.2908	0.3386	-0.0109	0.0627	0.8627
Covariance of b_i		*Independence*			*Independence*		
					0.0500		
$Var(b_{1i})^6$	$\sigma^2_{b_{1i}}$	1.1316	0.2170	**<0.0001**		0.0101	**<0.0001**
Residual variance							
$Var(\varepsilon_{ij})$	σ^2	0.4983	0.0544	**<0.0001**	0.0309	0.0034	**<0.0001**
Contrasts							
Day1 vs Day0		0.9992	0.1083	**<0.0001**	-0.1136	0.0270	**<0.0001**
Day3 vs Day0		1.5158	0.1083	**<0.0001**	-0.1112	0.0270	**<0.0001**

[1]Par = parameter, [2]S.E = standard error, [3]Age = age-64.6082474, [4]Rheumatic = rheumatic disease, [5]Chronic renal = chronic renal insufficiency, * bold = significant at 0.05 level, [6]Var = variance

The variance-covariance structure for the random effects in the model based on GP9 was unstructured while for the rest of the glycans, an independence structure was found to be most convenient. Further, the differences "day1 – day0" and "day3 – day0" were found to statistically significant (p-value < 0.0001) for all the plasma glycans levels. The latter results can be found in Appendix 2.

4.3. Pairwise Bivariate Linear Mixed Models

Despite the independence variance-covariance structure found above for the random effects in most of the models, and the random intercept and slope model for GP14 levels, the bivariate joint models were fitted as suggested by Thiébaut et al. (2002) with an unstructured variance-covariance for the random effects and with random intercepts models for the levels of all ten glycans since the inclusion of random slopes led to convergence issues. The variables age, sex, hypertension and rheumatic disease were found to be significant in the models having GP10, GP13 and GP15 in the pairs just as in the univariate case (the estimated values of the bivariate models are found in Appendix 3). Further, for most of the bivariate models, the parameter estimates and standard errors for the fixed effects remained the same as in the univariate models. Parameters which changed were either slightly bigger or smaller with the most drastic changes experienced for the intercepts of the models. Also, the p-values for the parameters were mostly smaller than the ones in the univariate models and in the rest of the cases, they were more or less similar in both type of models. Since the association of

the levels of the ten glycans was of primary interest, the correlation of the random intercepts in each pairwise bivariate joint model was examined. The highest correlation between the random intercepts – 0.9209 – was observed for the levels of glycans GP13 and GP15 (b_{71i}, b_{91i}) as shown on Table 4. This suggests that GP13 can be used to explain GP15 and vice-versa. Further, the highest negative association is between the levels of log-transformed GP11 and those of log-transformed GP16 (-0.7907). That of log-transformed GP8 and GP9 levels comes at the third position for highest negative association with the value, -0.7593, slightly higher than before in magnitude. An almost zero-correlation was between the intercepts of GP10 and GP15 levels suggesting that, none of these glycans can explain the other.

Table 4: *Correlation between the random intercepts of the pairwise bivariate joint models: highlighted are the correlations greater than 0.6, i.e a moderate correlation*

	b_{11i}	b_{21i}	b_{31i}	b_{41i}	b_{51i}	b_{61i}	b_{71i}	b_{81i}	b_{91i}	$b_{10,1i}$
b_{11i}	1.0000	0.4767	**-0.6388**	0.4287	**0.9145**	**0.6700**	0.1838	**-0.7291**	0.0544	-0.5630
b_{21i}		1.0000	**-0.7593**	0.5328	**0.8297**	0.1789	-0.0663	-0.5719	0.1119	-0.2349
b_{31i}			1.0000	**-0.7818**	**-0.6819**	-0.2707	-0.2207	0.2131	-0.3982	-0.1403
b_{41i}				1.0000	**0.6434**	-0.0256	-0.3040	-0.2279	-0.0042	-0.0429
b_{51i}					1.0000	0.5250	-0.0878	**-0.6406**	-0.1947	**-0.7907**
b_{61i}						1.0000	**0.6692**	**-0.6244**	0.4422	-0.3016
b_{71i}							1.0000	-0.2393	**0.9209**	0.4223
b_{81i}								1.0000	-0.2941	0.3778
b_{91i}									1.0000	**0.7821**
$b_{10,1i}$										1.0000

These correlations can be interpreted as the individual deviations from the overall profile[28].

In order to answer the research question of the study, it was decided that instead of using the blood parameters as phenotypic variables as intended by the data providers, it would be good to make a joint modelling of the levels of the glycans and the blood parameters since they are identifiers, namely, - leucocytes and platelets[1], creatinine - and known markers, namely CRP, of inflammatory response[7,23,36]. Due to the incompleteness of the data on the blood parameters; leukocytes, thrombocytes, CRP at day 0 are not available and creatinine levels at day 0 and 1 are also missing, the joint modeling was done based on the data available for all the parameters at day 1 and day 3 adjusting for the other covariates.

The joint modeling as before was limited to bivariate joint models in order to avoid the computational problems raised in section 3.2.2. In this effect, CRP was rescaled by dividing its value by 100, and leukocytes and thrombocyctes which exhibit skewed distributions (not showned) were log-transformed. In most models, the covariance parameter between the random intercepts was found not to be needed, the p-value was not significant and a mixture of Chi-square test was used to investigate the need of this parameter and the test confirmed that it was not needed (results not shown). The models based on the pairs (log(GP8), log(thrombocytes)), and (log(GP12), CRP) had significant covariance parameters (Appendix 4). The pair (log(GP12), CRP) had a higher correlation – -0.6001 – in the negative direction .

5. DISCUSSION AND CONCLUSION

The identification of potential targets controlling the inflammatory response after cardiac surgery was the topic of this study. In order to identify them, the changes of total plasma glycans occurring within the individual during the early course of systemic inflammation caused by cardiac surgery were followed and the selection of potential biomarkers, namely these plasma glycans, of inflammatory response was the final objective. To achieve this goal, linear mixed models were used. Ten plasma N-linked glycans were analyzed on 109 patients prior to surgery, on the first and on the third postoperative day. Linear mixed models were used since the outcomes were continuous. These models are advantageous since they are more flexible and use all the available data on each subject. They handle missing observations and unbalanced designs efficiently. Furthermore, they easily model time-effects and allow usage of variance and covariance patterns[37].

Since this was a multivariate longitudinal observational study, the patients differed with respect to their baseline information especially with respect to their medication intake. Also there were a lot of missing values with respect to the phenotypic variables: all the blood parameters had their day 0 levels missing. Due to this missingness, there was a need to reformulate the main objective of the study into a three-goal plan. First, we investigated if for the levels of the glycans whether there was a difference between their day 1 and day 0 measurements on one hand, and between their day 3 and day 0 measurements on the other hand. Since those glycans showing a change as early as possible, that is, at day 1, could be used as a potential target. Secondly, based on those plasma glycans which showed a difference, a joint modeling approach was to be carried out in other to investigate the association of their evolutions. In this way, one plasma glycan could easily be used in the absence of the other as a target. To confirm their biomarker status, modeling them with the available information received from the data collectors on known biomarkers and identifiers of inflammatory response after cardiac surgery was the final step.

Some patients' glycans levels were deleted due to the failure of the analysis conducted by the data collectors. Due to missing values issues, some others were discarded during the exploratory data analysis (EDA) phase. The study was finally conducted based on the information obtained from 97 patients. There was a lot of variability between patients at the start of the study and less within patients which suggested the use of random intercepts only.

To test for the differences "day 1 - day 0" and "day 3 - day 0", univariate linear mixed models were used assuming both random intercepts and slopes models for each plasma glycans and including all covariates except for the blood parameters. A mixture of Chi-square test confirmed the use of random intercepts only except for GP14. Further, the differences were statistically significant based on all glycans. These findings confirmed what was observed during the EDA. Though model selection was not of interest, it is worth mentioning that the variables age, sex, hypertension and rheumatic disease had significant p-values in some models.

It must be mentioned that, these analyses did not take into account the extra variability that resulted from the correlation of the glycans collected from the same individual. Joint modeling was brought in for that aspect and also to help to determine whether the plasma glycans are associated or not. However, some issues arise with joint modeling such as computational problems during the fit since the random effects have a vector of higher dimension. Fieuws and Verbeke (2006) suggested the use of pairwise bivariate linear mixed models and for this project 45 bivariate models were fitted. As a result, the random intercepts of the pairwise model based on GP13 and GP15 had an almost perfect correlation. This finding suggests that both glycans are highly associated since their correlation is captured entirely by the correlation of the random intercepts. This suggests that GP13 can be used in place of GP15 as a potential target of the inflammatory response and vice-versa. Further, GP11 was associated with the glycans GP7, GP8, GP9 and GP10 though with the two latter it was just a moderate association. In addition, the joint approach did not show much difference from the univariate one in terms of fixed parameter estimates. This is because the pairwise approach yields unbiased estimates with robust standard errors reflecting the true sampling variability[26].

The bivariate joint modeling of the glycans and the blood parameters (leukocytes, thrombocytes and C_reactive protein (CRP)) was carried out based on the information for day 1 and day 3. The results suggested that GP12 (log-transformed) had a moderate negative association with CRP. One could then be tempted to conclude that GP12 (log-transformed) is a potential biomarker of the inflammatory response. However, this conclusion cannot be drawn from the given data since a part of the variability related to CRP is missing. Indeed, Gornic and Lauc (2008) suggested that the value of CRP rises up to 100 times in the first 24 hours response to initial stimulus, especially bacterial infection.

The greatest limitation of this study was the absence of the baseline values for the blood parameters. Hence, the conclusions related to the initial research objective cannot be drawn due to the fact that these baseline values were not provided by the data collectors. It is therefore advisable, whenever enough or better still complete observations are available from new patients, to reconduct the analysis, this time using joint modeling on all available time points[33].

Furthermore this analysis did not consider the techniques for dealing with missing values of the covariates. However it would be advisable to do so in future.

The most important aspect of this study is the application of the joint modeling approach. The most flexible of multivariate joint modeling approaches is the random-effects approach[21,27]. While giving an answer to the association or not of two or more outcomes, this latter approach also gives an answer to the question on the association of the evolution of these outcomes and/or to the question of how the evolution of each specific outcome is associated with the evolution of the others[27]. These questions are of particular interest in clinical trials and in toxicology studies. Further, it deals with highly unbalanced data and can be used in very different situations.

In conclusion, this study suggested that the plasma N-linked glycans levels GP12 may be potential biomarker of the inflammatory response after cardiac surgery. However additional investigation is necessary to get more evidence of the potential of GP12 as the biomarker in this setting. It should be emphasized that the flexibility of the joint linear mixed models framework allows to model complex associations between the glycans and blood parameters.

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7. APPENDIX

7.1. Appendix 1: EDA Results
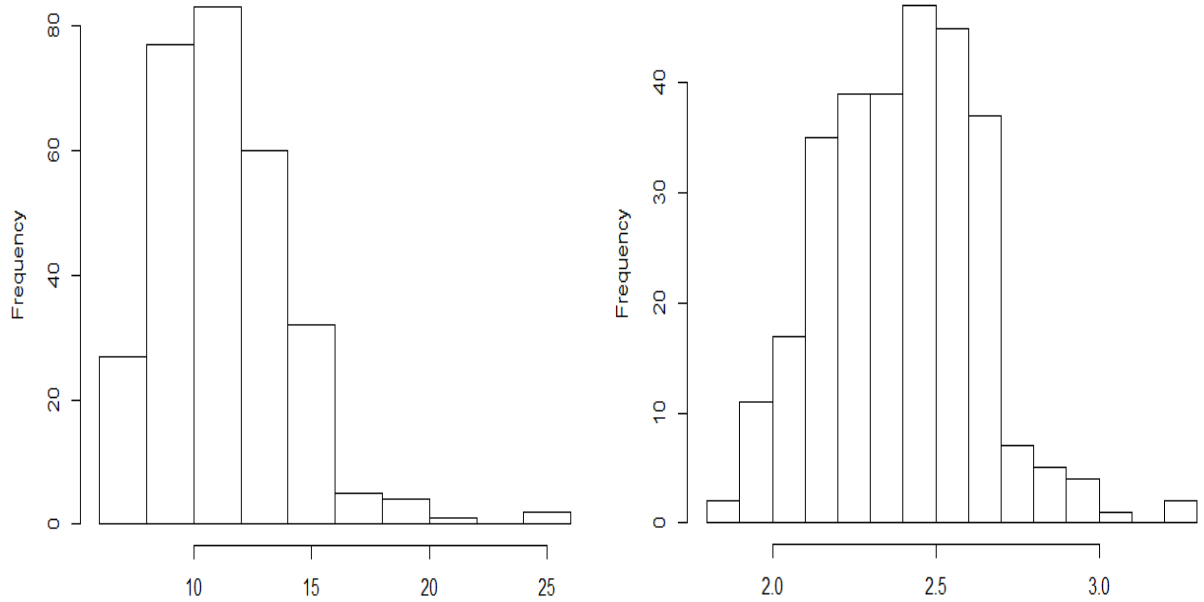
a. Levels of GP8 on the original scale (left) and on the Log-transformed scale (right)
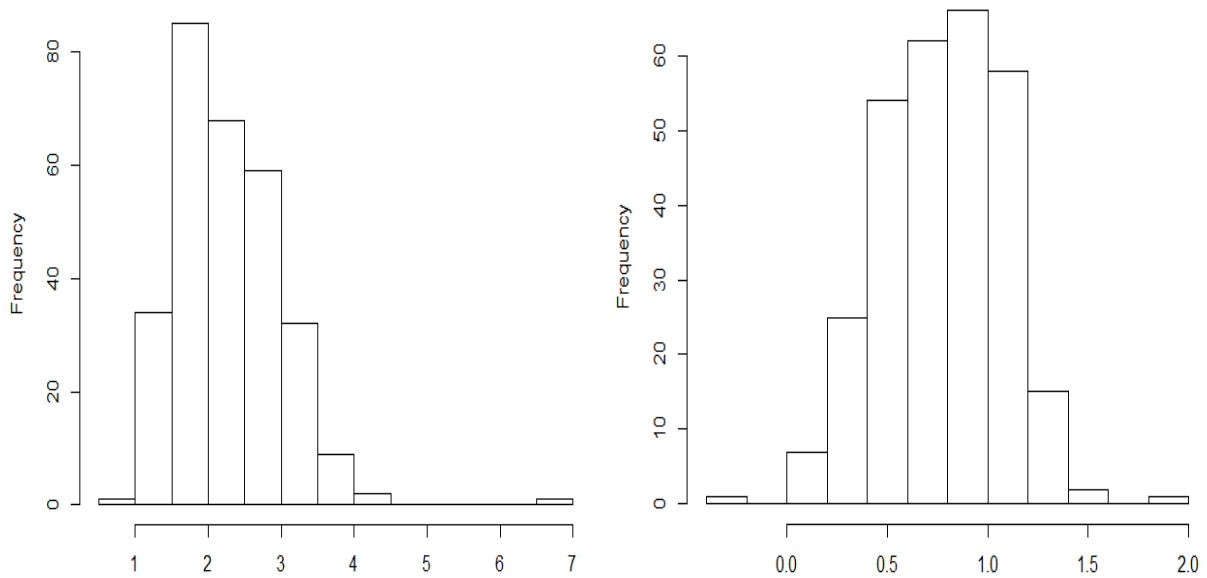
b. Levels of GP11 on the original scale (left) and on the Log-transformed scale (right)
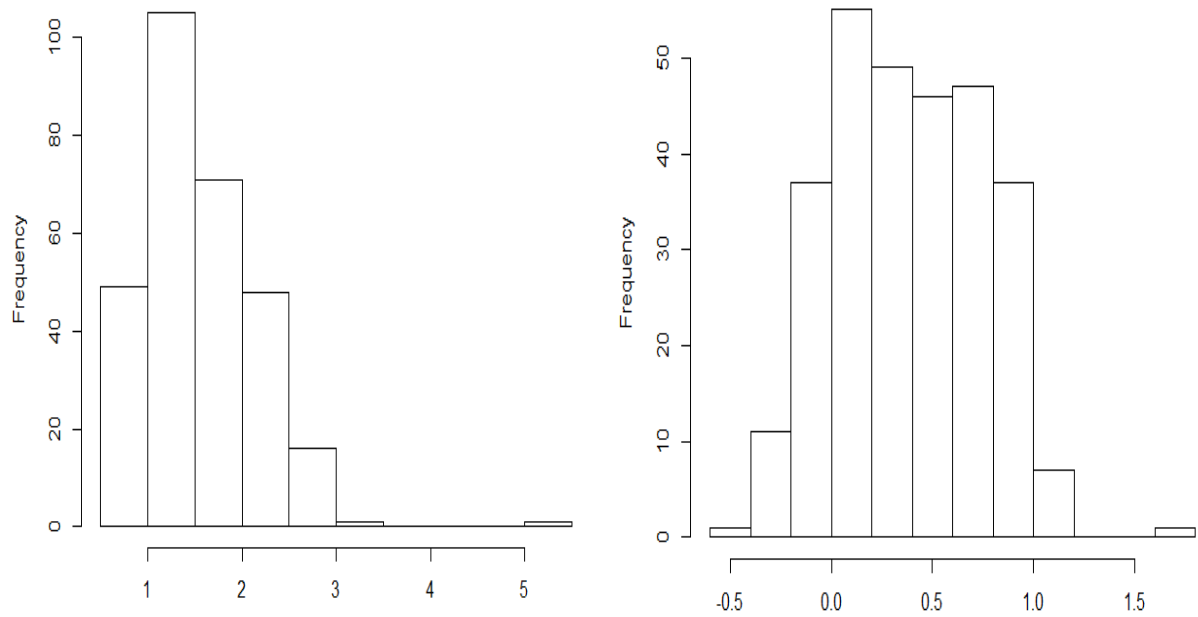
c. Levels of GP12 on the original scale (left) and on the Log-transformed scale (right)
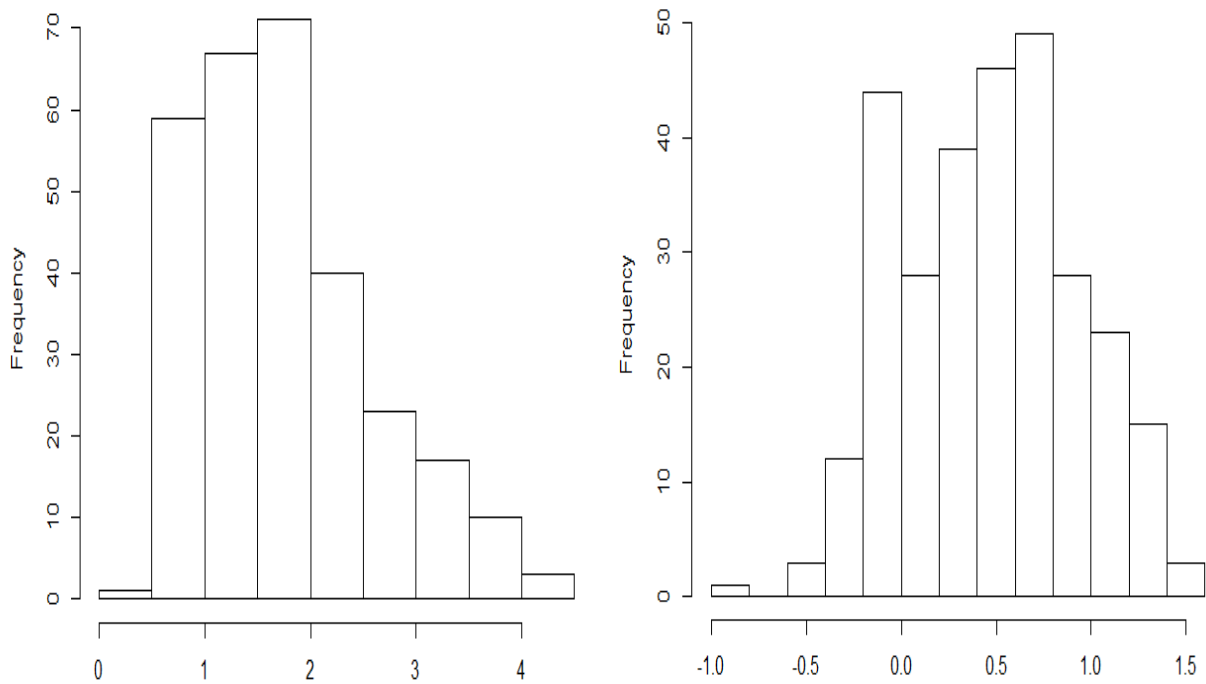
d. Levels of GP16 on the original scale (left) and on the Log-transformed scale (right)

Figure 1A: *Histograms of plasma N-linked glycans GP8, GP11, GP12, GP16 levels on the original and on the log-transformed scale*
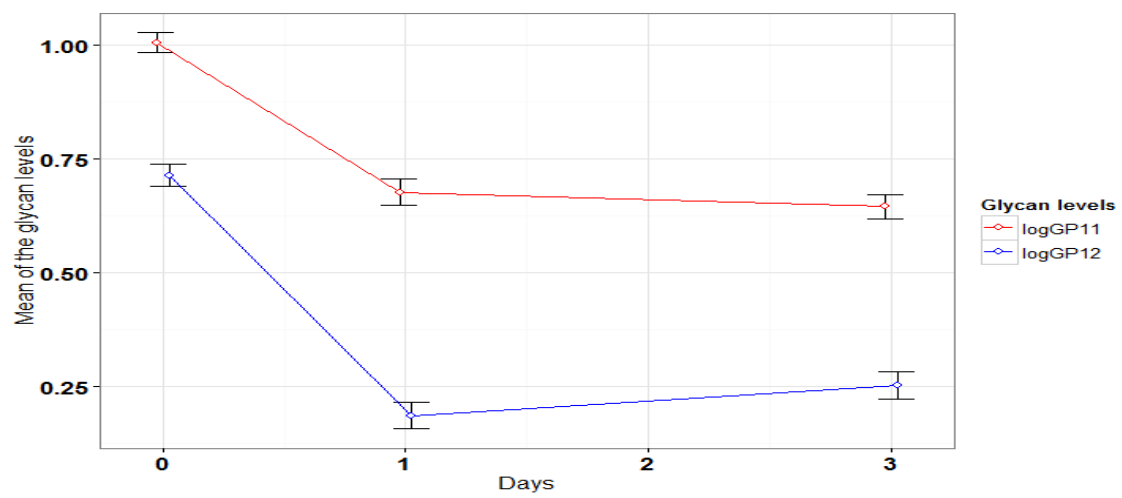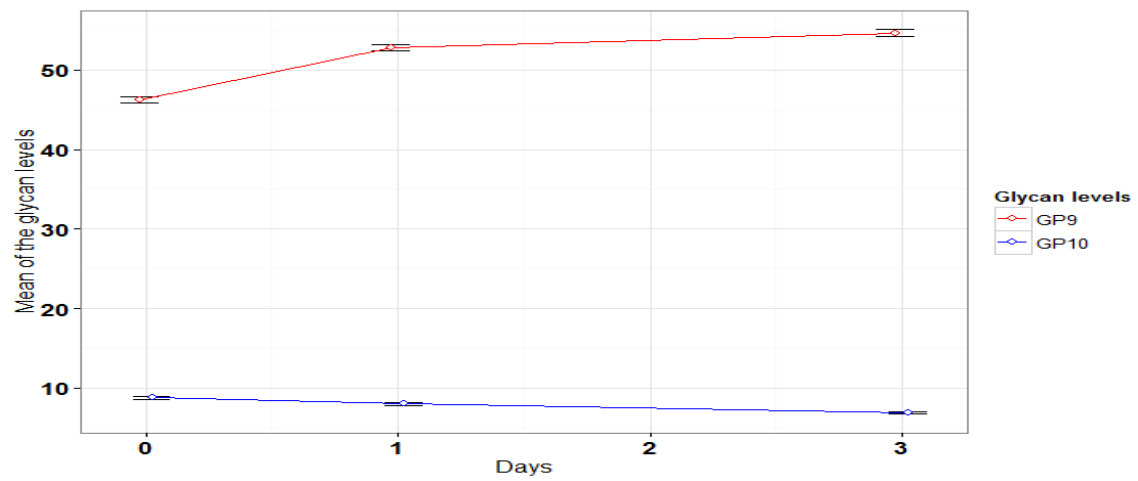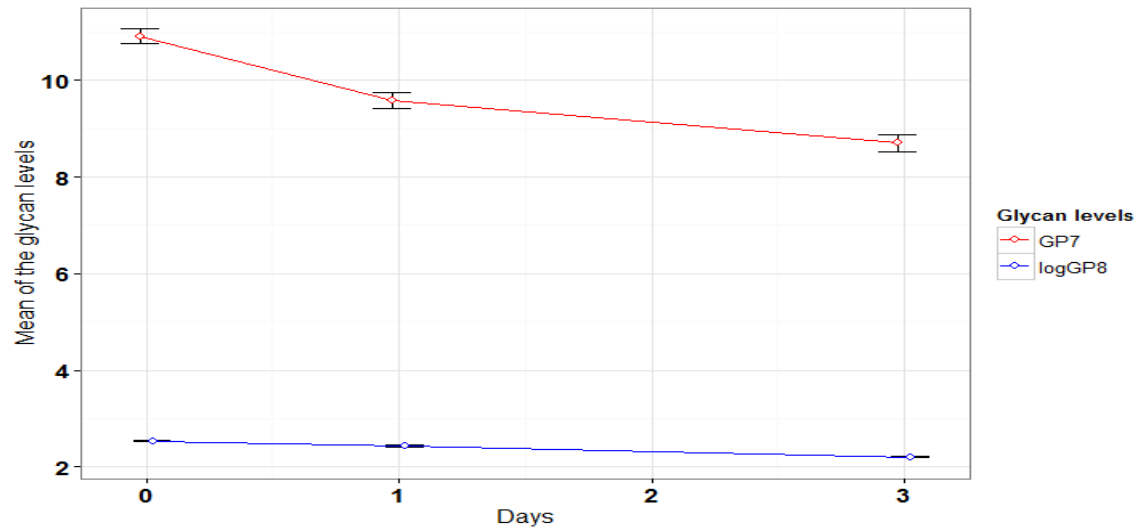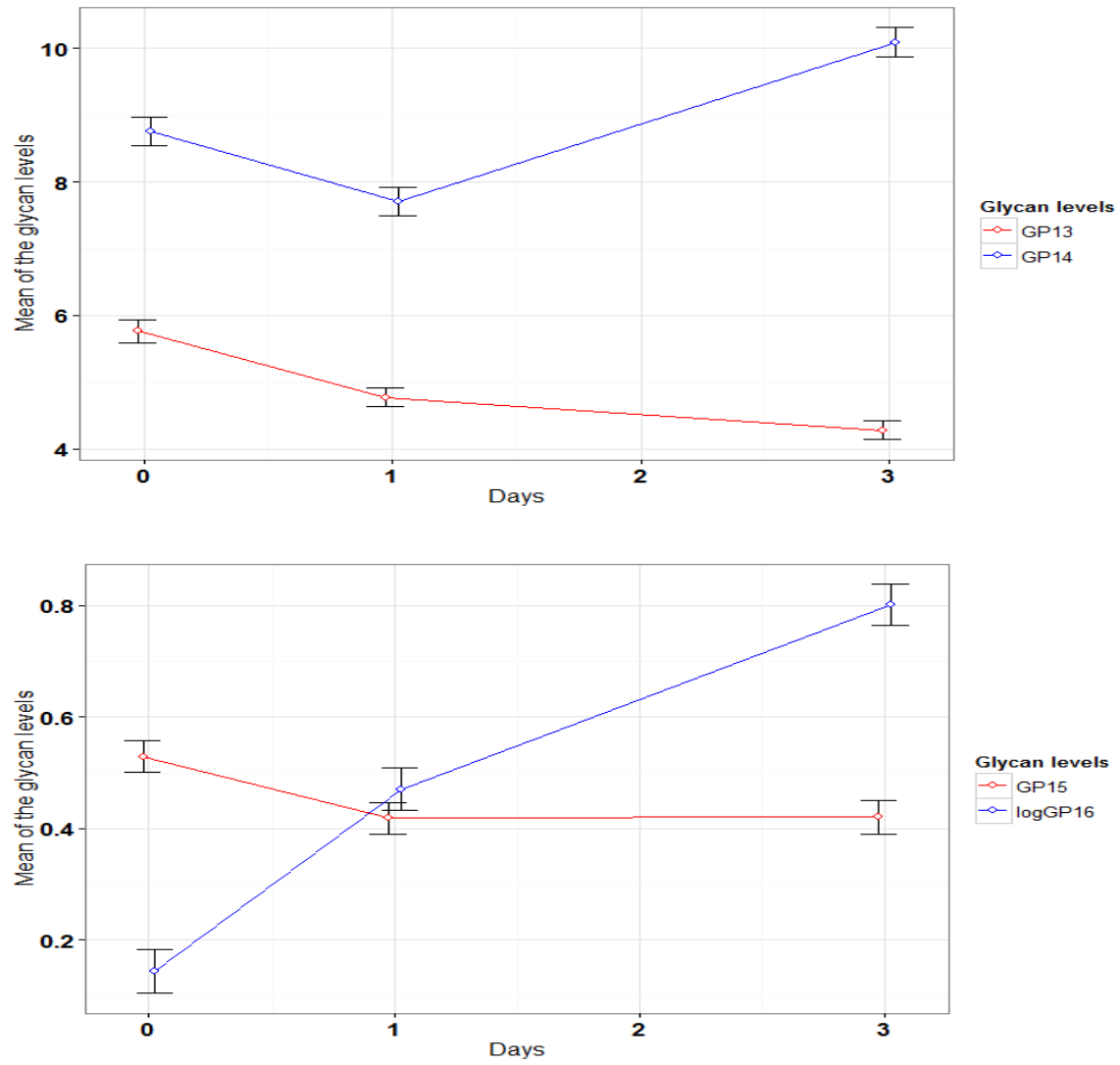
Figure 1B: *Mean and standard deviation of the levels of glycans per day of follow-up*
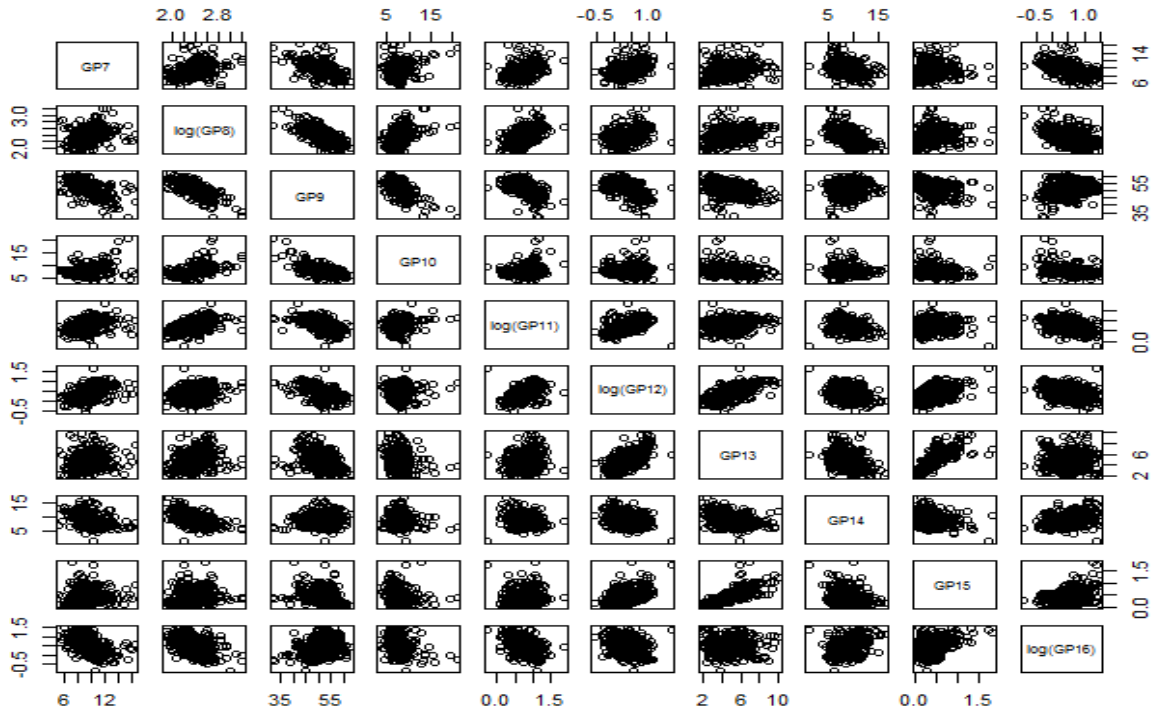
Figure 1C: *Scatter plot matrix of the levels of 10 glycans*

In the Appendices that follow; Par = parameter, S.E = standard error, Age = age-64.6082474, Rheumatic = rheumatic disease, Chronic renal=chronic renal insufficiency, bold = significant at 0.05 level, Var = variance, Cov = Covariance, Corr = correlation

7.2. Appendix 2: Univariate Models Results

Table 2A: *Linear mixed model estimates for GP10 and GP7 levels with statistical significant covariates with independence covariance structure for the random effects of both models*

Effects	Par.	GP10 - Independence			GP7 - Independence		
		Estimate	S.E	p-value	Estimate	S.E	p-value
Intercept	β_0	8.6304	0.7561	**<0.0001**	11.4663	0.5172	**<0.0001**
day1	β_1	-0.7256	0.1387	**<0.0001**	-1.3285	0.2055	**<0.0001**
day3	β_2	-1.9015	0.1387	**<0.0001**	-2.1847	0.2055	**<0.0001**
Age	β_3	0.0147	0.0196	0.4540	0.0153	0.0131	0.2468
Sex	β_4	0.5070	0.4799	0.2943	-0.1689	0.3213	0.6008
Hyperlipidemia	β_5	0.1120	0.4732	0.8136	0.1308	0.3168	0.6810
Hypertension	β_6	-0.2511	0.6065	0.6802	-0.5661	0.4061	0.1676
Rheumatic	β_7	2.1335	0.8804	**0.0179**	0.5356	0.5894	0.3666
Chronic renal	β_8	-0.3398	1.2706	0.7899	0.0013	0.8507	0.9988
Dialysis	β_9	0.5231	2.2954	0.8204	0.4607	1.5368	0.7652

Beta blockers	β_{10}	0.1337	0.5633	0.8131	0.2323	0.3772	0.5399
ACE inhibitors	β_{11}	-0.4033	0.5410	0.4585	0.1334	0.3622	0.7138
Statins	β_{12}	-0.3940	0.5210	0.4520	-0.4296	0.3488	0.2221
Amiodarone	β_{13}	-0.0492	0.8208	0.9523	-0.4115	0.5495	0.4564
Diuretic	β_{14}	0.2829	0.4775	0.5554	-0.0099	0.3197	0.9755
Covariance of b$_i$		*Independence*			*Independence*		
Var(b$_{1i}$)	$\sigma^2_{b_{1i}}$	3.2274	0.5841	**<0.0001**	0.9710	0.2700	**0.0002**
Residual variance							
Var(ε_{ij})	σ^2	0.8172	0.0892	**<0.0001**	1.7940	0.1960	**<0.0001**
Contrasts							
Day1 vs Day0		-0.7256	0.1387	**<0.0001**	-1.3285	0.2055	**<0.0001**
Day3 vs Day0		-1.9015	0.1387	**<0.0001**	-2.1847	0.2055	**<0.0001**

Table 2B: *Linear mixed model estimates for log(GP8) and GP9 levels with statistical significant covariates with independence covariance structure for the random effects of the former model and unstructured for the latter*

		Log(GP8)			GP9		
Effects	**Par.**	**Estimate**	**S.E**	**p-value**	**Estimate**	**S.E**	**p-value**
Intercept	β_0	2.5934	0.0729	**<0.0001**	45.5838	1.5582	**<0.0001**
day1	β_1	-0.1114	0.0141	**<0.0001**	6.6971	0.1933	**<0.0001**
day3	β_2	-0.3405	0.0141	**<0.0001**	8.6215	0.2855	**<0.0001**
Age	β_3	0.0003	0.0019	0.8656	-0.0165	0.0404	0.6845
Sex	β_4	0.0077	0.0462	0.8687	0.4565	0.9905	0.6463
Hyperlipidemia	β_5	0.0188	0.0456	0.6812	0.0041	0.9766	0.9966
Hypertension	β_6	-0.0018	0.0584	0.9756	-0.4546	1.2517	0.7175
Rheumatic	β_7	-0.0076	0.0848	0.9284	-1.4772	1.8169	0.4189
Chronic renal	β_8	-0.0931	0.1223	0.4493	2.2202	2.6221	0.4000
Dialysis	β_9	-0.1757	0.2210	0.4292	-0.3050	4.7371	0.9488
Beta blockers	β_{10}	-0.0212	0.0542	0.6973	-1.4221	1.1626	0.2252
ACE inhibitors	β_{11}	-0.0370	0.0521	0.4802	1.3947	1.1166	0.2157
Statins	β_{12}	-0.0129	0.0502	0.7981	0.7330	1.0753	0.4976
Amiodarone	β_{13}	0.0108	0.0790	0.8915	0.0438	1.6938	0.9794
Diuretic	β_{14}	-0.0368	0.0460	0.4255	0.9513	0.9855	0.3376
Covariance of b$_i$		*Independence*			*Unstructured*		
Var(b$_{1i}$)	$\sigma^2_{b_{1i}}$	0.0290	0.0050	**<0.0001**	14.2530	2.5939	**<0.0001**
Residual variance							
Var(ε_{ij})	σ^2	0.0080	0.0009	**<0.0001**	2.7368	0.3171	**<0.0001**
Contrasts							

| Day1 vs Day0 | -0.1114 | 0.0141 | **<0.0001** | 6.7096 | 0.2615 | **<0.0001** |
| Day3 vs Day0 | -0.3405 | 0.0141 | **<0.0001** | 8.5954 | 0.2615 | **<0.0001** |

Table 2C: *Linear mixed model estimates for log(GP11) and log(GP12) with statistical significant covariates with independence covariance structure for the random effects of both models.*

Effects	Par.	Log(GP11)			Log(GP12)		
		Estimate	S.E	p-value	Estimate	S.E	p-value
Intercept	β_0	1.0187	0.0734	**<0.0001**	0.6704	0.0921	**<0.0001**
day1	β_1	-0.3372	0.0340	**<0.0001**	-0.5336	0.0275	**<0.0001**
day3	β_2	-0.3605	0.0340	**<0.0001**	-0.4691	0.0275	**<0.0001**
Age	β_3	0.0023	0.0018	0.2093	-0.0001	0.0024	0.9578
Sex	β_4	0.0022	0.0452	0.9618	-0.0522	0.0579	0.3701
Hyperlipidemia	β_5	-0.0462	0.0445	0.3028	0.0397	0.0571	0.4893
Hypertension	β_6	0.0568	0.0571	0.3227	0.1254	0.0732	0.0907
Rheumatic	β_7	-0.0091	0.0828	0.9130	0.0136	0.1062	0.8987
Chronic renal	β_8	0.0104	0.1196	0.9308	-0.0891	0.1533	0.5629
Dialysis	β_9	-0.1882	0.2160	0.3865	-0.0623	0.2769	0.8225
Beta blockers	β_{10}	-0.0158	0.0530	0.7668	-0.0179	0.0680	0.7931
ACE inhibitors	β_{11}	-0.0395	0.0509	0.4403	-0.0360	0.0653	0.5829
Statins	β_{12}	0.0363	0.0490	0.4617	0.0737	0.0628	0.2449
Amiodarone	β_{13}	-0.0217	0.0772	0.7797	-0.0663	0.0990	0.5053
Diuretic	β_{14}	-0.0513	0.0449	0.2575	-0.0817	0.0576	0.1606
Covariance of b_i		*Independence*			*Independence*		
Var(b_{1i})	$\sigma^2_{b_{1i}}$	0.0147	0.0055	**0.0037**	0.0402	0.2006	**<0.0001**
Residual variance							
Var(ε_{ij})	σ^2	0.0490	0.0053	**<0.0001**	0.0320	0.1790	**<0.0001**
Contrasts							
Day1 vs Day0		-0.3372	0.0340	**<0.0001**	-0.5336	0.0275	**<0.0001**
Day3 vs Day0		-0.3605	0.0340	**<0.0001**	-0.4691	0.0275	**<0.0001**

Table 2D: *Linear mixed model estimates for GP14 and log(GP16) with statistical significant covariates with independence covariance structure for the random effects of both models and a random interceptand slope model for GP14.*

Effects	Par.	GP14			Log(GP16)		
		Estimate	S.E	p-value	Estimate	S.E	p-value
Intercept	β_0	8.4687	0.7623	**<0.0001**	0.0059	0.1388	0.9661
day1	β_1	-1.1026	0.1276	**<0.0001**	0.3246	0.0329	**<0.0001**
day3	β_2	1.2715	0.1647	**<0.0001**	0.6575	0.0329	**<0.0001**
Age	β_3	0.0230	0.0197	0.2473	-0.0046	0.0036	0.1999
Sex	β_4	0.5268	0.4843	0.2803	-0.0281	0.0878	0.7501
Hyperlipidemia	β_5	-0.7073	0.4775	0.1429	-0.0558	0.0865	0.5212
Hypertension	β_6	-0.3330	0.6120	0.5880	0.1224	0.1109	0.2734
Rheumatic	β_7	0.6469	0.8884	0.4688	-0.1957	0.1610	0.2282
Chronic renal	β_8	0.7112	1.2821	0.5808	-0.0194	0.2323	0.9337
Dialysis	β_9	2.2530	2.3162	0.3340	0.0763	0.4197	0.8563
Beta blockers	β_{10}	0.9728	0.5684	0.0913	0.0887	0.1030	0.3919
ACE inhibitors	β_{11}	-0.1534	0.5460	0.7796	-0.0238	0.0989	0.8108
Statins	β_{12}	-0.2442	0.4818	0.6138	0.0396	0.0953	0.6786
Amiodarone	β_{13}	-0.1003	0.5257	0.8492	0.0355	0.1501	0.8137
Diuretic	β_{14}	0.6399	0.8282	0.4422	0.0204	0.0873	0.8159
Covariance of b_i		*Independence*			*Independence*		
Var(b$_{1i}$)	$\sigma^2_{b_{1i}}$	3.2612	0.5991	**<0.0001**	0.1017	0.0196	**<0.0001**
Var(b$_{2i}$)	$\sigma^2_{b_{2i}}$	0.1056	0.0418	**0.0058**	-	-	
Residual variance							
Var(ε_{ij})	σ^2	0.6503	0.0998	**<0.0001**	0.0459	0.0050	**<0.0001**
Contrasts							
Day1 vs Day0		-1.1026	0.1286	**<0.0001**	0.3246	0.0329	**<0.0001**
Day3 vs Day0		1.2715	0.1627	**<0.0001**	0.6575	0.0329	**<0.0001**

7.3. Appendix 3: Pairwise Bivariate Models Results

Table 3A: *Bivariate joint Linear mixed model estimates for the pairs (GP7, log(GP8)) and (GP7, GP9) with r=1, s=2 and s=3*

Effect	Par.	GP7 - log(GP8)			GP7 - GP9		
		Estimate	S.E	P-value	Estimate	S.E	P-value
Intercept	β_{r0}	8.8729	0.4967	**<.0001**	-34.0457	1.8918	**<.0001**
Intercept	β_{s0}	2.5934	0.0729	**<.0001**	45.5120	1.5921	**<.0001**
day1	β_{r1}	-1.3285	0.2055	**<.0001**	-1.3285	0.2055	**<.0001**

day1	β_{s1}	-0.1114	0.0141	**<.0001**	6.7096	0.2615	**<.0001**
day3	β_{r2}	-2.1847	0.2055	**<.0001**	-2.1847	0.2055	**<.0001**
day3	β_{s2}	-0.3405	0.0141	**<.0001**	8.5954	0.2615	**<.0001**
Age	β_{r3}	0.0153	0.0131	0.2438	0.0153	0.0131	0.2438
Age	β_{s3}	0.0003	0.0019	0.8652	-0.0199	0.0413	0.6305
Sex	β_{r4}	-0.1689	0.3213	0.5995	-0.1689	0.3213	0.5995
Sex	β_{s4}	0.0077	0.0462	0.8683	0.5085	1.0116	0.6155
Hyperlipidemia	β_{r5}	0.1308	0.3168	0.6801	0.1308	0.3168	0.6801
Hyperlipidemia	β_{s5}	0.0188	0.0456	0.6803	-0.1011	0.9975	0.9193
Hypertension	β_{r6}	-0.5661	0.4061	0.1642	-0.5661	0.4061	0.1642
Hypertension	β_{s6}	-0.0018	0.0584	0.9755	-0.3741	1.2785	0.7700
Rheumatic	β_{r7}	0.5356	0.5894	0.3642	0.5356	0.5894	0.3642
Rheumatic	β_{s7}	-0.0076	0.0848	0.9282	-1.4049	1.8557	0.4495
Chronic renal	β_{r8}	0.0013	0.8507	0.9988	0.0013	0.8507	0.9988
Chronic renal	β_{s8}	-0.0931	0.1223	0.4474	1.8430	2.6782	0.4918
Dialysis	β_{r9}	0.4607	1.5368	0.7645	0.4607	1.5368	0.7645
Dialysis	β_{s9}	-0.1757	0.2210	0.4271	0.4577	4.8385	0.9247
Beta blockers	β_{r10}	0.2323	0.3772	0.5384	0.2323	0.3772	0.5384
Beta blockers	β_{s10}	-0.0212	0.0542	0.6964	-1.3741	1.1875	0.2480
ACE inhibitors	β_{r11}	0.1334	0.3622	0.7129	0.1334	0.3622	0.7129
ACE inhibitors	β_{s11}	-0.0370	0.0521	0.4784	1.3384	1.1405	0.2414
Statins	β_{r12}	-0.4296	0.3488	0.2190	-0.4296	0.3488	0.2190
Statins	β_{s12}	-0.0129	0.0502	0.7975	0.7227	1.0982	0.5110
Amiodarone	β_{r13}	-0.4115	0.5495	0.4544	-0.4115	0.5495	0.4544
Amiodarone	β_{s13}	0.0108	0.0790	0.8912	0.1927	1.7301	0.9114
Diuretic	β_{r14}	-0.0099	0.3197	0.9754	-0.0099	0.3197	0.9754
Diuretic	β_{s14}	-0.0369	0.0460	0.4234	1.0466	1.0065	0.2992
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.9708	0.2695	**0.0002**	0.9708	0.2695	**0.0002**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	0.0809	0.0283	**0.0042**	-2.4037	0.6474	**0.0002**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.0296	0.0054	**<.0001**	14.5820	2.5939	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	1.7941	0.1958	**<.0001**	1.7941	0.1958	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0084	0.0009	**<.0001**	2.9062	0.3171	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		0.4767			*-0.6388*		

Table 3B: *Bivariate joint Linear mixed model estimates for the pairs (GP7, GP10) and (GP7, log(GP11)) with r=1, s=3 and s=4*

Effect	Par.	GP7 - GP10			GP7 - log(GP11)		
		Estimate	S.E	P-value	Estimate	S.E	P-value
Intercept	β_{r0}	2.8359	0.7708	**0.0003**	10.4476	0.4875	**<.0001**
Intercept	β_{s0}	8.6304	0.7561	**<.0001**	1.0187	0.0734	**<.0001**
day1	β_{r1}	-1.3285	0.2055	**<.0001**	-1.3285	0.2055	**<.0001**
day1	β_{s1}	-0.7256	0.1387	**<.0001**	-0.3372	0.0340	**<.0001**
day3	β_{r2}	-2.1847	0.2055	**<.0001**	-2.1847	0.2055	**<.0001**
day3	β_{s2}	-1.9015	0.1387	**<.0001**	-0.3605	0.0340	**<.0001**
Age	β_{r3}	0.0153	0.0131	0.2438	0.0153	0.0131	0.2438
Age	β_{s3}	0.0147	0.0196	0.4520	0.0023	0.0018	0.2061
Sex	β_{r4}	-0.1689	0.3213	0.5995	-0.1689	0.3213	0.5995
Sex	β_{s4}	0.5070	0.4799	0.2916	0.0022	0.0452	0.9617
Hyperlipidemia	β_{r5}	0.1308	0.3168	0.6801	0.1308	0.3168	0.6801
Hyperlipidemia	β_{s5}	0.1120	0.4732	0.8130	-0.0462	0.0445	0.3000
Hypertension	β_{r6}	-0.5661	0.4061	0.1642	-0.5661	0.4061	0.1642
Hypertension	β_{s6}	-0.2511	0.6065	0.6792	0.0568	0.0571	0.3201
Rheumatic	β_{r7}	0.5356	0.5894	0.3642	0.5356	0.5894	0.3642
Rheumatic	β_{s7}	2.1335	0.8804	**0.0159**	-0.0091	0.0828	0.9128
Chronic renal	β_{r8}	0.0013	0.8507	0.9988	0.0013	0.8507	0.9988
Chronic renal	β_{s8}	-0.3398	1.2706	0.7893	0.0104	0.1196	0.9306
Dialysis	β_{r9}	0.4607	1.5368	0.7645	0.4607	1.5368	0.7645
Dialysis	β_{s9}	0.5231	2.2954	0.8199	-0.1882	0.2160	0.3842
Beta blockers	β_{r10}	0.2323	0.3772	0.5384	0.2323	0.3772	0.5384
Beta blockers	β_{s10}	0.1337	0.5633	0.8126	-0.0158	0.0530	0.7662
ACE inhibitors	β_{r11}	0.1334	0.3622	0.7129	0.1334	0.3622	0.7129
ACE inhibitors	β_{s11}	-0.4033	0.5410	0.4566	-0.0395	0.0509	0.4383
Statins	β_{r12}	-0.4296	0.3488	0.2190	-0.4296	0.3488	0.2190
Statins	β_{s12}	-0.3940	0.5210	0.4501	0.0363	0.0490	0.4598
Amiodarone	β_{r13}	-0.4115	0.5495	0.4544	-0.4115	0.5495	0.4544
Amiodarone	β_{s13}	-0.0492	0.8208	0.9522	-0.0217	0.0772	0.7791
Diuretic	β_{r14}	-0.0099	0.3197	0.9754	-0.0099	0.3197	0.9754
Diuretic	β_{s14}	0.2829	0.4775	0.5540	-0.0513	0.0449	0.2546
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.9708	0.2695	**0.0002**	0.9708	0.2695	**0.0002**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	0.7588	0.2903	**0.0089**	0.1091	0.0290	**0.0002**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	3.2274	0.5841	**<.0001**	0.0147	0.0055	**0.0037**
Residual variance							

Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	1.7941	0.1958	**<.0001**	1.7941	0.1958	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.8172	0.0892	**<.0001**	0.0490	0.0053	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		0.4287			*0.9145*		

Table 3C: Bivariate joint Linear mixed model estimates for the pairs (GP7, log(GP12)) and (GP7, GP13) with r=1, s=6 and s=7

		GP7 - log(GP12)			GP7 - GP13		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	10.7959	0.4829	**<.0001**	5.3401	0.6471	**<.0001**
Intercept	β_{s0}	0.6704	0.0921	**<.0001**	6.1263	0.4621	**<.0001**
day1	β_{r1}	-1.3285	0.2055	**<.0001**	-1.3285	0.2055	**<.0001**
day1	β_{s1}	-0.5336	0.0275	**<.0001**	-0.9992	0.1083	**<.0001**
day3	β_{r2}	-2.1847	0.2055	**<.0001**	-2.1847	0.2055	**<.0001**
day3	β_{s2}	-0.4691	0.0275	**<.0001**	-1.5158	0.1083	**<.0001**
Age	β_{r3}	0.0153	0.0131	0.2438	0.0153	0.0131	0.2438
Age	β_{s3}	-0.0001	0.0024	0.9577	-0.0269	0.0119	**0.0245**
Sex	β_{r4}	-0.1689	0.3213	0.5995	-0.1689	0.3213	0.5995
Sex	β_{s4}	-0.0522	0.0579	0.3678	-1.1990	0.2922	**<.0001**
Hyperlipidemia	β_{r5}	0.1308	0.3168	0.6801	0.1308	0.3168	0.6801
Hyperlipidemia	β_{s5}	0.0397	0.0571	0.4875	0.3463	0.2881	0.2303
Hypertension	β_{r6}	-0.5661	0.4061	0.1642	-0.5661	0.4061	0.1642
Hypertension	β_{s6}	0.1254	0.0732	0.0873	1.0017	0.3693	**0.0070**
Rheumatic	β_{r7}	0.5356	0.5894	0.3642	0.5356	0.5894	0.3642
Rheumatic	β_{s7}	0.0136	0.1062	0.8985	-1.1900	0.5361	**0.0271**
Chronic renal	β_{r8}	0.0013	0.8507	0.9988	0.0013	0.8507	0.9988
Chronic renal	β_{s8}	-0.0891	0.1533	0.5615	-1.0738	0.7737	0.1661
Dialysis	β_{r9}	0.4607	1.5368	0.7645	0.4607	1.5368	0.7645
Dialysis	β_{s9}	-0.0623	0.2769	0.8220	-1.6482	1.3977	0.2391
Beta blockers	β_{r10}	0.2323	0.3772	0.5384	0.2323	0.3772	0.5384
Beta blockers	β_{s10}	-0.0179	0.0680	0.7925	0.0373	0.3430	0.9134
ACE inhibitors	β_{r11}	0.1334	0.3622	0.7129	0.1334	0.3622	0.7129
ACE inhibitors	β_{s11}	-0.0360	0.0653	0.5815	-0.4367	0.3295	0.1859
Statins	β_{r12}	-0.4296	0.3488	0.2190	-0.4296	0.3488	0.2190
Statins	β_{s12}	0.0737	0.0629	0.2418	0.0704	0.3173	0.8245
Amiodarone	β_{r13}	-0.4115	0.5495	0.4544	-0.4115	0.5495	0.4544
Amiodarone	β_{s13}	-0.0663	0.0990	0.5036	-0.2574	0.4998	0.6068
Diuretic	β_{r14}	-0.0099	0.3197	0.9754	-0.0099	0.3197	0.9754

Diuretic	β_{s14}	-0.0817	0.0576	0.1572	-0.2801	0.2908	0.3361
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.9708	0.2695	**0.0002**	0.9708	0.2695	**0.0002**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}, b_{s1i}}$	0.1324	0.0368	**0.0003**	0.1926	0.1697	0.2563
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.0403	0.0086	**<.0001**	1.1316	0.2170	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	1.7941	0.1958	**<.0001**	1.7941	0.1958	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0320	0.0035	**<.0001**	0.4983	0.0544	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		*0.6700*				*0.1838*	

Table 3D: Bivariate joint Linear mixed model estimates for the pairs (GP7, GP14) and (GP7, GP15) with r=1, s=8 and s=9

Effect	Par.	GP7 - GP14			GP7 - GP15		
		Estimate	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	2.9833	1.1283	**0.0091**	10.9815	0.5231	**<.0001**
Intercept	β_{s0}	8.4830	0.7651	**<.0001**	0.4849	0.0999	**<.0001**
day1	β_{r1}	-1.3285	0.2055	**<.0001**	-1.3285	0.2055	**<.0001**
day1	β_{s1}	-1.1026	0.1458	**<.0001**	-0.1136	0.0270	**<.0001**
day3	β_{r2}	-2.1847	0.2055	**<.0001**	-2.1847	0.2055	**<.0001**
day3	β_{s2}	1.2715	0.1458	**<.0001**	-0.1112	0.0270	**<.0001**
Age	β_{r3}	0.0153	0.0131	0.2438	0.0153	0.0131	0.2438
Age	β_{s3}	0.0236	0.0198	0.2340	-0.0054	0.0026	**0.0370**
Sex	β_{r4}	-0.1689	0.3213	0.5995	-0.1689	0.3213	0.5995
Sex	β_{s4}	0.4677	0.4854	0.3360	-0.1187	0.0630	0.0603
Hyperlipidemia	β_{r5}	0.1308	0.3168	0.6801	0.1308	0.3168	0.6801
Hyperlipidemia	β_{s5}	-0.6276	0.4786	0.1906	0.0162	0.0621	0.7946
Hypertension	β_{r6}	-0.5661	0.4061	0.1642	-0.5661	0.4061	0.1642
Hypertension	β_{s6}	-0.2539	0.6134	0.6792	0.1722	0.0796	**0.0312**
Rheumatic	β_{r7}	0.5356	0.5894	0.3642	0.5356	0.5894	0.3642
Rheumatic	β_{s7}	0.5809	0.8904	0.5146	-0.1969	0.1155	0.0893
Chronic renal	β_{r8}	0.0013	0.8507	0.9988	0.0013	0.8507	0.9988
Chronic renal	β_{s8}	0.7885	1.2851	0.5399	-0.1422	0.1668	0.3944
Dialysis	β_{r9}	0.4607	1.5368	0.7645	0.4607	1.5368	0.7645
Dialysis	β_{s9}	2.3326	2.3216	0.3157	-0.1476	0.3013	0.6244
Beta blockers	β_{r10}	0.2323	0.3772	0.5384	0.2323	0.3772	0.5384
Beta blockers	β_{s10}	0.9569	0.5698	0.0940	-0.0012	0.0739	0.9875
ACE inhibitors	β_{r11}	0.1334	0.3622	0.7129	0.1334	0.3622	0.7129

ACE inhibitors	β_{s11}	-0.1927	0.5472	0.7250	-0.0201	0.0710	0.7777
Statins	β_{r12}	-0.4296	0.3488	0.2190	-0.4296	0.3488	0.2190
Statins	β_{s12}	-0.1364	0.5270	0.7959	0.0424	0.0684	0.5354
Amiodarone	β_{r13}	-0.4115	0.5495	0.4544	-0.4115	0.5495	0.4544
Amiodarone	β_{s13}	0.5471	0.8301	0.5103	-0.0804	0.1077	0.4558
Diuretic	β_{r14}	-0.0099	0.3197	0.9754	-0.0099	0.3197	0.9754
Diuretic	β_{s14}	-0.2711	0.4830	0.5750	-0.0109	0.0627	0.8624
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.9708	0.2695	**0.0002**	0.9708	0.2695	**0.0002**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-1.3009	0.3186	**<.0001**	0.0120	0.0363	**0.7410**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	3.2792	0.5976	**<.0001**	0.0500	0.0101	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	1.7941	0.1958	**<.0001**	1.7941	0.1958	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.9030	0.0985	**<.0001**	0.0309	0.0034	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		*-0.7291*				0.0544	

Table 3E: *Bivariate joint Linear mixed model estimates for the pairs (GP7, log(GP16)) with r=1 and s=10, and (log(GP8), GP9) with r=2 and s=3*

		GP7 - log(GP16)			log(GP8) - GP9		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	11.4604	0.5864	**<.0001**	-42.9186	1.6436	**<.0001**
Intercept	β_{s0}	0.0059	0.1388	0.9661	45.5120	1.5921	**<.0001**
day1	β_{r1}	-1.3285	0.2055	**<.0001**	-0.1114	0.0141	**<.0001**
day1	β_{s1}	0.3246	0.0329	**<.0001**	6.7096	0.2615	**<.0001**
day3	β_{r2}	-2.1847	0.2055	**<.0001**	-0.3405	0.0141	**<.0001**
day3	β_{s2}	0.6575	0.0329	**<.0001**	8.5954	0.2615	**<.0001**
Age	β_{r3}	0.0153	0.0131	0.2438	0.0003	0.0019	0.8652
Age	β_{s3}	-0.0046	0.0036	0.1967	-0.0199	0.0413	0.6305
Sex	β_{r4}	-0.1689	0.3213	0.5995	0.0077	0.0462	0.8683
Sex	β_{s4}	-0.0281	0.0878	0.7494	0.5085	1.0116	0.6155
Hyperlipidemia	β_{r5}	0.1308	0.3168	0.6801	0.0188	0.0456	0.6803
Hyperlipidemia	β_{s5}	-0.0558	0.0865	0.5196	-0.1011	0.9975	0.9193
Hypertension	β_{r6}	-0.5661	0.4061	0.1642	-0.0018	0.0584	0.9755
Hypertension	β_{s6}	0.1224	0.1109	0.2705	-0.3741	1.2785	0.7700
Rheumatic	β_{r7}	0.5356	0.5894	0.3642	-0.0076	0.0848	0.9282
Rheumatic	β_{s7}	-0.1957	0.1610	0.2250	-1.4049	1.8557	0.4495
Chronic renal	β_{r8}	0.0013	0.8507	0.9988	-0.0931	0.1223	0.4474

Effect	Par.	Estimate	S.E	P-value	Estimate	S.E	P-value
Chronic renal	β_{s8}	-0.0194	0.2323	0.9335	1.8430	2.6782	0.4918
Dialysis	β_{r9}	0.4607	1.5368	0.7645	-0.1757	0.2210	0.4271
Dialysis	β_{s9}	0.0763	0.4197	0.8559	0.4577	4.8385	0.9247
Beta blockers	β_{r10}	0.2323	0.3772	0.5384	-0.0212	0.0542	0.6964
Beta blockers	β_{s10}	0.0887	0.1030	0.3897	-1.3741	1.1875	0.2480
ACE inhibitors	β_{r11}	0.1334	0.3622	0.7129	-0.0370	0.0521	0.4784
ACE inhibitors	β_{s11}	-0.0238	0.0989	0.8102	1.3384	1.1405	0.2414
Statins	β_{r12}	-0.4296	0.3488	0.2190	-0.0129	0.0502	0.7975
Statins	β_{s12}	0.0396	0.0953	0.6777	0.7227	1.0982	0.5110
Amiodarone	β_{r13}	-0.4115	0.5495	0.4544	0.0108	0.0790	0.8912
Amiodarone	β_{s13}	0.0355	0.1501	0.8132	0.1927	1.7301	0.9114
Diuretic	β_{r14}	-0.0099	0.3197	0.9754	-0.0369	0.0460	0.4234
Diuretic	β_{s14}	0.0204	0.0873	0.8154	1.0466	1.0065	0.2992
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.9708	0.2695	**0.0002**	0.0296	0.0054	**<.0001**
Cov(b_{r1i},b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.1769	0.0546	**0.0012**	-0.4992	0.1023	**<.0001**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.1017	0.0196	**<.0001**	14.5820	2.5939	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	1.7941	0.1958	**<.0001**	0.0084	0.0009	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0459	0.0050	**<.0001**	2.9062	0.3171	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i},b_{s1i})		-0.5630			*-0.7593*		

Table 3F: *Bivariate joint Linear mixed model estimates for the pairs (log(GP8), GP10) and (log(GP8), log(GP11)) with r=2, s=4 and s=5*

Effect	Par.	log(GP8) - GP10			log(GP8) - log(GP11)		
		Estimate	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	-6.0370	0.7238	**<.0001**	1.5747	0.0715	**<.0001**
Intercept	β_{s0}	8.6304	0.7561	**<.0001**	1.0187	0.0734	**<.0001**
day1	β_{r1}	-0.1114	0.0141	**<.0001**	-0.1114	0.0141	**<.0001**
day1	β_{s1}	-0.7256	0.1387	**<.0001**	-0.3372	0.0340	**<.0001**
day3	β_{r2}	-0.3405	0.0141	**<.0001**	-0.3405	0.0141	**<.0001**
day3	β_{s2}	-1.9015	0.1387	**<.0001**	-0.3605	0.0340	**<.0001**
Age	β_{r3}	0.0003	0.0019	0.8652	0.0003	0.0019	0.8652
Age	β_{s3}	0.0147	0.0196	0.4520	0.0023	0.0018	0.2061
Sex	β_{r4}	0.0077	0.0462	0.8683	0.0077	0.0462	0.8683
Sex	β_{s4}	0.5070	0.4799	0.2916	0.0022	0.0452	0.9617

Hyperlipidemia	β_{r5}	0.0188	0.0456	0.6803	0.0188	0.0456	0.6803
Hyperlipidemia	β_{s5}	0.1120	0.4732	0.8130	-0.0462	0.0445	0.3000
Hypertension	β_{r6}	-0.0018	0.0584	0.9755	-0.0018	0.0584	0.9755
Hypertension	β_{s6}	-0.2511	0.6065	0.6792	0.0568	0.0571	0.3201
Rheumatic	β_{r7}	-0.0076	0.0848	0.9282	-0.0076	0.0848	0.9282
Rheumatic	β_{s7}	2.1335	0.8804	**0.0159**	-0.0091	0.0828	0.9128
Chronic renal	β_{r8}	-0.0931	0.1223	0.4474	-0.0931	0.1223	0.4474
Chronic renal	β_{s8}	-0.3398	1.2706	0.7893	0.0104	0.1196	0.9306
Dialysis	β_{r9}	-0.1757	0.2210	0.4271	-0.1757	0.2210	0.4271
Dialysis	β_{s9}	0.5231	2.2954	0.8199	-0.1882	0.2160	0.3842
Beta blockers	β_{r10}	-0.0212	0.0542	0.6964	-0.0212	0.0542	0.6964
Beta blockers	β_{s10}	0.1337	0.5633	0.8126	-0.0158	0.0530	0.7662
ACE inhibitors	β_{r11}	-0.0370	0.0521	0.4784	-0.0370	0.0521	0.4784
ACE inhibitors	β_{s11}	-0.4033	0.5410	0.4566	-0.0395	0.0509	0.4383
Statins	β_{r12}	-0.0129	0.0502	0.7975	-0.0129	0.0502	0.7975
Statins	β_{s12}	-0.3940	0.5210	0.4501	0.0363	0.0490	0.4598
Amiodarone	β_{r13}	0.0108	0.0790	0.8912	0.0108	0.0790	0.8912
Amiodarone	β_{s13}	-0.0492	0.8208	0.9522	-0.0217	0.0772	0.7791
Diuretic	β_{r14}	-0.0369	0.0460	0.4234	-0.0369	0.0460	0.4234
Diuretic	β_{s14}	0.2829	0.4775	0.5540	-0.0513	0.0449	0.2546
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.0296	0.0054	**<.0001**	0.0296	0.0054	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	0.1648	0.0442	**0.0002**	0.0173	0.0043	**<.0001**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	3.2274	0.5841	**<.0001**	0.0147	0.0055	**0.0037**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.0084	0.0009	**<.0001**	0.0084	0.0009	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.8172	0.0892	**<.0001**	0.0490	0.0053	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		0.5328			*0.8297*		

Table 3G: *Bivariate joint Linear mixed model estimates for the pairs (log(GP8), log(GP12)) and (log(GP8), GP13) with r=2, s=6 and s=7*

		log(GP8) - log(GP12)			log(GP8) - GP13		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	1.9230	0.1086	**<.0001**	-3.5328	0.4720	**<.0001**
Intercept	β_{s0}	0.6704	0.0921	**<.0001**	6.1263	0.4621	**<.0001**
day1	β_{r1}	-0.1114	0.0141	**<.0001**	-0.1114	0.0141	**<.0001**
day1	β_{s1}	-0.5336	0.0275	**<.0001**	-0.9992	0.1083	**<.0001**

day3	β_{r2}	-0.3405	0.0141	**<.0001**	-0.3405	0.0141	**<.0001**
day3	β_{s2}	-0.4691	0.0275	**<.0001**	-1.5158	0.1083	**<.0001**
Age	β_{r3}	0.0003	0.0019	0.8652	0.0003	0.0019	0.8652
Age	β_{s3}	-0.0001	0.0024	0.9577	-0.0269	0.0119	**0.0245**
Sex	β_{r4}	0.0077	0.0462	0.8683	0.0077	0.0462	0.8683
Sex	β_{s4}	-0.0522	0.0579	0.3678	-1.1990	0.2922	**<.0001**
Hyperlipidemia	β_{r5}	0.0188	0.0456	0.6803	0.0188	0.0456	0.6803
Hyperlipidemia	β_{s5}	0.0397	0.0571	0.4875	0.3463	0.2881	0.2303
Hypertension	β_{r6}	-0.0018	0.0584	0.9755	-0.0018	0.0584	0.9755
Hypertension	β_{s6}	0.1254	0.0732	0.0873	1.0017	0.3693	**0.0070**
Rheumatic	β_{r7}	-0.0076	0.0848	0.9282	-0.0076	0.0848	0.9282
Rheumatic	β_{s7}	0.0136	0.1062	0.8985	-1.1900	0.5361	**0.0271**
Chronic renal	β_{r8}	-0.0931	0.1223	0.4474	-0.0931	0.1223	0.4474
Chronic renal	β_{s8}	-0.0891	0.1533	0.5615	-1.0738	0.7737	0.1661
Dialysis	β_{r9}	-0.1757	0.2210	0.4271	-0.1757	0.2210	0.4271
Dialysis	β_{s9}	-0.0623	0.2769	0.8220	-1.6482	1.3977	0.2391
Beta blockers	β_{r10}	-0.0212	0.0542	0.6964	-0.0212	0.0542	0.6964
Beta blockers	β_{s10}	-0.0179	0.0680	0.7925	0.0373	0.3430	0.9134
ACE inhibitors	β_{r11}	-0.0370	0.0521	0.4784	-0.0370	0.0521	0.4784
ACE inhibitors	β_{s11}	-0.0360	0.0653	0.5815	-0.4367	0.3295	0.1859
Statins	β_{r12}	-0.0129	0.0502	0.7975	-0.0129	0.0502	0.7975
Statins	β_{s12}	0.0737	0.0629	0.2418	0.0704	0.3173	0.8245
Amiodarone	β_{r13}	0.0108	0.0790	0.8912	0.0108	0.0790	0.8912
Amiodarone	β_{s13}	-0.0663	0.0990	0.5036	-0.2574	0.4998	0.6068
Diuretic	β_{r14}	-0.0369	0.0460	0.4234	-0.0369	0.0460	0.4234
Diuretic	β_{s14}	-0.0817	0.0576	0.1572	-0.2801	0.2908	0.3361
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.0296	0.0054	**<.0001**	0.0296	0.0054	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	0.0062	0.0048	0.2023	-0.0121	0.0242	0.6162
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.0403	0.0086	**<.0001**	1.1316	0.2170	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.0084	0.0009	**<.0001**	0.0084	0.0009	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0320	0.0035	**<.0001**	0.4983	0.0544	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		0.1789			-0.0663		

Table 3H: *Bivariate joint Linear mixed model estimates for the pairs (log(GP8), GP14) and (log(GP8), GP15) with r=2, s=8 and s=9*

Effect	Par.	log(GP8) - GP14			log(GP8) - GP15		
		Estimate	S.E	P-value	Estimate	S.E	P-value
Intercept	β_{r0}	-5.8896	0.8052	**<.0001**	2.1085	0.1179	**<.0001**
Intercept	β_{s0}	8.4830	0.7651	**<.0001**	0.4849	0.0999	**<.0001**
day1	β_{r1}	-0.1114	0.0141	**<.0001**	-0.1114	0.0141	**<.0001**
day1	β_{s1}	-1.1026	0.1458	**<.0001**	-0.1136	0.0270	**<.0001**
day3	β_{r2}	-0.3405	0.0141	**<.0001**	-0.3405	0.0141	**<.0001**
day3	β_{s2}	1.2715	0.1458	**<.0001**	-0.1112	0.0270	**<.0001**
Age	β_{r3}	0.0003	0.0019	0.8652	0.0003	0.0019	0.8652
Age	β_{s3}	0.0236	0.0198	0.2340	-0.0054	0.0026	**0.0370**
Sex	β_{r4}	0.0077	0.0462	0.8683	0.0077	0.0462	0.8683
Sex	β_{s4}	0.4677	0.4854	0.3360	-0.1187	0.0630	0.0603
Hyperlipidemia	β_{r5}	0.0188	0.0456	0.6803	0.0188	0.0456	0.6803
Hyperlipidemia	β_{s5}	-0.6276	0.4786	0.1906	0.0162	0.0621	0.7946
Hypertension	β_{r6}	-0.0018	0.0584	0.9755	-0.0018	0.0584	0.9755
Hypertension	β_{s6}	-0.2539	0.6134	0.6792	0.1722	0.0796	**0.0312**
Rheumatic	β_{r7}	-0.0076	0.0848	0.9282	-0.0076	0.0848	0.9282
Rheumatic	β_{s7}	0.5809	0.8904	0.5146	-0.1969	0.1155	0.0893
Chronic renal	β_{r8}	-0.0931	0.1223	0.4474	-0.0931	0.1223	0.4474
Chronic renal	β_{s8}	0.7885	1.2851	0.5399	-0.1422	0.1668	0.3944
Dialysis	β_{r9}	-0.1757	0.2210	0.4271	-0.1757	0.2210	0.4271
Dialysis	β_{s9}	2.3326	2.3216	0.3157	-0.1476	0.3013	0.6244
Beta blockers	β_{r10}	-0.0212	0.0542	0.6964	-0.0212	0.0542	0.6964
Beta blockers	β_{s10}	0.9569	0.5698	0.0940	-0.0012	0.0739	0.9875
ACE inhibitors	β_{r11}	-0.0370	0.0521	0.4784	-0.0370	0.0521	0.4784
ACE inhibitors	β_{s11}	-0.1927	0.5472	0.7250	-0.0201	0.0710	0.7777
Statins	β_{r12}	-0.0129	0.0502	0.7975	-0.0129	0.0502	0.7975
Statins	β_{s12}	-0.1364	0.5270	0.7959	0.0424	0.0684	0.5354
Amiodarone	β_{r13}	0.0108	0.0790	0.8912	0.0108	0.0790	0.8912
Amiodarone	β_{s13}	0.5471	0.8301	0.5103	-0.0804	0.1077	0.4558
Diuretic	β_{r14}	-0.0369	0.0460	0.4234	-0.0369	0.0460	0.4234
Diuretic	β_{s14}	-0.2711	0.4830	0.5750	-0.0109	0.0627	0.8624
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.0296	0.0054	**<.0001**	0.0296	0.0054	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.1783	0.0453	**<.0001**	0.0043	0.0052	0.4108
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	3.2792	0.5976	**<.0001**	0.0500	0.0101	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.0084	0.0009	**<.0001**	0.0084	0.0009	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.9030	0.0985	**<.0001**	0.0309	0.0034	**<.0001**

Correlation of random intercepts		
Corr(b_{r1i}, b_{s1i})	-0.5719	0.1119

Table 3I: *Bivariate joint Linear mixed model estimates for the pairs (log(GP8), log(GP16)) with r=2 and s=10, and (GP9, GP10)) with r=3 and s=4*

Effect	Par.	log(GP8) - log(GP16)			GP9 - GP10		
		Estimate	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	0.0059	0.1388	0.9661	8.6304	0.7561	**<.0001**
Intercept	β_{s0}	2.5875	0.1695	**<.0001**	36.8816	2.1998	**<.0001**
day1	β_{r1}	-0.1114	0.0141	**<.0001**	6.7096	0.2615	**<.0001**
day1	β_{s1}	0.3246	0.0329	**<.0001**	-0.7256	0.1387	**<.0001**
day3	β_{r2}	-0.3405	0.0141	**<.0001**	8.5954	0.2615	**<.0001**
day3	β_{s2}	0.6575	0.0329	**<.0001**	-1.9015	0.1387	**<.0001**
Age	β_{r3}	0.0003	0.0019	0.8652	-0.0199	0.0413	0.6305
Age	β_{s3}	-0.0046	0.0036	0.1967	0.0147	0.0196	0.4520
Sex	β_{r4}	0.0077	0.0462	0.8683	0.5085	1.0116	0.6155
Sex	β_{s4}	-0.0281	0.0878	0.7494	0.5070	0.4799	0.2916
Hyperlipidemia	β_{r5}	0.0188	0.0456	0.6803	-0.1011	0.9975	0.9193
Hyperlipidemia	β_{s5}	-0.0558	0.0865	0.5196	0.1120	0.4732	0.8130
Hypertension	β_{r6}	-0.0018	0.0584	0.9755	-0.3741	1.2785	0.7700
Hypertension	β_{s6}	0.1224	0.1109	0.2705	-0.2511	0.6065	0.6792
Rheumatic	β_{r7}	-0.0076	0.0848	0.9282	-1.4049	1.8557	0.4495
Rheumatic	β_{s7}	-0.1957	0.1610	0.2250	2.1335	0.8804	0.0159
Chronic renal	β_{r8}	-0.0931	0.1223	0.4474	1.8430	2.6782	0.4918
Chronic renal	β_{s8}	-0.0194	0.2323	0.9335	-0.3398	1.2706	0.7893
Dialysis	β_{r9}	-0.1757	0.2210	0.4271	0.4577	4.8385	0.9247
Dialysis	β_{s9}	0.0763	0.4197	0.8559	0.5231	2.2954	0.8199
Beta blockers	β_{r10}	-0.0212	0.0542	0.6964	-1.3741	1.1875	0.2480
Beta blockers	β_{s10}	0.0887	0.1030	0.3897	0.1337	0.5633	0.8126
ACE inhibitors	β_{r11}	-0.0370	0.0521	0.4784	1.3384	1.1405	0.2414
ACE inhibitors	β_{s11}	-0.0238	0.0989	0.8102	-0.4033	0.5410	0.4566
Statins	β_{r12}	-0.0129	0.0502	0.7975	0.7227	1.0982	0.5110
Statins	β_{s12}	0.0396	0.0953	0.6777	-0.3940	0.5210	0.4501
Amiodarone	β_{r13}	0.0108	0.0790	0.8912	0.1927	1.7301	0.9114
Amiodarone	β_{s13}	0.0355	0.1501	0.8132	-0.0492	0.8208	0.9522
Diuretic	β_{r14}	-0.0369	0.0460	0.4234	1.0466	1.0065	0.2992
Diuretic	β_{s14}	0.0204	0.0873	0.8154	0.2829	0.4775	0.5540
Covariance of b_{k1i}							

Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.0296	0.0054	**<.0001**	14.5820	2.5939	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.0129	0.0074	0.0821	-5.3630	1.0749	**<.0001**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.1017	0.0196	**<.0001**	3.2274	0.5841	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.0084	0.0009	**<.0001**	2.9062	0.3171	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0459	0.0050	**<.0001**	0.8172	0.0892	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		-0.2349			*-0.7818*		

Table 3J: *Bivariate joint Linear mixed model estimates for the pairs (GP9, log(GP11)) and (GP9, log(GP12)) with r=3, s=5 and s=6*

Effect	Par.	GP9 - log(GP11)			GP9 - log(GP12)		
		Estimate	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	1.0187	0.0734	**<.0001**	0.6704	0.0921	**<.0001**
Intercept	β_{s0}	44.4933	1.6254	**<.0001**	44.8416	1.6156	**<.0001**
day1	β_{r1}	6.7096	0.2615	**<.0001**	6.7096	0.2615	**<.0001**
day1	β_{s1}	-0.3372	0.0340	**<.0001**	-0.5336	0.0275	**<.0001**
day3	β_{r2}	8.5954	0.2615	**<.0001**	8.5954	0.2615	**<.0001**
day3	β_{s2}	-0.3605	0.0340	**<.0001**	-0.4691	0.0275	**<.0001**
Age	β_{r3}	-0.0199	0.0413	0.6305	-0.0199	0.0413	0.6305
Age	β_{s3}	0.0023	0.0018	0.2061	-0.0001	0.0024	0.9577
Sex	β_{r4}	0.5085	1.0116	0.6155	0.5085	1.0116	0.6155
Sex	β_{s4}	0.0022	0.0452	0.9617	-0.0522	0.0579	0.3678
Hyperlipidemia	β_{r5}	-0.1011	0.9975	0.9193	-0.1011	0.9975	0.9193
Hyperlipidemia	β_{s5}	-0.0462	0.0445	0.3000	0.0397	0.0571	0.4875
Hypertension	β_{r6}	-0.3741	1.2785	0.7700	-0.3741	1.2785	0.7700
Hypertension	β_{s6}	0.0568	0.0571	0.3201	0.1254	0.0732	0.0873
Rheumatic	β_{r7}	-1.4049	1.8557	0.4495	-1.4049	1.8557	0.4495
Rheumatic	β_{s7}	-0.0091	0.0828	0.9128	0.01356	0.1062	0.8985
Chronic renal	β_{r8}	1.8430	2.6782	0.4918	1.843	2.6782	0.4918
Chronic renal	β_{s8}	0.0104	0.1196	0.9306	-0.08908	0.1533	0.5615
Dialysis	β_{r9}	0.4577	4.8385	0.9247	0.4577	4.8385	0.9247
Dialysis	β_{s9}	-0.1882	0.2160	0.3842	-0.06234	0.2769	0.8220
Beta blockers	β_{r10}	-1.3741	1.1875	0.2480	-1.3741	1.1875	0.2480
Beta blockers	β_{s10}	-0.0158	0.0530	0.7662	-0.01789	0.06795	0.7925
ACE inhibitors	β_{r11}	1.3384	1.1405	0.2414	1.3384	1.1405	0.2414
ACE inhibitors	β_{s11}	-0.0395	0.0509	0.4383	-0.03601	0.06527	0.5815
Statins	β_{r12}	0.7227	1.0982	0.5110	0.7227	1.0982	0.5110

Statins	β_{s12}	0.0363	0.0490	0.4598	0.07369	0.06285	0.2418
Amiodarone	β_{r13}	0.1927	1.7301	0.9114	0.1927	1.7301	0.9114
Amiodarone	β_{s13}	-0.0217	0.0772	0.7791	-0.06628	0.09901	0.5036
Diuretic	β_{r14}	1.0466	1.0065	0.2992	1.0466	1.0065	0.2992
Diuretic	β_{s14}	-0.0513	0.0449	0.2546	-0.08165	0.0576	0.1572
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	14.5820	2.5939	**<.0001**	14.582	2.5939	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.3152	0.0899	**0.0005**	-0.2074	0.1077	0.0541
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.0147	0.0055	**0.0037**	0.0403	0.0086	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	2.9062	0.3171	**<.0001**	2.9062	0.3171	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0490	0.0053	**<.0001**	0.0320	0.0035	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		*-0.6819*			-0.2707		

Table 3K: *Bivariate joint Linear mixed model estimates for the pairs (GP9, GP13) and (GP9, GP14) with r=3, s=7 and s=8*

		GP9 - GP13			GP9 - GP14		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	6.1263	0.4621	**<.0001**	8.4830	0.7651	**<.0001**
Intercept	β_{s0}	39.3858	1.7430	**<.0001**	37.0290	1.6261	**<.0001**
day1	β_{r1}	6.7096	0.2615	**<.0001**	6.7096	0.2615	**<.0001**
day1	β_{s1}	-0.9992	0.1083	**<.0001**	-1.1026	0.1458	**<.0001**
day3	β_{r2}	8.5954	0.2615	**<.0001**	8.5954	0.2615	**<.0001**
day3	β_{s2}	-1.5158	0.1083	**<.0001**	1.2715	0.1458	**<.0001**
Age	β_{r3}	-0.0199	0.0413	0.6305	-0.0199	0.0413	0.6305
Age	β_{s3}	-0.0269	0.0119	**0.0245**	0.0236	0.0198	0.2340
Sex	β_{r4}	0.5085	1.0116	0.6155	0.5085	1.0116	0.6155
Sex	β_{s4}	-1.1990	0.2922	**<.0001**	0.4677	0.4854	0.3360
Hyperlipidemia	β_{r5}	-0.1011	0.9975	0.9193	-0.1011	0.9975	0.9193
Hyperlipidemia	β_{s5}	0.3463	0.2881	0.2303	-0.6276	0.4786	0.1906
Hypertension	β_{r6}	-0.3741	1.2785	0.7700	-0.3741	1.2785	0.7700
Hypertension	β_{s6}	1.0017	0.3693	**0.0070**	-0.2539	0.6134	0.6792
Rheumatic	β_{r7}	-1.4049	1.8557	0.4495	-1.4049	1.8557	0.4495
Rheumatic	β_{s7}	-1.1900	0.5361	**0.0271**	0.5809	0.8904	0.5146

Effect	Par.						
Chronic renal	β_{r8}	1.8430	2.6782	0.4918	1.8430	2.6782	0.4918
Chronic renal	β_{s8}	-1.0738	0.7737	0.1661	0.7885	1.2851	0.5399
Dialysis	β_{r9}	0.4577	4.8385	0.9247	0.4577	4.8385	0.9247
Dialysis	β_{s9}	-1.6482	1.3977	0.2391	2.3326	2.3216	0.3157
Beta blockers	β_{r10}	-1.3741	1.1875	0.2480	-1.3741	1.1875	0.2480
Beta blockers	β_{s10}	0.0373	0.3430	0.9134	0.9569	0.5698	0.0940
ACE inhibitors	β_{r11}	1.3384	1.1405	0.2414	1.3384	1.1405	0.2414
ACE inhibitors	β_{s11}	-0.4367	0.3295	0.1859	-0.1927	0.5472	0.7250
Statins	β_{r12}	0.7227	1.0982	0.5110	0.7227	1.0982	0.5110
Statins	β_{s12}	0.0704	0.3173	0.8245	-0.1364	0.5270	0.7959
Amiodarone	β_{r13}	0.1927	1.7301	0.9114	0.1927	1.7301	0.9114
Amiodarone	β_{s13}	-0.2574	0.4998	0.6068	0.5471	0.8301	0.5103
Diuretic	β_{r14}	1.0466	1.0065	0.2992	1.0466	1.0065	0.2992
Diuretic	β_{s14}	-0.2801	0.2908	0.3361	-0.2711	0.4830	0.5750
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	14.5820	2.5939	**<.0001**	14.5820	2.5939	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.8965	0.5399	0.0968	1.4734	0.8963	0.1002
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	1.1316	0.2170	**<.0001**	3.2792	0.5976	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	2.9062	0.3171	**<.0001**	2.9062	0.3171	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.4983	0.0544	**<.0001**	0.9030	0.0985	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		-0.2207			0.2131		

Table 3L: *Bivariate joint Linear mixed model estimates for the pairs (GP9, GP15) and (GP9, log(GP16)) with r=3, s=9 and s=10*

		GP9 - GP15			**GP9 - log(GP16)**		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	0.4849	0.0999	**<.0001**	0.0059	0.1388	0.9661
Intercept	β_{s0}	45.0271	1.6293	**<.0001**	45.5061	1.6153	**<.0001**
day1	β_{r1}	6.7096	0.2615	**<.0001**	6.7096	0.2615	**<.0001**
day1	β_{s1}	-0.1136	0.0270	**<.0001**	0.3246	0.0329	**<.0001**
day3	β_{r2}	8.5954	0.2615	**<.0001**	8.5954	0.2615	**<.0001**
day3	β_{s2}	-0.1112	0.0270	**<.0001**	0.6575	0.0329	**<.0001**
Age	β_{r3}	-0.0199	0.0413	0.6305	-0.0199	0.0413	0.6305

Effect	Par.	Estimate	S.E	P-value	Estimate	S.E	P-value
Age	β_{s3}	-0.0054	0.0026	**0.0370**	-0.0046	0.0036	0.1967
Sex	β_{r4}	0.5085	1.0116	0.6155	0.5085	1.0116	0.6155
Sex	β_{s4}	-0.1187	0.0630	0.0603	-0.0281	0.0878	0.7494
Hyperlipidemia	β_{r5}	-0.1011	0.9975	0.9193	-0.1011	0.9975	0.9193
Hyperlipidemia	β_{s5}	0.0162	0.0621	0.7946	-0.0558	0.0865	0.5196
Hypertension	β_{r6}	-0.3741	1.2785	0.7700	-0.3741	1.2785	0.7700
Hypertension	β_{s6}	0.1722	0.0796	0.0312	0.1224	0.1109	0.2705
Rheumatic	β_{r7}	-1.4049	1.8557	0.4495	-1.4049	1.8557	0.4495
Rheumatic	β_{s7}	-0.1969	0.1155	0.0893	-0.1957	0.1610	0.2250
Chronic renal	β_{r8}	1.8430	2.6782	0.4918	1.8430	2.6782	0.4918
Chronic renal	β_{s8}	-0.1422	0.1668	0.3944	-0.0194	0.2323	0.9335
Dialysis	β_{r9}	0.4577	4.8385	0.9247	0.4577	4.8385	0.9247
Dialysis	β_{s9}	-0.1476	0.3013	0.6244	0.0763	0.4197	0.8559
Beta blockers	β_{r10}	-1.3741	1.1875	0.2480	-1.3741	1.1875	0.2480
Beta blockers	β_{s10}	-0.0012	0.0739	0.9875	0.0887	0.1030	0.3897
ACE inhibitors	β_{r11}	1.3384	1.1405	0.2414	1.3384	1.1405	0.2414
ACE inhibitors	β_{s11}	-0.0201	0.0710	0.7777	-0.0238	0.0989	0.8102
Statins	β_{r12}	0.7227	1.0982	0.5110	0.7227	1.0982	0.5110
Statins	β_{s12}	0.0424	0.0684	0.5354	0.0396	0.0953	0.6777
Amiodarone	β_{r13}	0.1927	1.7301	0.9114	0.1927	1.7301	0.9114
Amiodarone	β_{s13}	-0.0804	0.1077	0.4558	0.0355	0.1501	0.8132
Diuretic	β_{r14}	1.0466	1.0065	0.2992	1.0466	1.0065	0.2992
Diuretic	β_{s14}	-0.0109	0.0627	0.8624	0.0204	0.0873	0.8154
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	14.5820	2.5939	**<.0001**	14.5820	2.5939	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.3400	0.1209	**0.0049**	-0.1708	0.1602	0.2863
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.0500	0.0101	**<.0001**	0.1017	0.0196	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	2.9062	0.3171	**<.0001**	2.9062	0.3171	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0309	0.0034	**<.0001**	0.0459	0.0050	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		-0.3982			-0.1403		

Table 3M: *Bivariate joint Linear mixed model estimates for the pairs (GP10, log(GP11)) and (GP10, log(GP12)) with r=4, s=5 and s=6*

Effect	Par.	GP10 -log(GP11)			GP10 -log(GP12)		
		Estimate	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	5.8137	0.7030	**<.0001**	7.9600	0.7637	**<.0001**

Intercept	β_{s0}	2.8167	0.1636	**<.0001**	0.6704	0.0921	**<.0001**
day1	β_{r1}	-0.7256	0.1387	**<.0001**	-0.7256	0.1387	**<.0001**
day1	β_{s1}	-0.7435	0.0735	**<.0001**	-0.5336	0.0275	**<.0001**
day3	β_{r2}	-1.9015	0.1387	**<.0001**	-1.9015	0.1387	**<.0001**
day3	β_{s2}	-0.8047	0.0735	**<.0001**	-0.4691	0.0275	**<.0001**
Age	β_{r3}	0.0147	0.0196	0.4520	0.0147	0.0196	0.4520
Age	β_{s3}	0.0050	0.0041	0.2255	-0.0001	0.0024	0.9577
Sex	β_{r4}	0.5070	0.4799	0.2916	0.5070	0.4799	0.2916
Sex	β_{s4}	-0.0072	0.1009	0.9436	-0.0522	0.0579	0.3678
Hyperlipidemia	β_{r5}	0.1120	0.4732	0.8130	0.1120	0.4732	0.8130
Hyperlipidemia	β_{s5}	-0.1148	0.0994	0.2493	0.0397	0.0571	0.4875
Hypertension	β_{r6}	-0.2511	0.6065	0.6792	-0.2511	0.6065	0.6792
Hypertension	β_{s6}	0.1148	0.1275	0.3682	0.1254	0.0732	0.0873
Rheumatic	β_{r7}	2.1335	0.8804	**0.0159**	2.1335	0.8804	**0.0159**
Rheumatic	β_{s7}	0.0076	0.1850	0.9674	0.0136	0.1062	0.8985
Chronic renal	β_{r8}	-0.3398	1.2706	0.7893	-0.3398	1.2706	0.7893
Chronic renal	β_{s8}	0.0404	0.2670	0.8798	-0.0891	0.1533	0.5615
Dialysis	β_{r9}	0.5231	2.2954	0.8199	0.5231	2.2954	0.8199
Dialysis	β_{s9}	-0.4164	0.4824	0.3886	-0.0623	0.2769	0.8220
Beta blockers	β_{r10}	0.1337	0.5633	0.8126	0.1337	0.5633	0.8126
Beta blockers	β_{s10}	-0.0164	0.1184	0.8897	-0.0179	0.0680	0.7925
ACE inhibitors	β_{r11}	-0.4033	0.5410	0.4566	-0.4033	0.5410	0.4566
ACE inhibitors	β_{s11}	-0.0767	0.1137	0.5003	-0.0360	0.0653	0.5815
Statins	β_{r12}	-0.3940	0.5210	0.4501	-0.3940	0.5210	0.4501
Statins	β_{s12}	0.0744	0.1095	0.4975	0.0737	0.0629	0.2418
Amiodarone	β_{r13}	-0.0492	0.8208	0.9522	-0.0492	0.8208	0.9522
Amiodarone	β_{s13}	-0.0105	0.1725	0.9514	-0.0663	0.0990	0.5036
Diuretic	β_{r14}	0.2829	0.4775	0.5540	0.2829	0.4775	0.5540
Diuretic	β_{s14}	-0.1297	0.1003	0.1970	-0.0817	0.0576	0.1572
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	3.2274	0.5841	**<.0001**	3.2274	0.5841	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	0.3229	0.0947	**0.0006**	-0.0092	0.0498	0.8530
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.0780	0.0271	**0.0020**	0.0403	0.0086	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.8172	0.0892	**<.0001**	0.8172	0.0892	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.2296	0.0251	**<.0001**	0.0320	0.0035	**<.0001**

Correlation of random intercepts

Corr(b_{r1i}, b_{s1i})	*0.6434*	-0.0256

Table 3N: *Bivariate joint Linear mixed model estimates for the pairs (GP10, GP13) and (GP10, GP14) with r=4, s=7 and s=8*

		GP10 - GP13			GP10 - GP14		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	2.5042	0.9864	**0.0122**	0.1474	1.1818	0.9009
Intercept	β_{s0}	6.1263	0.4621	**<.0001**	8.4830	0.7651	**<.0001**
day1	β_{r1}	-0.7256	0.1387	**<.0001**	-0.7256	0.1387	**<.0001**
day1	β_{s1}	-0.9992	0.1083	**<.0001**	-1.1026	0.1458	**<.0001**
day3	β_{r2}	-1.9015	0.1387	**<.0001**	-1.9015	0.1387	**<.0001**
day3	β_{s2}	-1.5158	0.1083	**<.0001**	1.2715	0.1458	**<.0001**
Age	β_{r3}	0.0147	0.0196	0.4520	0.0147	0.0196	0.4520
Age	β_{s3}	-0.0269	0.0119	**0.0245**	0.0236	0.0198	0.2340
Sex	β_{r4}	0.5070	0.4799	0.2916	0.5070	0.4799	0.2916
Sex	β_{s4}	-1.1990	0.2922	**<.0001**	0.4677	0.4854	0.3360
Hyperlipidemia	β_{r5}	0.1120	0.4732	0.8130	0.1120	0.4732	0.8130
Hyperlipidemia	β_{s5}	0.3463	0.2881	0.2303	-0.6276	0.4786	0.1906
Hypertension	β_{r6}	-0.2511	0.6065	0.6792	-0.2511	0.6065	0.6792
Hypertension	β_{s6}	1.0017	0.3693	**0.0070**	-0.2539	0.6134	0.6792
Rheumatic	β_{r7}	2.1335	0.8804	**0.0159**	2.1335	0.8804	**0.0159**
Rheumatic	β_{s7}	-1.1900	0.5361	**0.0271**	0.5809	0.8904	0.5146
Chronic renal	β_{r8}	-0.3398	1.2706	0.7893	-0.3398	1.2706	0.7893
Chronic renal	β_{s8}	-1.0738	0.7737	0.1661	0.7885	1.2851	0.5399
Dialysis	β_{r9}	0.5231	2.2954	0.8199	0.5231	2.2954	0.8199
Dialysis	β_{s9}	-1.6482	1.3977	0.2391	2.3326	2.3216	0.3157
Beta blockers	β_{r10}	0.1337	0.5633	0.8126	0.1337	0.5633	0.8126
Beta blockers	β_{s10}	0.0373	0.3430	0.9134	0.9569	0.5698	0.0940
ACE inhibitors	β_{r11}	-0.4033	0.5410	0.4566	-0.4033	0.5410	0.4566
ACE inhibitors	β_{s11}	-0.4367	0.3295	0.1859	-0.1927	0.5472	0.7250
Statins	β_{r12}	-0.3940	0.5210	0.4501	-0.3940	0.5210	0.4501
Statins	β_{s12}	0.0704	0.3173	0.8245	-0.1364	0.5270	0.7959
Amiodarone	β_{r13}	-0.0492	0.8208	0.9522	-0.0492	0.8208	0.9522
Amiodarone	β_{s13}	-0.2574	0.4998	0.6068	0.5471	0.8301	0.5103
Diuretic	β_{r14}	0.2829	0.4775	0.5540	0.2829	0.4775	0.5540
Diuretic	β_{s14}	-0.2801	0.2908	0.3361	-0.2711	0.4830	0.5750

Covariance of b_{k1i}

$\text{Var}(b_{r1i})$	$\sigma^2_{b_{r1i}}$	3.2274	0.5841	**<.0001**	3.2274	0.5841	**<.0001**
$\text{Cov}(b_{r1i}, b_{s1i})$	$\sigma_{b_{r1i}b_{s1i}}$	-0.5810	0.2603	**0.0256**	-0.7414	0.4262	0.0820
$\text{Var}(b_{s1i})$	$\sigma^2_{b_{s1i}}$	1.1316	0.2170	**<.0001**	3.2792	0.5976	**<.0001**
Residual variance							
$\text{Var}(\varepsilon_{rij})$	$\sigma^2_{\varepsilon_{rij}}$	0.8172	0.0892	**<.0001**	0.8172	0.0892	**<.0001**
$\text{Var}(\varepsilon_{sij})$	$\sigma^2_{\varepsilon_{sij}}$	0.4983	0.0544	**<.0001**	0.9030	0.0985	**<.0001**
Correlation of random intercepts							
$\text{Corr}(b_{r1i}, b_{s1i})$		-0.3040			-0.2279		

Table 3O: *Bivariate joint Linear mixed model estimates for the pairs (GP10, GP15) and (GP10, log(GP16)) with r=4, s=9 and s=10*

Effect	Par.	GP10 - GP15			GP10 -log(GP16)		
		Estimate	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	0.4849	0.0999	**<.0001**	0.0059	0.1388	0.9661
Intercept	β_{s0}	8.1456	0.7631	**<.0001**	8.6245	0.7739	**<.0001**
day1	β_{r1}	-0.7256	0.1387	**<.0001**	-0.7256	0.1387	**<.0001**
day1	β_{s1}	-0.1136	0.0270	**<.0001**	0.3246	0.0329	**<.0001**
day3	β_{r2}	-1.9015	0.1387	**<.0001**	-1.9015	0.1387	**<.0001**
day3	β_{s2}	-0.1112	0.0270	**<.0001**	0.6575	0.0329	**<.0001**
Age	β_{r3}	0.0147	0.0196	0.4520	0.0147	0.0196	0.4520
Age	β_{s3}	-0.0054	0.0026	**0.0370**	-0.0046	0.0036	0.1967
Sex	β_{r4}	0.5070	0.4799	0.2916	0.5070	0.4799	0.2916
Sex	β_{s4}	-0.1187	0.0630	0.0603	-0.0281	0.0878	0.7494
Hyperlipidemia	β_{r5}	0.1120	0.4732	0.8130	0.1120	0.4732	0.8130
Hyperlipidemia	β_{s5}	0.0162	0.0621	0.7946	-0.0558	0.0865	0.5196
Hypertension	β_{r6}	-0.2511	0.6065	0.6792	-0.2511	0.6065	0.6792
Hypertension	β_{s6}	0.1722	0.0796	**0.0312**	0.1224	0.1109	0.2705
Rheumatic	β_{r7}	2.1335	0.8804	**0.0159**	2.1335	0.8804	**0.0159**
Rheumatic	β_{s7}	-0.1969	0.1155	0.0893	-0.1957	0.1610	0.2250
Chronic renal	β_{r8}	-0.3398	1.2706	0.7893	-0.3398	1.2706	0.7893
Chronic renal	β_{s8}	-0.1422	0.1668	0.3944	-0.0194	0.2323	0.9335
Dialysis	β_{r9}	0.5231	2.2954	0.8199	0.5231	2.2954	0.8199
Dialysis	β_{s9}	-0.1476	0.3013	0.6244	0.0763	0.4197	0.8559
Beta blockers	β_{r10}	0.1337	0.5633	0.8126	0.1337	0.5633	0.8126
Beta blockers	β_{s10}	-0.0012	0.0739	0.9875	0.0887	0.1030	0.3897
ACE inhibitors	β_{r11}	-0.4033	0.5410	0.4566	-0.4033	0.5410	0.4566
ACE inhibitors	β_{s11}	-0.0201	0.0710	0.7777	-0.0238	0.0989	0.8102
Statins	β_{r12}	-0.3940	0.5210	0.4501	-0.3940	0.5210	0.4501

Statins	β_{s12}	0.0424	0.0684	0.5354	0.0396	0.0953	0.6777
Amiodarone	β_{r13}	-0.0492	0.8208	0.9522	-0.0492	0.8208	0.9522
Amiodarone	β_{s13}	-0.0804	0.1077	0.4558	0.0355	0.1501	0.8132
Diuretic	β_{r14}	0.2829	0.4775	0.5540	0.2829	0.4775	0.5540
Diuretic	β_{s14}	-0.0109	0.0627	0.8624	0.0204	0.0873	0.8154
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	3.2274	0.5841	**<.0001**	3.2274	0.5841	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.0017	0.0541	0.9749	-0.0246	0.0755	0.7449
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.0500	0.0101	**<.0001**	0.1017	0.0196	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.8172	0.0892	**<.0001**	0.8172	0.0892	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0309	0.0034	**<.0001**	0.0459	0.0050	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		-0.0042			-0.0429		

Table 3P: *Bivariate joint Linear mixed model estimates for the pairs (log(GP11), log(GP12)) and (log(GP11), GP13) with r=5, s=6 and s=7*

Effect	Par.	log(GP11) - log(GP12)			log(GP11) - GP13		
		Estimate	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	0.6704	0.0921	**<.0001**	6.1263	0.4621	**<.0001**
Intercept	β_{s0}	0.3483	0.0987	**0.0006**	-5.1076	0.4718	**<.0001**
day1	β_{r1}	-0.3372	0.0340	**<.0001**	-0.3372	0.0340	**<.0001**
day1	β_{s1}	-0.5336	0.0275	**<.0001**	-0.9992	0.1083	**<.0001**
day3	β_{r2}	-0.3605	0.0340	**<.0001**	-0.3605	0.0340	**<.0001**
day3	β_{s2}	-0.4691	0.0275	**<.0001**	-1.5158	0.1083	**<.0001**
Age	β_{r3}	0.0023	0.0018	0.2061	0.0023	0.0018	0.2061
Age	β_{s3}	-0.0001	0.0024	0.9577	-0.0269	0.0119	**0.0245**
Sex	β_{r4}	0.0022	0.0452	0.9617	0.0022	0.0452	0.9617
Sex	β_{s4}	-0.0522	0.0579	0.3678	-1.1990	0.2922	**<.0001**
Hyperlipidemia	β_{r5}	-0.0462	0.0445	0.3000	-0.0462	0.0445	0.3000
Hyperlipidemia	β_{s5}	0.0397	0.0571	0.4875	0.3463	0.2881	0.2303
Hypertension	β_{r6}	0.0568	0.0571	0.3201	0.0568	0.0571	0.3201
Hypertension	β_{s6}	0.1254	0.0732	0.0873	1.0017	0.3693	**0.0070**
Rheumatic	β_{r7}	-0.0091	0.0828	0.9128	-0.0091	0.0828	0.9128
Rheumatic	β_{s7}	0.0136	0.1062	0.8985	-1.1900	0.5361	**0.0271**
Chronic renal	β_{r8}	0.0104	0.1196	0.9306	0.0104	0.1196	0.9306
Chronic renal	β_{s8}	-0.0891	0.1533	0.5615	-1.0738	0.7737	0.1661
Dialysis	β_{r9}	-0.1882	0.2160	0.3842	-0.1882	0.2160	0.3842

Effect	Par.	Estimate	S.E	P-value	Estimate	S.E	P-value
Dialysis	β_{s9}	-0.0623	0.2769	0.8220	-1.6482	1.3977	0.2391
Beta blockers	β_{r10}	-0.0158	0.0530	0.7662	-0.0158	0.0530	0.7662
Beta blockers	β_{s10}	-0.0179	0.0680	0.7925	0.0373	0.3430	0.9134
ACE inhibitors	β_{r11}	-0.0395	0.0509	0.4383	-0.0395	0.0509	0.4383
ACE inhibitors	β_{s11}	-0.0360	0.0653	0.5815	-0.4367	0.3295	0.1859
Statins	β_{r12}	0.0363	0.0490	0.4598	0.0363	0.0490	0.4598
Statins	β_{s12}	0.0737	0.0629	0.2418	0.0704	0.3173	0.8245
Amiodarone	β_{r13}	-0.0217	0.0772	0.7791	-0.0217	0.0772	0.7791
Amiodarone	β_{s13}	-0.0663	0.0990	0.5036	-0.2574	0.4998	0.6068
Diuretic	β_{r14}	-0.0513	0.0449	0.2546	-0.0513	0.0449	0.2546
Diuretic	β_{s14}	-0.0817	0.0576	0.1572	-0.2801	0.2908	0.3361
Covariance of b_{k1i}							
$\text{Var}(b_{r1i})$	$\sigma^2_{b_{r1i}}$	0.0147	0.0055	**0.0037**	0.0147	0.0055	**0.0037**
$\text{Cov}(b_{r1i}, b_{s1i})$	$\sigma_{b_{r1i}b_{s1i}}$	0.0128	0.0049	**0.0095**	-0.0113	0.0237	0.6330
$\text{Var}(b_{s1i})$	$\sigma^2_{b_{s1i}}$	0.0403	0.0086	**<.0001**	1.1316	0.2170	**<.0001**
Residual variance							
$\text{Var}(\varepsilon_{rij})$	$\sigma^2_{\varepsilon_{rij}}$	0.0490	0.0053	**<.0001**	0.0490	0.0053	**<.0001**
$\text{Var}(\varepsilon_{sij})$	$\sigma^2_{\varepsilon_{sij}}$	0.0320	0.0035	**<.0001**	0.4983	0.0544	**<.0001**
Correlation of random intercepts							
$\text{Corr}(b_{r1i}, b_{s1i})$		0.5250			-0.0878		

Table 3Q: *Bivariate joint Linear mixed model estimates for the pairs (log(GP11), GP14) and (log(GP11), GP15) with r=5, s=8 and s=9*

		log(GP11) - GP14			log(GP11) - GP15		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	8.4830	0.7651	**<.0001**	0.4849	0.0999	**<.0001**
Intercept	β_{s0}	-7.4643	0.7976	**<.0001**	0.5338	0.1307	**<.0001**
day1	β_{r1}	-0.3372	0.0340	**<.0001**	-0.3372	0.0340	**<.0001**
day1	β_{s1}	-1.1026	0.1458	**<.0001**	-0.1136	0.0270	**<.0001**
day3	β_{r2}	-0.3605	0.0340	**<.0001**	-0.3605	0.0340	**<.0001**
day3	β_{s2}	1.2715	0.1458	**<.0001**	-0.1112	0.0270	**<.0001**
Age	β_{r3}	0.0023	0.0018	0.2061	0.0023	0.0018	0.2061
Age	β_{s3}	0.0236	0.0198	0.2340	-0.0054	0.0026	**0.0370**
Sex	β_{r4}	0.0022	0.0452	0.9617	0.0022	0.0452	0.9617
Sex	β_{s4}	0.4677	0.4854	0.3360	-0.1187	0.0630	0.0603
Hyperlipidemia	β_{r5}	-0.0462	0.0445	0.3000	-0.0462	0.0445	0.3000
Hyperlipidemia	β_{s5}	-0.6276	0.4786	0.1906	0.0162	0.0621	0.7946
Hypertension	β_{r6}	0.0568	0.0571	0.3201	0.0568	0.0571	0.3201

Effect	Par.						
Hypertension	β_{s6}	-0.2539	0.6134	0.6792	0.1722	0.0796	**0.0312**
Rheumatic	β_{r7}	-0.0091	0.0828	0.9128	-0.0091	0.0828	0.9128
Rheumatic	β_{s7}	0.5809	0.8904	0.5146	-0.1969	0.1155	0.0893
Chronic renal	β_{r8}	0.0104	0.1196	0.9306	0.0104	0.1196	0.9306
Chronic renal	β_{s8}	0.7885	1.2851	0.5399	-0.1422	0.1668	0.3944
Dialysis	β_{r9}	-0.1882	0.2160	0.3842	-0.1882	0.2160	0.3842
Dialysis	β_{s9}	2.3326	2.3216	0.3157	-0.1476	0.3013	0.6244
Beta blockers	β_{r10}	-0.0158	0.0530	0.7662	-0.0158	0.0530	0.7662
Beta blockers	β_{s10}	0.9569	0.5698	0.0940	-0.0012	0.0739	0.9875
ACE inhibitors	β_{r11}	-0.0395	0.0509	0.4383	-0.0395	0.0509	0.4383
ACE inhibitors	β_{s11}	-0.1927	0.5472	0.7250	-0.0201	0.0710	0.7777
Statins	β_{r12}	0.0363	0.0490	0.4598	0.0363	0.0490	0.4598
Statins	β_{s12}	-0.1364	0.5270	0.7959	0.0424	0.0684	0.5354
Amiodarone	β_{r13}	-0.0217	0.0772	0.7791	-0.0217	0.0772	0.7791
Amiodarone	β_{s13}	0.5471	0.8301	0.5103	-0.0804	0.1077	0.4558
Diuretic	β_{r14}	-0.0513	0.0449	0.2546	-0.0513	0.0449	0.2546
Diuretic	β_{s14}	-0.2711	0.4830	0.5750	-0.0109	0.0627	0.8624
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.0147	0.0055	**0.0037**	0.0147	0.0055	**0.0037**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.1404	0.0426	**0.0010**	-0.0053	0.0051	0.3044
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	3.2792	0.5976	**<.0001**	0.0500	0.0101	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.0490	0.0053	**<.0001**	0.0490	0.0053	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.9030	0.0985	**<.0001**	0.0309	0.0034	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		*-0.6406*			*-0.1947*		

Table 3R: *Bivariate joint Linear mixed model estimates for the pairs (log(GP11), log(GP16)) with r=5 and s=10 and (log(GP12), GP13) with r=6 and s=7*

		log(GP11) - log(GP16)			log(GP12) - GP13		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	0.0059	0.1388	0.9661	6.1263	0.4621	**<.0001**
Intercept	β_{s0}	1.0128	0.1858	**<.0001**	-5.4558	0.4194	**<.0001**
day1	β_{r1}	-0.3372	0.0340	**<.0001**	-0.5336	0.0275	**<.0001**
day1	β_{s1}	0.3246	0.0329	**<.0001**	-0.9992	0.1083	**<.0001**
day3	β_{r2}	-0.3605	0.0340	**<.0001**	-0.4691	0.0275	**<.0001**
day3	β_{s2}	0.6575	0.0329	**<.0001**	-1.5158	0.1083	**<.0001**
Age	β_{r3}	0.0023	0.0018	0.2061	-0.0001	0.0024	0.9577

Effect	Par.	Estimate	S.E	P-value	Estimate	S.E	P-value
Age	β_{s3}	-0.0046	0.0036	0.1967	-0.0269	0.0119	**0.0245**
Sex	β_{r4}	0.0022	0.0452	0.9617	-0.0522	0.0579	0.3678
Sex	β_{s4}	-0.0281	0.0878	0.7494	-1.1990	0.2922	**<.0001**
Hyperlipidemia	β_{r5}	-0.0462	0.0445	0.3000	0.0397	0.0571	0.4875
Hyperlipidemia	β_{s5}	-0.0558	0.0865	0.5196	0.3463	0.2881	0.2303
Hypertension	β_{r6}	0.0568	0.0571	0.3201	0.1254	0.0732	0.0873
Hypertension	β_{s6}	0.1224	0.1109	0.2705	1.0017	0.3693	**0.0070**
Rheumatic	β_{r7}	-0.0091	0.0828	0.9128	0.0136	0.1062	0.8985
Rheumatic	β_{s7}	-0.1957	0.1610	0.2250	-1.1900	0.5361	**0.0271**
Chronic renal	β_{r8}	0.0104	0.1196	0.9306	-0.0891	0.1533	0.5615
Chronic renal	β_{s8}	-0.0194	0.2323	0.9335	-1.0738	0.7737	0.1661
Dialysis	β_{r9}	-0.1882	0.2160	0.3842	-0.0623	0.2769	0.8220
Dialysis	β_{s9}	0.0763	0.4197	0.8559	-1.6482	1.3977	0.2391
Beta blockers	β_{r10}	-0.0158	0.0530	0.7662	-0.0179	0.0680	0.7925
Beta blockers	β_{s10}	0.0887	0.1030	0.3897	0.0373	0.3430	0.9134
ACE inhibitors	β_{r11}	-0.0395	0.0509	0.4383	-0.0360	0.0653	0.5815
ACE inhibitors	β_{s11}	-0.0238	0.0989	0.8102	-0.4367	0.3295	0.1859
Statins	β_{r12}	0.0363	0.0490	0.4598	0.0737	0.0629	0.2418
Statins	β_{s12}	0.0396	0.0953	0.6777	0.0704	0.3173	0.8245
Amiodarone	β_{r13}	-0.0217	0.0772	0.7791	-0.0663	0.0990	0.5036
Amiodarone	β_{s13}	0.0355	0.1501	0.8132	-0.2574	0.4998	0.6068
Diuretic	β_{r14}	-0.0513	0.0449	0.2546	-0.0817	0.0576	0.1572
Diuretic	β_{s14}	0.0204	0.0873	0.8154	-0.2801	0.2908	0.3361
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.0147	0.0055	0.0037	0.0403	0.0086	**<.0001**
Cov(b_{r1i},b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.0305	0.0080	**0.0001**	0.1428	0.0347	**<.0001**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.1017	0.0196	**<.0001**	1.1316	0.2170	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.0490	0.0053	**<.0001**	0.0320	0.0035	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0459	0.0050	**<.0001**	0.4983	0.0544	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i},b_{s1i})		-0.7907			0.6692		

Table 3S: *Bivariate joint Linear mixed model estimates for the pairs (log(GP12), GP14) and (log(GP12), GP15) with r=6, s=8 and s=9*

		log(GP12) - GP14			log(GP12) - GP15		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	8.4830	0.7651	**<.0001**	0.4849	0.0999	**<.0001**

Intercept	β_{s0}	-7.8126	0.8168	**<.0001**	0.1855	0.1098	0.0932
day1	β_{r1}	-0.5336	0.0275	**<.0001**	-0.5336	0.0275	**<.0001**
day1	β_{s1}	-1.1026	0.1458	**<.0001**	-0.1136	0.0270	**<.0001**
day3	β_{r2}	-0.4691	0.0275	**<.0001**	-0.4691	0.0275	**<.0001**
day3	β_{s2}	1.2715	0.1458	**<.0001**	-0.1112	0.0270	**<.0001**
Age	β_{r3}	-0.0001	0.0024	0.9577	**-0.0001**	0.0024	0.9577
Age	β_{s3}	0.0236	0.0198	0.2340	-0.0054	0.0026	**0.0370**
Sex	β_{r4}	-0.0522	0.0579	0.3678	-0.0522	0.0579	0.3678
Sex	β_{s4}	0.4677	0.4854	0.3360	-0.1187	0.0630	0.0603
Hyperlipidemia	β_{r5}	0.0397	0.0571	0.4875	0.0397	0.0571	0.4875
Hyperlipidemia	β_{s5}	-0.6276	0.4786	0.1906	0.0162	0.0621	0.7946
Hypertension	β_{r6}	0.1254	0.0732	0.0873	0.1254	0.0732	0.0873
Hypertension	β_{s6}	-0.2539	0.6134	0.6792	0.1722	0.0796	**0.0312**
Rheumatic	β_{r7}	0.0136	0.1062	0.8985	0.0136	0.1062	0.8985
Rheumatic	β_{s7}	0.5809	0.8904	0.5146	-0.1969	0.1155	0.0893
Chronic renal	β_{r8}	-0.0891	0.1533	0.5615	-0.0891	0.1533	0.5615
Chronic renal	β_{s8}	0.7885	1.2851	0.5399	-0.1422	0.1668	0.3944
Dialysis	β_{r9}	-0.0623	0.2769	0.8220	-0.0623	0.2769	0.8220
Dialysis	β_{s9}	2.3326	2.3216	0.3157	-0.1476	0.3013	0.6244
Beta blockers	β_{r10}	-0.0179	0.0680	0.7925	-0.0179	0.0680	0.7925
Beta blockers	β_{s10}	0.9569	0.5698	0.0940	-0.0012	0.0739	0.9875
ACE inhibitors	β_{r11}	-0.0360	0.0653	0.5815	-0.0360	0.0653	0.5815
ACE inhibitors	β_{s11}	-0.1927	0.5472	0.7250	-0.0201	0.0710	0.7777
Statins	β_{r12}	0.0737	0.0629	0.2418	0.0737	0.0629	0.2418
Statins	β_{s12}	-0.1364	0.5270	0.7959	0.0424	0.0684	0.5354
Amiodarone	β_{r13}	-0.0663	0.0990	0.5036	-0.0663	0.0990	0.5036
Amiodarone	β_{s13}	0.5471	0.8301	0.5103	-0.0804	0.1077	0.4558
Diuretic	β_{r14}	-0.0817	0.0576	0.1572	-0.0817	0.0576	0.1572
Diuretic	β_{s14}	-0.2711	0.4830	0.5750	-0.0109	0.0627	0.8624
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.0403	0.0086	**<.0001**	0.0403	0.0086	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.2268	0.0570	**<.0001**	0.0198	0.0069	**0.0042**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	3.2792	0.5976	**<.0001**	0.0500	0.0101	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.0320	0.0035	**<.0001**	0.0320	0.0035	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.9030	0.0985	**<.0001**	0.0309	0.0034	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		*-0.6244*			*0.4422*		

Table 3T: *Bivariate joint Linear mixed model estimates for the pairs (log(GP12), log(GP16))*
r=6 and s=10

Effect	Par.	Estimate	S.E	P-value
		log(GP12) – log(GP16)		
Intercept	β_{r0}	0.0059	0.1388	0.9661
Intercept	β_{s0}	0.6645	0.1843	**0.0004**
day1	β_{r1}	-0.5336	0.0275	**<.0001**
day1	β_{s1}	0.3246	0.0329	**<.0001**
day3	β_{r2}	-0.4691	0.0275	**<.0001**
day3	β_{s2}	0.6575	0.0329	**<.0001**
Age	β_{r3}	-0.0001	0.0024	0.9577
Age	β_{s3}	-0.0046	0.0036	0.1967
Sex	β_{r4}	-0.0522	0.0579	0.3678
Sex	β_{s4}	-0.0281	0.0878	0.7494
Hyperlipidemia	β_{r5}	0.0397	0.0571	0.4875
Hyperlipidemia	β_{s5}	-0.0558	0.0865	0.5196
Hypertension	β_{r6}	0.1254	0.0732	0.0873
Hypertension	β_{s6}	0.1224	0.1109	0.2705
Rheumatic	β_{r7}	0.0136	0.1062	0.8985
Rheumatic	β_{s7}	-0.1957	0.1610	0.2250
Chronic renal	β_{r8}	-0.0891	0.1533	0.5615
Chronic renal	β_{s8}	-0.0194	0.2323	0.9335
Dialysis	β_{r9}	-0.0623	0.2769	0.8220
Dialysis	β_{s9}	0.0763	0.4197	0.8559
Beta blockers	β_{r10}	-0.0179	0.0680	0.7925
Beta blockers	β_{s10}	0.0887	0.1030	0.3897
ACE inhibitors	β_{r11}	-0.0360	0.0653	0.5815
ACE inhibitors	β_{s11}	-0.0238	0.0989	0.8102
Statins	β_{r12}	0.0737	0.0629	0.2418
Statins	β_{s12}	0.0396	0.0953	0.6777
Amiodarone	β_{r13}	-0.0663	0.0990	0.5036
Amiodarone	β_{s13}	0.0355	0.1501	0.8132
Diuretic	β_{r14}	-0.0817	0.0576	0.1572
Diuretic	β_{s14}	0.0204	0.0873	0.8154
Covariance of b_{k1i}				
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.0403	0.0086	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.0193	0.0094	**0.0396**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.1017	0.0196	**<.0001**
Residual variance				

Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.0320	0.0035	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0459	0.0050	**<.0001**
Correlation of random intercepts				
Corr(b_{r1i}, b_{s1i})		-0.3016		

Table 3U: *Bivariate joint Linear mixed model estimates for the pairs (GP13, GP14) and (GP13, GP15) with r=7, s=8 and s=9*

		GP13 - GP14			GP13 - GP15		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	8.4830	0.7651	**<.0001**	0.4849	0.0999	**<.0001**
Intercept	β_{s0}	-2.3568	0.9736	**0.0167**	5.6414	0.3908	**<.0001**
day1	β_{r1}	-0.9992	0.1083	**<.0001**	-0.9992	0.1083	**<.0001**
day1	β_{s1}	-1.1026	0.1458	**<.0001**	-0.1136	0.0270	**<.0001**
day3	β_{r2}	-1.5158	0.1083	**<.0001**	-1.5158	0.1083	**<.0001**
day3	β_{s2}	1.2715	0.1458	**<.0001**	-0.1112	0.0270	**<.0001**
Age	β_{r3}	-0.0269	0.0120	**0.0245**	-0.0269	0.0120	**0.0245**
Age	β_{s3}	0.0236	0.0198	0.2340	-0.0054	0.0026	**0.0370**
Sex	β_{r4}	-1.199	0.2922	**<.0001**	-1.1990	0.2922	**<.0001**
Sex	β_{s4}	0.4677	0.4854	0.3360	-0.1187	0.0630	0.0603
Hyperlipidemia	β_{r5}	0.3463	0.2881	0.2303	0.3463	0.2881	0.2303
Hyperlipidemia	β_{s5}	-0.6276	0.4786	0.1906	0.0162	0.0621	0.7946
Hypertension	β_{r6}	1.0017	0.3693	**0.0070**	1.0017	0.3693	**0.0070**
Hypertension	β_{s6}	-0.2539	0.6134	0.6792	0.1722	0.0796	**0.0312**
Rheumatic	β_{r7}	-1.1900	0.5361	**0.0271**	-1.1900	0.5361	**0.0271**
Rheumatic	β_{s7}	0.5809	0.8904	0.5146	-0.1969	0.1155	0.0893
Chronic renal	β_{r8}	-1.0738	0.7737	0.1661	-1.0738	0.7737	0.1661
Chronic renal	β_{s8}	0.7885	1.2851	0.5399	-0.1422	0.1668	0.3944
Dialysis	β_{r9}	-1.6482	1.3977	0.2391	-1.6482	1.3977	0.2391
Dialysis	β_{s9}	2.3326	2.3216	0.3157	-0.1476	0.3013	0.6244
Beta blockers	β_{r10}	0.0373	0.3430	0.9134	0.0373	0.3430	0.9134
Beta blockers	β_{s10}	0.9569	0.5698	0.0940	-0.0012	0.0739	0.9875
ACE inhibitors	β_{r11}	-0.4367	0.3295	0.1859	-0.4367	0.3295	0.1859
ACE inhibitors	β_{s11}	-0.1927	0.5472	0.7250	-0.0201	0.07101	0.7777
Statins	β_{r12}	0.0704	0.3173	0.8245	0.0704	0.3173	0.8245
Statins	β_{s12}	-0.1364	0.5270	0.7959	0.0424	0.0684	0.5354
Amiodarone	β_{r13}	-0.2574	0.4998	0.6068	-0.2574	0.4998	0.6068
Amiodarone	β_{s13}	0.5471	0.8301	0.5103	-0.0804	0.1077	0.4558
Diuretic	β_{r14}	-0.2801	0.2908	0.3361	-0.2801	0.2908	0.3361

Diuretic	β_{s14}	-0.2711	0.4830	0.5750	-0.0109	0.0627	0.8624
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	1.1316	0.217	<.0001	1.1316	0.2170	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.4609	0.2598	0.0760	0.2190	0.04187	**<.0001**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	3.2792	0.5976	**<.0001**	0.0500	0.01011	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.4983	0.0544	**<.0001**	0.4983	0.0543	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.903	0.0985	**<.0001**	0.0309	0.0033	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		-0.2393			**0.9209**		

Table 3V: *Bivariate joint Linear mixed model estimates for the pairs (GP13, log(GP16)) with r=7, s=10 and (GP14, GP15) with r=8, s=9*

		GP13 - log(GP16)			GP14 - GP15		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	6.1203	0.4319	**<.0001**	7.9982	0.7961	**<.0001**
Intercept	β_{s0}	0.0059	0.1388	0.9661	0.4849	0.0999	**<.0001**
day1	β_{r1}	-0.9992	0.1083	**<.0001**	-1.1026	0.1458	**<.0001**
day1	β_{s1}	0.3246	0.0329	**<.0001**	-0.1136	0.0270	**<.0001**
day3	β_{r2}	-1.5158	0.1083	**<.0001**	1.2715	0.1458	**<.0001**
day3	β_{s2}	0.6575	0.0329	**<.0001**	-0.1112	0.0270	**<.0001**
Age	β_{r3}	-0.0269	0.0119	**0.0245**	0.0236	0.0198	0.2340
Age	β_{s3}	-0.0046	0.0036	0.1967	-0.0054	0.0026	**0.0370**
Sex	β_{r4}	-1.1990	0.2922	**<.0001**	0.4677	0.4854	0.3360
Sex	β_{s4}	-0.0281	0.0878	0.7494	-0.1187	0.0630	0.0603
Hyperlipidemia	β_{r5}	0.3463	0.2881	0.2303	-0.6276	0.4786	0.1906
Hyperlipidemia	β_{s5}	-0.0558	0.0865	0.5196	0.0162	0.0621	0.7946
Hypertension	β_{r6}	1.0017	0.3693	**0.0070**	-0.2539	0.6134	0.6792
Hypertension	β_{s6}	0.1224	0.1109	0.2705	0.1722	0.0796	**0.0312**
Rheumatic[4]	β_{r7}	-1.1900	0.5361	**0.0271**	0.5809	0.8904	0.5146
Rheumatic	β_{s7}	-0.1957	0.1610	0.2250	-0.1969	0.1155	0.0893
Chronic renal	β_{r8}	-1.0738	0.7737	0.1661	0.7885	1.2851	0.5399
Chronic renal	β_{s8}	-0.0194	0.2323	0.9335	-0.1422	0.1668	0.3944
Dialysis	β_{r9}	-1.6482	1.3977	0.2391	2.3326	2.3216	0.3157
Dialysis	β_{s9}	0.0763	0.4197	0.8559	-0.1476	0.3013	0.6244
Beta blockers	β_{r10}	0.0373	0.3430	0.9134	0.9569	0.5698	0.0940
Beta blockers	β_{s10}	0.0887	0.1030	0.3897	-0.0012	0.0739	0.9875
ACE inhibitors	β_{r11}	-0.4367	0.3295	0.1859	-0.1927	0.5472	0.7250

ACE inhibitors	β_{s11}	-0.0238	0.0989	0.8102	-0.0201	0.0710	0.7777
Statins	β_{r12}	0.0704	0.3173	0.8245	-0.1364	0.5270	0.7959
Statins	β_{s12}	0.0396	0.0953	0.6777	0.0424	0.0684	0.5354
Amiodarone	β_{r13}	-0.2574	0.4998	0.6068	0.5471	0.8301	0.5103
Amiodarone	β_{s13}	0.0355	0.1501	0.8132	-0.0804	0.1077	0.4558
Diuretic	β_{r14}	-0.2801	0.2908	0.3361	-0.2711	0.4830	0.5750
Diuretic	β_{s14}	0.0204	0.0873	0.8154	-0.0109	0.0627	0.8624
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	1.1316	0.2170	**<.0001**	3.2792	0.5976	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	0.1433	0.0489	**0.0034**	-0.1191	0.0565	**0.0352**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.1017	0.0196	**<.0001**	0.0500	0.0101	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.4983	0.0544	**<.0001**	0.9030	0.0985	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0459	0.0050	**<.0001**	0.0309	0.0034	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		0.4223			-0.2941		

Table 3W: *Bivariate joint Linear mixed model estimates for the pairs (GP14, log(GP16)) with r=8 and s=10 and (GP14, log(GP16)) with r=9 and s=10*

Effect	Par.	GP14 - log(GP16)			GP15 - log(GP16)		
		Estimate	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	8.4771	0.7309	**<.0001**	0.4790	0.0904	**<.0001**
Intercept	β_{s0}	0.0059	0.1388	0.9661	0.0059	0.1250	0.9623
day1	β_{r1}	-1.1026	0.1458	**<.0001**	-0.1136	0.0276	**<.0001**
day1	β_{s1}	0.3246	0.0329	**<.0001**	0.3246	0.0307	**<.0001**
day3	β_{r2}	1.2715	0.1458	**<.0001**	-0.1112	0.0290	**0.0002**
day3	β_{s2}	0.6575	0.0329	**<.0001**	0.6575	0.0348	**<.0001**
Age	β_{r3}	0.0236	0.0198	0.2340	-0.0054	0.0024	**0.0274**
Age	β_{s3}	-0.0046	0.0036	0.1967	-0.0046	0.0036	0.2020
Sex	β_{r4}	0.4677	0.4854	0.3360	-0.1187	0.0563	**0.0358**
Sex	β_{s4}	-0.0281	0.0878	0.7494	-0.0281	0.0819	0.7323
Hyperlipidemia	β_{r5}	-0.6276	0.4786	0.1906	0.0162	0.0551	0.7693
Hyperlipidemia	β_{s5}	-0.0558	0.0865	0.5196	-0.0558	0.0750	0.4576
Hypertension	β_{r6}	-0.2539	0.6134	0.6792	0.1722	0.0921	0.0625
Hypertension	β_{s6}	0.1224	0.1109	0.2705	0.1224	0.1168	0.2953
Rheumatic	β_{r7}	0.5809	0.8904	0.5146	-0.1969	0.0636	**0.0021**
Rheumatic	β_{s7}	-0.1957	0.1610	0.2250	-0.1957	0.0872	**0.0255**
Chronic renal	β_{r8}	0.7885	1.2851	0.5399	-0.1422	0.1098	0.1962

Chronic renal	β_{s8}	-0.0194	0.2323	0.9335	-0.0194	0.2451	0.9370
Dialysis	β_{r9}	2.3326	2.3216	0.3157	-0.1476	0.1115	0.1865
Dialysis	β_{s9}	0.0763	0.4197	0.8559	0.0763	0.2471	0.7578
Beta blockers	β_{r10}	0.9569	0.5698	0.0940	-0.0012	0.0580	0.9841
Beta blockers	β_{s10}	0.0887	0.1030	0.3897	0.0887	0.0928	0.3400
ACE inhibitors	β_{r11}	-0.1927	0.5472	0.7250	-0.0201	0.0727	0.7827
ACE inhibitors	β_{s11}	-0.0238	0.0989	0.8102	-0.0238	0.1053	0.8216
Statins	β_{r12}	-0.1364	0.5270	0.7959	0.0424	0.0619	0.4935
Statins	β_{s12}	0.0396	0.0953	0.6777	0.0396	0.0829	0.6327
Amiodarone	β_{r13}	0.5471	0.8301	0.5103	-0.0804	0.0690	0.2444
Amiodarone	β_{s13}	0.0355	0.1501	0.8132	0.0355	0.1579	0.8222
Diuretic	β_{r14}	-0.2711	0.4830	0.5750	-0.0109	0.0607	0.8578
Diuretic	β_{s14}	0.0204	0.0873	0.8154	0.0204	0.0790	0.7964
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	3.2792	0.5976	**<.0001**	0.0500	0.0101	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	0.2182	0.0805	**0.0067**	0.0558	0.0119	**<.0001**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.1017	0.0196	**<.0001**	0.1017	0.0196	**<.0001**
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.9030	0.0985	**<.0001**	0.0309	0.0034	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0459	0.0050	**<.0001**	0.0459	0.0050	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		0.3778			*0.7821*		

7.4. Appendix 4: Bivariate joint models for the levels of glycans and the blood parameters which showed an association

Table 4A: Bivariate joint Linear mixed model estimates for the pairs (log(GP8), log(thrombocytes)) and (log(GP12), CRP)

		log(GP8) - log(thrombocytes)			log(GP12) - log(CRP)		
Effect	**Par.**	**Estimate**	**S.E**	**P-value**	**Estimate**	**S.E**	**P-value**
Intercept	β_{r0}	5.1021	0.1500	**<.0001**	-1.1936	0.2330	**<.0001**
Intercept	β_{s0}	-2.8399	0.1837	**<.0001**	1.3993	0.1817	**<.0001**
day	β_{r1}	0.2291	0.0154	**<.0001**	-0.0645	0.0294	**0.0301**
day	β_{s1}	-0.1389	0.0468	**0.0035**	-0.4798	0.0856	**<.0001**
Age	β_{r2}	0.0006	0.0019	0.7555	-0.0009	0.0027	0.7359
Age	β_{s2}	-0.0110	0.0039	**0.0052**	-0.00005	0.0047	0.9915
Sex	β_{r3}	0.0146	0.0470	0.7572	-0.0397	0.0656	0.5461
Sex	β_{s3}	-0.0410	0.0943	0.6640	-0.0560	0.1212	0.6449

Hyperlipidemia	β_{r4}	0.0025	0.0464	0.9576	0.0380	0.0646	0.5573
Hyperlipidemia	β_{s4}	0.0174	0.0929	0.8519	0.2558	0.1171	**0.0306**
Hypertension	β_{r5}	-0.0034	0.0594	0.9549	0.0857	0.0828	0.3026
Hypertension	β_{s5}	-0.0280	0.1213	0.8180	-0.0355	0.1476	0.8102
Rheumatic	β_{r6}	-0.0095	0.0862	0.9124	0.0709	0.1203	0.5562
Rheumatic	β_{s6}	0.1396	0.1768	0.4308	-0.1168	0.2284	0.6100
Chronic renal	β_{r7}	-0.1493	0.1244	0.2320	-0.0816	0.1735	0.6389
Chronic renal	β_{s7}	-0.0664	0.2482	0.7893	-0.1197	0.3398	0.7251
Dialysis	β_{r8}	-0.1639	0.2248	0.4670	-0.0048	0.3135	0.9879
Dialysis	β_{s8}	0.0989	0.4482	0.8256	0.1110	0.6483	0.8643
Beta blockers	β_{r9}	-0.0105	0.0552	0.8499	-0.0240	0.0769	0.7557
Beta blockers	β_{s9}	0.0908	0.1112	0.4151	0.1143	0.1379	0.4084
ACE inhibitors	β_{r10}	-0.0645	0.0530	0.2255	-0.0239	0.0739	0.7466
ACE inhibitors	β_{s10}	-0.0087	0.1071	0.9351	-0.0309	0.1319	0.8148
Statins	β_{r11}	0.0000	0.0510	0.9998	0.0942	0.0712	0.1877
Statins	β_{s11}	-0.0983	0.1026	0.3394	-0.1326	0.1281	0.3021
Amiodarone	β_{r12}	0.0295	0.0804	0.7139	-0.0336	0.1121	0.7650
Amiodarone	β_{s12}	-0.1049	0.1603	0.5137	0.2505	0.2262	0.2700
Diuretic	β_{r13}	-0.0403	0.0468	0.3897	-0.0897	0.0652	0.1712
Diuretic	β_{s13}	-0.2825	0.0935	**0.0029**	-0.0138	0.1184	0.9072
Covariance of b_{k1i}							
Var(b_{r1i})	$\sigma^2_{b_{r1i}}$	0.0285	0.0056	**<.0001**	0.0469	0.0113	**<.0001**
Cov(b_{r1i}, b_{s1i})	$\sigma_{b_{r1i}b_{s1i}}$	-0.0178	0.0082	**0.0296**	-0.0325	0.0142	**0.0221**
Var(b_{s1i})	$\sigma^2_{b_{s1i}}$	0.0888	0.0236	**<.0001**	0.0626	0.4198	0.0678
Residual variance							
Var(ε_{rij})	$\sigma^2_{\varepsilon_{rij}}$	0.0101	0.0016	**<.0001**	0.0368	0.0057	**<.0001**
Var(ε_{sij})	$\sigma^2_{\varepsilon_{sij}}$	0.0888	0.0141	**<.0001**	0.2342	0.0435	**<.0001**
Correlation of random intercepts							
Corr(b_{r1i}, b_{s1i})		*-0.3543*			*-0.6001*		

7.5. Appendix 5: SAS macro – jointpair% - for joint modeling

```
%macro jointpair( data=,
respons=,
fixed=,
random=,
outcome_ind=,
errorstructure=UN(1),
id=,
timecl=,
mixedoptions=    );
```

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Richting: **Master of Statistics-Biostatistics**
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Datum: **13/09/2014**