RELATIONSHIP OF CLINICAL FACTORS WITH ADIPONECTIN AND LEPTIN IN CHILDREN WITH NEWLY DIAGNOSED TYPE 1 DIABETES

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ABSTRACT

Aim: To investigate potential predictors for adiponectin, leptin, and adiponectin/leptin ratio in children with newly diagnosed type 1 diabetes (T1D).

Methods: Medical records were reviewed from 175 subjects (165 Caucasian, 8 African American (AA), 59.4% male, mean age 9.7 ± 3.8 yrs) with new onset T1D diabetes diagnosed between January 2004 and December 2006 at Children's Hospital of Pittsburgh of UPMC. Adiponectin, leptin, islet cell autoantibodies including ICA, glutamic acid decarboxylase (GAD) (65 kDa isoform), insulin antibody (IA2), insulin autoantibody (IAA) and zinc transporter 8 (ZnT8A), anthropometric and clinical variables including systolic and diastolic blood pressure, height, weight, waist circumference (with calculation of body mass index (BMI), waist percentile and waist/height ratio) and insulin dose, laboratory data including hemoglobin A1c(HbA1c), glucose, lipid profile (low-density lipoprotein (LDL) and high-density lipoprotein (HDL), cholesterol, and triglycerides) and C-peptide were all measured at 3 months after start of insulin therapy. HLA typing was determined for the presence of the DQ2 and/or DQ8 haplotypes.

Results: Univariate and multivariate linear regression analyses were performed assessing factors related with adiponectin and leptin, using two different procedures. Nine candidate models were identified and examined for consistency. Adiponectin was significantly associated with age, waist percentile and greater number of positive antibodies. Leptin was significantly associated

with gender, BMI z-score, central obesity, C-peptide, GAD, HbA1c, and insulin dose adjusted by HbA1c. Adiponectin/leptin ratio was significantly associated with gender, age waist percentile, waist/height ratio, insulin dose adjusted by HbA1c, HbA1c, glucose, and C-peptide.

Public health focused conclusion: Adiponectin, leptin and adiponectin/leptin ratio had different significant predictors. However there were a set of factors that where in common. Insulin resistance has been recognized to be present in youth with T1D. Adiponectin and leptin have an influence on insulin sensitivity. Identifying the significant predictors for these hormones may contribute to our understanding of their role in the pathogenesis of T1D. The identification of potential modifiable risk factors in children with this condition would be high priority.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

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1.0 INTRODUCTION

Type 1diabetes (T1D) is the most common form of diabetes mellitus in children and young adults. Although there has been substantial progress in the knowledge of the pathogenesis and natural history of T1D in recent years, there is no effective treatment available to cure the disease [1,2] .Worldwide, the incidence of T1D continues to increase at a rate of nearly 3% per year [3]. In 2011, an estimated 490,100 children, worldwide, below the age of 15 years were living with T1D [4].

The obesity epidemic is widely blamed for a startling rise in the incidence of type 2 diabetes (T2D) among children. Intriguing new research suggests it may also play a role for the increase in T1D [5]. A marked increase in the prevalence of overweight and obesity in type T1D has been demonstrated [6].

Insulin resistance may play a role in the pathogenesis of T1D [7]. Adiponectin and leptin are hormones secreted by the adipose tissue and have an influence on insulin sensitivity [8]. Adiponectin levels are low in human obesity, cardiovascular disease, and T2D. Paradoxically, high adiponectin levels, specifically the high molecular weight isoform, have been reported in established T1D. Leptin, the adipocytokine product of the *Ob(Lep)* gene, reflects the degree of adiposity and is stimulated by insulin, rising acutely with insulin therapy in both in vitro rodent studies and in children with new onset T1D. The adiponectin/leptin ratio also has been used in studies of T1D and T2D as a surrogate measure of insulin sensitivity [9].

Previous studies have explored racial differences in adiponectin and leptin and their relationship with islet autoimmunity in equally matched children of African American (AA) and Caucasian with new onset T1D. Adiponectin levels increase as early as three days after initiation of insulin therapy with a statistically significant increase by day 5. No significant racial differences in adiponectin, leptin, and adiponectin/leptin ratio levels were found after adjustment for BMI. Subjects with higher number of positive autoantibodies had higher adiponectin levels, lower leptin levels, and higher adiponectin/leptin ratios than those with lower numbers of positive antibodies [9].

This study aimed to evaluate adiponectin and leptin measured 3 months after diagnosis of T1D and their relationships with number of islet-cell autoantibodies and measures of adiposity.

2.0 METHODS

2.1 DATA PREPARATION

Two data sets were combined to form the data file used for this analysis. Subjects included were 351 children diagnosed with T1D from January 2004 to December 2006 at the Children's Hospital of Pittsburgh of UPMC. Inclusion criteria was as follows: 1) informed consent signed, 2) diagnosis of diabetes requiring insulin, 3) insulin treatment at time of hospital discharge, and 4) available research laboratory results for three or more β-cell autoantibodies, including islet cell autoantibodies (ICA), glutamic acid decarboxylase (GAD) (65 kDa isoform), insulin antibody (IA2), and insulin autoantibody (IAA). Cases with clinical maturity-onset diabetes of the young, T2D, and without AA were excluded. Of the 351 subjects recruited, 295 met the inclusion criteria of 3 or more AA measured [10].

Of these 295 patients, 175 patients had measurements of adiponectin and leptin and were included in the analysis.

2.2 INDEPENDENT VARIABLES

2.2.1 Demographic variables

2.2.1.1 Age and gender

Age and gender were considered as potential predictors or confounders of adiponectin, leptin and adiponectin/leptin ratio.

2.2.1.2 Measure of Adiposity

Body Mass Index (BMI), BMI percentile (BMI %), BMI z-score, height, weight

BMI was defined as weight/height^2 (kg/m^2). Height (cm) and weight (kg) were collected to calculate BMI. Instead of using fixed BMI values to classify individuals (as typically done with adults), children's BMI was classified using thresholds that vary to take into account the child's age and gender.

BMI thresholds were defined in terms of a specific BMI z-score, or BMI percentile (BMI %), on a child growth reference [11].

Waist, Waist/height Ratio, Central Obesity

The waist circumference (cm) and waist/height ratio were two indicators of obesity among young children [12]. Waist/height ratio had been proposed as an easily measurable anthropometric index for detection of central obesity [13]. Central obesity was defined as having a ratio exceeding 0.5. Waist circumference was the actual recording of circumference in centimeters. In addition, waist percentile (waist %) was available and is standardized to age and sex specific norms for children.

2.2.2 Measure of autoimmunity

Initially, four types of antibodies including insulin antoantibodies(IAA,) insulin antibody(IA2), islet cell antibodies(ICA), and glutamic acid decarboxylase(GAD) (65 kDa isoform) were measured. The appearance of autoantibodies to one or several of the autoantigens signaled an underlying autoimmune process [14]. Each antibody was classified as having a positive or negative response in the analysis. Additionally, a composite variable for the number of positive antibodies among IAA, ICA, IA2 and GAD was created.

In addition, information was available for a fifth autoantibody , Zinc transporter 8(ZnT8A) Studies following the T1D progression from the prodrome stage to onset among high risk patients found that the emergence of ZnT8A autoantibody usually preceded the appearance of T1D clinical symptoms and persisted to disease onset [15].

2.2.3 Clinical and laboratory measures

Blood pressure was assessed and percentiles were determined based on gender, age and height. Laboratory measures included HbA1c and glucose. HbA1c measured glycated hemoglobin and indicated the average blood sugar levels in the past two to three months.

Lipids including LDL, HDL, cholesterol and triglycerides, C-peptide and insulin dose were measured.

2.2.4 DQ2/DQ8

HLA typing was available for the presence of DQ2, DQ8, DQ2 /DQ8. These haplotypes are related to risk of diabetes and were also considered as potential confounders of adiponectin, leptin and the adiponectin/leptin ratio in this study.

2.2.5 Derived variables

Some new independent variables were created for investigating more specific statistical relationship between predictors and outcomes.

2.2.5.1 Categorical groups for number of positive antibodies

The values of number of positive antibodies ranged from 0 to 4.We examined the number of positive antibodies by using several different groupings.

Class 1: 0 versus ≥1.

0 --- people who have 0 positive antibody;

≥1 --- people who have more than 1 positive antibodies.

Class 2: 0-1 versus ≥2.

0-1 --- people who have 0 or 1 positive antibody;

≥2 --- people who have 2, 3 or 4 positive antibodies.

Class 3: 0, 1, 2 versus ≥3.

0 --- people who have 0 positive antibody;

1--- people who have 1 positive antibody;

2 --- people who have 2 positive antibodies;

≥3 --- people who have 3 or 4 positive antibodies.

2.2.5.2 Insulin dose adjusted by HbA1c

Insulin dose adjusted by HbA1c =HbA1c (percentile) + [4 * insulin dose (units per kilogram per 24 h)]

In previous studies, a negative association between stimulated C-peptide and HbA1c (regression coefficient -0.21, $P < 0.001$) and insulin dose (-0.94, $P < 0.001$) was shown. Insulin dose adjusted by HbA1c reflected residual β-cell function and had better stability compared with the conventional definitions [16].

2.2.5.3 Zinc transporter 8 autoantibodies classes (+ and -)

The ZnT8A variable was developed into two categories.

When ZnT8A was greater than 0.02, then the class was defined as +, when ZnT8A was less than 0.02, the class was defined as - .

2.2.5.4 Glucose categorical classes (<120 and >= 120)

The glucose variable was dichotomized into two categories: greater than or equal to 120 and less than 120.

2.3 STATISTICAL ANALYSIS

All continuous variables of interest were described by means, standard deviations, number of missing, number of observations, medians and percentages. For all the categorical variables, proportion summaries were used. Log transformations of adiponectin, leptin and adiponectin/leptin ratio were created to normalize the distributions of the outcome variables. The log scale of the three outcome variables would be used as the dependent variables in the regression analysis. Correlations between different independent continuous variables were assessed using Pearson correlation coefficients. Univariate linear regression and multivariate linear regression analysis were performed to investigate potential predictors of adiponectin, leptin and adiponectin/leptin ratio separately.

Analyses were performed using SAS 9.3. All statistical hypothesis testing was conducted as two-sided tests, and with statistical significance $p < 0.05$.

3.0 RESULTS

3.1 DEPENDENT VARIABLES SUMMARY

Table 1. Statistical summary for dependent variables

Variable	Minimum	Maximum	Mean	Median	N	N miss	Std Dev	Lower Quartile	Upper Quartile	Skewness
Adiponectin(ug/ml)	2.0	54.40	13.53	12.10	175	0	7.41	8.60	16.90	1.69
Leptin(ug/ml)	0.78	58.60	6.84	4.55	160	15	7.5	2.80	7.50	3.58
Adiponectin/leptin ratio	0.11	28.25	3.98	2.65	160	15	4.37	1.49	4.77	2.90
Log(adiponectin)	0.69	3.99	2.47	2.49	175	0	0.54	2.15	2.83	-0.32
Log(leptin)	-0.25	4.07	1.57	1.52	160	15	0.81	1.03	2.01	0.30
Log (adiponectin/leptin)	-2.23	3.34	0.94	0.97	160	15	0.96	0.4	1.56	-0.21

As shown in **Table 1**, 15 observations were missing for leptin and adiponectin/leptin ratio. The range of adiponectin was from 2 to 54ug/ml, the range of leptin was from 0.78 to 58.6ug/ml, and the ratio was from 0.11 to 28.25.

All distributions of the three variables were right skewed (**Figure 1**). Using the log transformation, the skewness was reduced near to 0. Using the Kolmogorov-Smirnov test for normality (**Table 2**), all three transformed variables were normally distributed, with each p-value >0.15. In the regression analysis, the log transformed variables would be used as the outcome variables.

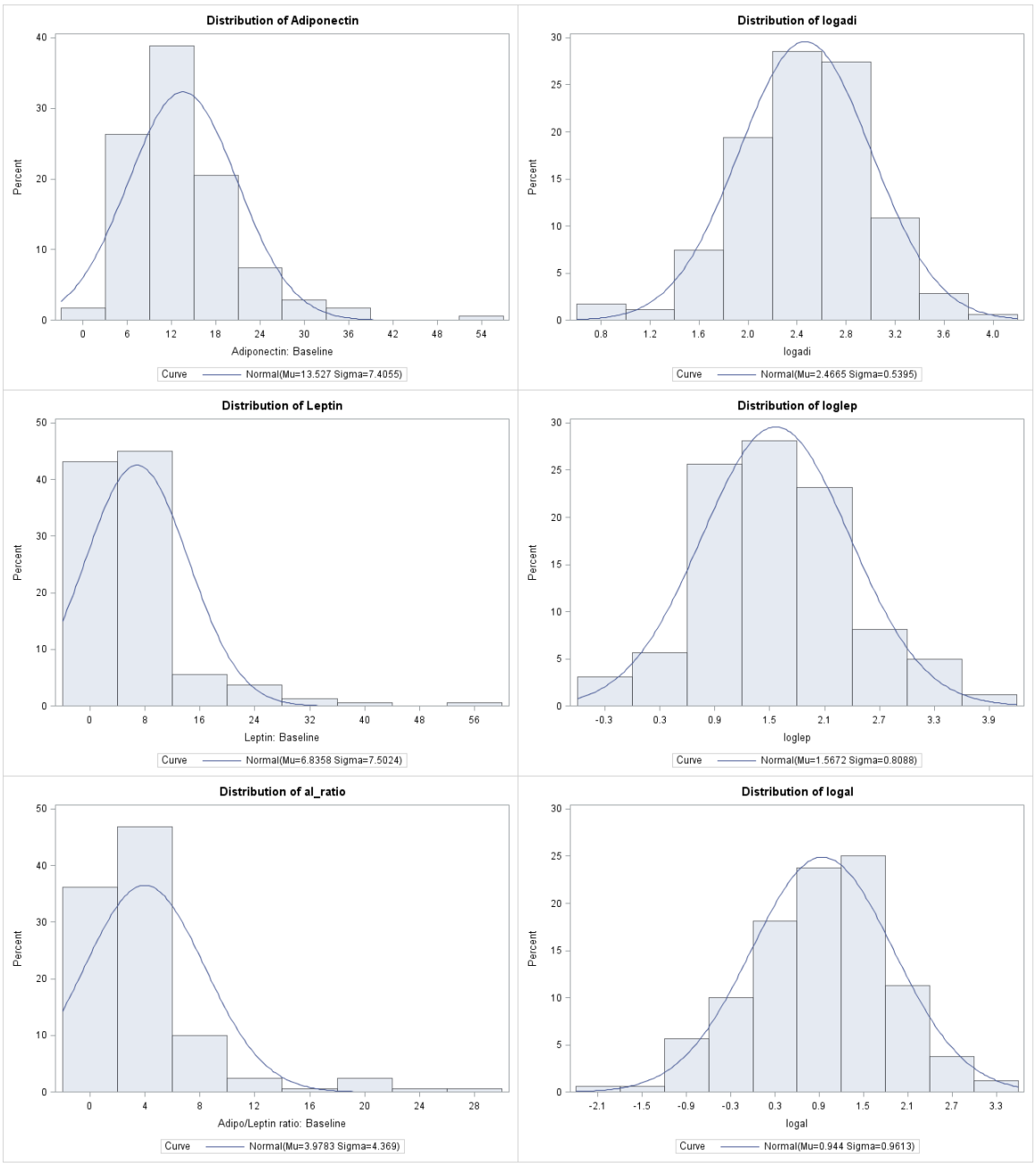


Figure 1. Comparison histograms of adiponectin, leptin, adiponectin/leptin ratio, log (adiponectin),log (leptin), log (adiponectin/leptin) and normal distribution

Table 2. Kolmogorov-Smirnov test for normality on dependent variables

Variable	P-value for Kolmogorov-Smirnov test
Log(adiponectin)	>0.150
Log(leptin)	>0.150
log (adiponectin/leptin)	>0.150

3.2 INDEPENDENT VARIABLES SUMMARY

3.2.1 Continuous independent variables

Table 3. Statistical summary for continuous independent variables

Variable	Minimum	Maximum	Mean	Median	N	N Miss	Std Dev	Lower Quartile	Upper Quartile
BMI %	16.64	99.67	74.04	78.35	169	6	20.32	60.27	90.39
BMI z-score	-0.97	2.71	0.82	0.78	169	6	0.77	0.26	1.3
Waist/height	0.24	0.67	0.47	0.46	143	32	0.06	0.43	0.51
Age(months)	17	230	116.62	117	175	0	45.73	80	150
Height(cm)	82.55	183.3	138.85	140.3	171	4	22.7	123.9	155.8
IAA	0	6.53	0.79	0.17	50	125	1.41	0.06	0.7
ICA	0	160	14.61	20	175	0	13.97	5	20
GAD	-0.02	1.15	0.25	0.1	175	0	0.32	0.02	0.37
IA2	-0.01	1.97	0.59	0.5	175	0	0.54	0	1.13
HbA1c	5.4	9.6	7.35	7.3	164	11	0.81	6.8	7.9
Cholesterol	80	293	156.02	156	167	8	29.16	137	172
LDL	35	228	90.68	88	97	78	29.02	73	105
HDL	20.8	85.9	49.08	48.6	167	8	11.44	40.7	56.6
Triglyceride	38	299	122.25	113	167	8	55.19	79	149
Diastolic blood pressure	10.29	99.95	60.77	62.3	145	30	20.38	49.17	74.62

Table 3 Continued

percentile									
Systolic blood pressure percentile	1.47	99.98	66.45	73.34	145	30	26.47	47.71	89.14
Glucose	37	409	157.48	136	163	12	75.18	100	202
C-peptide	0.05	10.2	1.88	1.48	166	9	1.55	0.77	2.64
Insulin dose	0.1	2.12	0.49	0.45	162	13	0.28	0.3	0.6
ZnT8A	-0.01	1.09	0.22	0.12	164	11	0.27	0.01	0.38

Descriptive results for the continuous independent variables were provided in **Table 3**.

The mean level of BMI percentile was 74% and the lower quartile was 60.3%, which indicated that the subjects in this study were heavier than typical child at their same age. Ages of the patients ranged from 17 to 230 months (1.4 to 19.2 yrs). The mean age was 116.7 months (9.7 yrs), close to the median age, which was 117 months (9.8 yrs). Waist/height ratios ranged from 0.24 to 0.67.The mean value was 0.47, close to the lower quartile value of 0.43, and the upper quartile value was 0.51. The waist/height ratios of most observations were between 0.43 and 0.51, and did not indicate central obesity (waist/height ratio$\geq$0.5).

Values for the other variable values were all in expected ranges. There was an appreciable number of subjects missing IAA (n=125) and LDL (n=78) information which limited our ability to include these variables in further analysis. In the later analysis, the two variables would be excluded.

3.2.2 Categorical variables

For the categorical variables, the frequency and missing numbers were provided by PROC FREQ in SAS 9.3 (**Table 4**). Over half were males (59.4%) and 42 (29.4%) had central

obesity participated in the study. Over 90% of the subjects had at least one positive antibody. With respect to DQ2/DQ8 less than 20% of the subjects were in the low risk group of X. For waist percentile, only 15.9% of the subjects were considered having large waist circumferences.

Table 4. Statistical summary for categorical independent variables

Variables	Values	Frequency	Percent	Frequency Missing
Gender	Male	104	59.43	0
	Female	71	40.57	
Central obesity	No	101	70.63	32
	Yes	42	29.37	
DQ2/DQ8	X	33	18.86	0
	DQ2	47	26.86	
	DQ8	61	34.86	
	DQ2/DQ8	34	19.43	
Waist %	<25%	62	43.06	31
	25%-75%	59	40.97	
	>75%	23	15.97	
Number of positive antibodies	0	15	8.57	0
	1	25	14.29	
	2	58	33.14	
	3	64	36.57	
	4	13	7.43	

3.3 CORRELATIONS

The Pearson correlation coefficients assessed the linear associations between different continuous variables. The correlation coefficient between log (adiponectin) and log (leptin) was -

0.0096, with a p-value of 0.9, which indicated that log (adiponectin) and log (leptin) were not linearly associated.

In the correlation matrix (**Table 5** and **Table 6)**, the red shaded values indicated correlations greater than 0.75 and the blue shade values were from 0.5 to 0.75. The two colors indicated that the variables were highly correlated. The cyan shaded values indicated moderate correlations from 0.25 to 0.5. Careful consideration as to which variables of the highly correlated factors should be used in the regression models. Groups of highly correlated variables were summarized in **Table 7**.

Table 5. Pearson correlation coefficients for continuous independent variables

	BMI %	BMI z-score	Waist	Waist/height	Age	Height	IAA	ICA	GAD	IA2	HbA1c	Cholesterol
BMI %*	1.00	**0.96**	**0.50**	**0.63**	0.00	0.07	-0.04	0.01	-0.19	-0.21	-0.03	-0.02
		<.0001	**<.0001**	**<.0001**	0.97	0.34	0.78	0.94	0.01	0.01	0.71	0.83
BMI z-score	**0.96**	1.00	**0.58**	**0.73**	0.00	0.08	-0.05	-0.01	-0.18	-0.21	-0.02	0.01
	<.0001		**<.0001**	**<.0001**	1.00	0.27	0.73	0.89	0.02	0.01	0.84	0.94
Waist	**0.50**	**0.58**	1.00	**0.63**	**0.68**	**0.75**	-0.20	-0.10	0.09	-0.17	-0.15	-0.15
	<.0001	**<.0001**		**<.0001**	**<.0001**	**<.0001**	0.21	0.21	0.29	0.04	0.08	0.07
Waist/height	**0.63**	**0.73**	**0.63**	1.00	-0.04	-0.02	0.13	-0.01	-0.09	-0.15	0.00	0.01
	<.0001	**<.0001**	**<.0001**		0.63	0.85	0.42	0.93	0.29	0.07	0.96	0.94
Age	0.00	0.00	**0.68**	-0.04	1.00	**0.95**	**-0.31**	-0.10	0.17	-0.08	**-0.30**	-0.17
	0.97	1.00	**<.0001**	0.63		**<.0001**	**0.03**	0.18	0.03	0.27	**<.0001**	0.03
Height	0.07	0.08	**0.75**	-0.02	**0.95**	1.00	**-0.33**	-0.13	0.16	-0.07	**-0.31**	-0.22
	0.34	0.27	**<.0001**	0.85	**<.0001**		**0.02**	0.10	0.04	0.39	**<.0001**	0.01
IAA	-0.04	-0.05	-0.20	0.13	**-0.31**	**-0.33**	1.00	0.13	-0.01	0.23	-0.02	-0.07
	0.78	0.73	0.21	0.42	**0.03**	**0.02**		0.39	0.97	0.11	0.88	0.62
ICA	0.01	-0.01	-0.10	-0.01	-0.10	-0.13	0.13	1.00	0.11	**0.31**	0.07	-0.02
	0.94	0.89	0.21	0.93	0.18	0.10	0.39		0.16	**<.0001**	0.35	0.83
GAD	-0.19	-0.18	0.09	-0.09	0.17	0.16	-0.01	0.11	1.00	0.09	0.06	-0.14
	0.01	0.02	0.29	0.29	0.03	0.04	0.97	0.16		0.23	0.42	0.08
IA2	-0.21	-0.21	-0.17	-0.15	-0.08	-0.07	0.23	**0.31**	0.09	1.00	0.08	-0.04
	0.01	0.01	0.04	0.07	0.27	0.39	0.11	**<.0001**	0.23		0.34	0.65
HbA1c	-0.03	-0.02	-0.15	0.00	**-0.30**	**-0.31**	-0.02	0.07	0.06	0.08	1.00	0.11
	0.71	0.84	0.08	0.96	**<.0001**	**<.0001**	0.88	0.35	0.42	0.34		0.16
Cholesterol	-0.02	0.01	-0.15	0.01	-0.17	-0.22	-0.07	-0.02	-0.14	-0.04	0.11	1.00
	0.83	0.94	0.07	0.94	0.03	0.01	0.62	0.83	0.08	0.65	0.16	
LDL	0.17	0.18	0.14	0.25	0.04	-0.04	-0.19	-0.03	-0.11	-0.21	0.06	**0.59**
	0.10	0.08	0.21	0.03	0.68	0.70	0.28	0.76	0.26	0.04	0.55	**<.0001**
HDL	-0.24	**-0.25**	**-0.28**	**-0.28**	-0.15	-0.17	-0.13	0.00	-0.03	0.16	0.12	**0.29**
	<.0001	**<.0001**	**<.0001**	**<.0001**	0.05	0.03	0.37	0.99	0.72	0.04	0.14	**<.0001**
Triglyceride	0.04	0.06	-0.03	0.11	-0.10	-0.12	0.20	0.05	-0.07	0.00	-0.05	0.16
	0.61	0.46	0.76	0.21	0.19	0.14	0.17	0.48	0.37	0.96	0.56	0.04

Table 5 Continued

Percentile for diastolic blood pressure	0.07	0.09	-0.25	0.23	**-0.47**	**-0.50**	0.19	0.02	-0.03	0.02	0.10	0.11
	0.42	0.29	0.01	0.01	**<.0001**	**<.0001**	0.22	0.80	0.76	0.80	0.22	0.18
Percentile for systolic blood pressure	0.17	0.24	0.03	**0.35**	**-0.30**	**-0.28**	-0.07	-0.03	-0.18	-0.05	-0.09	0.14
	0.04	0.00	0.71	**<.0001**	**<.0001**	**<.0001**	0.64	0.73	0.03	0.53	0.27	0.10
Glucose	-0.09	-0.10	**-0.27**	-0.10	**-0.27**	**-0.26**	0.13	0.08	0.05	0.21	**0.31**	0.03
	0.25	0.21	**<.0001**	0.25	**<0.01**	**<0.01**	0.39	0.31	0.53	0.01	**<.0001**	0.67
Insulin dose adjusted by HbA1c	0.08	0.08	0.10	0.12	-0.02	-0.07	-0.13	0.03	0.19	0.05	**0.71**	0.10
	0.31	0.31	0.26	0.18	0.79	0.38	0.40	0.69	0.02	0.56	**<.0001**	0.23
C-peptide	0.11	0.09	0.22	0.00	**0.29**	**0.34**	0.11	0.04	0.01	-0.07	**-0.31**	-0.15
	0.15	0.25	0.01	0.96	**<.0001**	**<.0001**	0.45	0.63	0.91	0.34	**<.0001**	0.06
Insulin Dose	0.12	0.11	0.20	0.15	0.18	0.11	-0.14	-0.01	0.16	0.02	**0.27**	0.07
	0.12	0.16	0.02	0.09	0.02	0.15	0.34	0.91	0.04	0.78	**<0.05**	0.38
ZnT8A	-0.15	-0.16	-0.01	-0.05	0.05	0.07	-0.25	**0.29**	0.15	**0.39**	0.08	-0.09
	0.06	0.04	0.90	0.60	0.53	0.38	0.08	**<.0001**	0.05	**<.0001**	0.31	0.25

*The first line for each variables was the correlation coefficient, the second line is the p-value (Prob > |r| under H0: Rho=0).

Table 6. Pearson correlation coefficients for continuous independent variables

	LDL	**HDL**	**Triglyceride**	**Percentile for diastolic blood presuure**	**Percentile for systolic blood presuure**	**Glucose**	**Insulin dose adjusted by HbA1c**	**C-peptide**	**Insulin dose**	**ZnT8A**
BMI %*	0.17	-0.24	0.04	0.07	0.17	-0.09	0.08	0.11	0.12	-0.15
	0.10	0.00	0.61	0.42	0.04	0.25	0.31	0.15	0.12	0.06
BMI z-score	0.18	-0.25	0.06	0.09	0.24	-0.10	0.08	0.09	0.11	-0.16
	0.08	<.0001	0.46	0.29	0.00	0.21	0.31	0.25	0.16	0.04
Waist	0.14	-0.28	-0.03	-0.25	0.03	-0.27	0.10	0.22	0.20	-0.01
	0.21	<.0001	0.76	0.01	0.71	<.0001	0.26	0.01	0.02	0.90
Waist/height	0.25	-0.28	0.11	0.23	0.35	-0.10	0.12	0.00	0.15	-0.05
	0.03	<.0001	0.21	0.01	<.0001	0.25	0.18	0.96	0.09	0.60
Age	0.04	-0.15	-0.10	-0.47	-0.30	-0.27	-0.02	0.29	0.18	0.05
	0.68	0.05	0.19	<.0001	<.0001	<.0001	0.79	<.0001	0.02	0.53
Height	-0.04	-0.17	-0.12	-0.50	-0.28	-0.26	-0.07	0.34	0.11	0.07
	0.70	0.03	0.14	<.0001	<.0001	<.0001	0.38	<.0001	0.15	0.38
IAA	-0.19	-0.13	0.20	0.19	-0.07	0.13	-0.13	0.11	-0.14	-0.25
	0.28	0.37	0.17	0.22	0.64	0.39	0.40	0.45	0.34	0.08
ICA	-0.03	0.00	0.05	0.02	-0.03	0.08	0.03	0.04	-0.01	0.29
	0.76	0.99	0.48	0.80	0.73	0.31	0.69	0.63	0.91	<.0001
GAD	-0.11	-0.03	-0.07	-0.03	-0.18	0.05	0.19	0.01	0.16	0.15
	0.26	0.72	0.37	0.76	0.03	0.53	0.02	0.91	0.04	0.05
IA2	-0.21	0.16	0.00	0.02	-0.05	0.21	0.05	-0.07	0.02	0.39
	0.04	0.04	0.96	0.80	0.53	0.01	0.56	0.34	0.78	<.0001
HbA1c	0.06	0.12	-0.05	0.10	-0.09	0.31	0.71	-0.31	0.27	0.08
	0.55	0.14	0.56	0.22	0.27	<.0001	<.0001	<.0001	<.0001	0.31
Cholesterol	0.59	0.29	0.16	0.11	0.14	0.03	0.10	-0.15	0.07	-0.09
	<.0001	<.0001	0.04	0.18	0.10	0.67	0.23	0.06	0.38	0.25
LDL	1.00	0.01	0.02	0.12	0.07	-0.02	0.11	-0.02	0.11	-0.17
		0.93	0.82	0.31	0.56	0.83	0.31	0.84	0.28	0.10
HDL	0.01	1.00	-0.30	-0.05	-0.01	0.00	-0.04	-0.13	-0.08	-0.01

Table 6 Continued

	0.93		<.0001	0.58	0.94	0.99	0.63	0.10	0.34	0.88
Triglyceride	0.02	-0.30	1.00	0.12	0.15	0.06	0.04	0.06	0.08	-0.10
	0.82	<.0001		0.17	0.09	0.49	0.61	0.48	0.31	0.20
Percentile for diastolic blood pressure	0.12	-0.05	0.12	1.00	0.39	0.08	0.04	-0.13	-0.04	0.04
	0.31	0.58	0.17		<.0001	0.38	0.67	0.13	0.68	0.61
Percentile for systolic blood pressure	0.07	-0.01	0.15	0.39	1.00	-0.03	-0.01	-0.03	0.06	0.06
	0.56	0.94	0.09	<.0001		0.76	0.93	0.69	0.48	0.45
Glucose	-0.02	0.00	0.06	0.08	-0.03	1.00	0.03	-0.03	-0.14	0.11
	0.83	0.99	0.49	0.38	0.76		0.76	0.70	0.09	0.20
Insulin dose adjusted by HbA1c	0.11	-0.04	0.04	0.04	-0.01	0.03	1.00	-0.30	0.87	0.05
	0.31	0.63	0.61	0.67	0.93	0.76		<.0001	<.0001	0.52
C-peptide	-0.02	-0.13	0.06	-0.13	-0.03	-0.03	-0.30	1.00	-0.20	0.05
	0.84	0.10	0.48	0.13	0.69	0.70	<.0001		0.01	0.51
Insulin dose	0.11	-0.08	0.08	-0.04	0.06	-0.14	0.87	-0.20	1.00	-0.01
	0.28	0.34	0.31	0.68	0.48	0.09	<.0001	0.01		0.94
ZnT8A	-0.17	-0.01	-0.10	0.04	0.06	0.11	0.05	0.05	-0.01	1.00
	0.10	0.88	0.20	0.61	0.45	0.20	0.52	0.51	0.94	

*The first line for each variables was the correlation coefficient, the second line is the p-value (Prob > |r| under H0: Rho=0).

Table 7. Highly correlated groups among independent variables

Highly correlated groups	Variables	Pearson Correlation Coefficients
1: BMI %, BMI z-score, waist/height, waist	BMI % & BMI z-score	0.96
	BMI % & waist/height	0.63
	BMI z-score & waist	0.58
	BMI z-score & waist/height	0.73
2: Waist, waist/height, age, height	Waist & waist/height	0.63
	Waist & age	0.68
	Age & height	0.95
	Height & waist	0.75
3: LDL, cholesterol	LDL & cholesterol	0.59
4: Insulin dose adjusted by HbA1c, Insulin dose, HbA1c	Insulin dose adjusted by HbA1c & HbA1c	0.71
	Insulin dose adjusted by HbA1c & insulin dose	0.87

3.4 UNIVARIATE LINEAR REGRESSION WITH SIMPLE ADJUSTMENT

3.4.1 Simple regression of log (adiponectin)

Table 8. Univariate regression and univariate regression with age adjustment of log (adiponectin)

Independent Var	β	P-value	Adjusted Var	β	P-value	R^2	Pr > F	N of missing
BMI %*	-0.002	0.33				0.004		6
BMI %	-0.002	0.315	Age	-0.0029	0.002	0.063	0.0045	6
BMI z-score	-0.07	0.185				0.01		6
BMI z-score	-0.072	0.173	Age	-0.0029	0.0017	0.07	0.003	6
Central obesity	-0.13	0.18				0.013		32
Central obesity	-0.118	0.224	Age	-0.0025	0.013	0.055	0.0185	32
Waist	-0.009	0.0045				0.054		29
Waist	-0.0075	0.085	Age	-0.0007	0.58	0.057	0.0155	29
Height	-0.005	0.0057				0.044		4
Height	0.0053	0.34	Age	-0.005	0.056	0.065	0.0036	4
Waist/height	-1.3	0.06				0.025		32
Waist/height	-1.38	0.043	Age	-0.0027	0.0078	0.073	0.005	32
HbA1c	0.076	0.15				0.013		11
HbA1c	0.032	0.56	Age	-0.0026	0.0081	0.055	0.01	11
Cholesterol	0.0006	0.7				0.0009		8
Cholesterol	-0.00007	0.96	Age	-0.0024	0.011	0.0399	0.0355	8
LDL	-0.002	0.17				0.02		78
LDL	-0.003	0.19	Age	-0.003	0.009	0.088	0.013	78
HDL	0.004	0.23				0.008		8
HDL	0.003	0.4	Age	-0.0023	0.015	0.044	0.025	8
DQ2/DQ8		0.8007				0.0058	0.8007	0
X	0	0						
DQ2	0.081	0.512						
DQ2/DQ8 class	0.012	0.927						
DQ8	0.096	0.414						
DQ2/DQ8		0.9912	Age	-0.0024	0.0056	0.0498	0.0679	0
X	0	0						
DQ2	0.108	0.374						

Table 8 Continued

DQ2/DQ8 class	0.019	0.882						
DQ8	0.116	0.316						
Triglycerides	-0.0001	0.89				0.0001		8
Triglycerides	-0.0003	0.68	Age	-0.0024	0.0091	0.041	0.033	8
Percentile for diastolic blood pressure	0.0022	0.34				0.006		30
Percentile for diastolic blood pressure	-0.0004	0.87	Age	-0.002	0.032	0.038	0.063	30
Percentile for systolic blood pressure	2.3	0.26				0.009		30
Percentile for systolic blood pressure	0.0008	0.64	Age	-0.002	0.03	0.039	0.05	30

*The shaded rows are univariate regression analysis without adjustment for age.

Table 8 provided the results of the univariate regression and univariate regression with age adjustment of log (adiponectin).

P-value: The p-values indicated if the independent variable was significant for predicting the outcome variable. In the univariate regression analysis, only waist, height, and waist/height ratio were significant for predicting log (adiponectin). After adjusting for age, waist and height became non-significant. However, waist/height ratio was still significant. This change indicated that after accounting for the effect of age on adiponectin, waist and height no longer added to the model.

β coefficients: The β coefficients of waist, height and waist/height ratio in univariate regression models were negative, indicating a negative linear relationship between the three independent variables and log (adiponectin).

R^2: Although in the univariate analysis, waist, height and waist/height ratio were significant, the R^2 were very small, demonstrating that the variation explained by those variables were very low, only between 4 to 8 percent. Even after age adjustment, the amount of variation explained remained small.

All β coefficients were small, close to zero. This was in part because the univariate regression models only predicted small percentages of the variability of the dependent variable.

Covariate adjustment variable: The p-values indicated that age was significant for predicting log (adiponectin). The β coefficients indicated that age had a negative linear relationship with log (adiponectin).

Table 9. Univariate regression and univariate regression with BMI percentile adjustment of log (adiponectin)

Independent Var	β	P-value	Adjusted Var	β	P-value	R^2	Pr > F	N of missing
IA2	-0.01	0.89				0.0001		0
IA2	-0.017	0.83	BMI %	-0.002	0.32	0.006	0.61	6
IAA	0.067	0.22				0.03		125
IAA	0.068	0.21	BMI %	-0.003	0.42	0.049	0.32	126
ICA	-0.001	0.73				0.0007		0
ICA	-0.001	0.73	BMI %	-0.002	0.33	0.006	0.59	6
GAD	0.024	0.86				0.0002		0
GAD	0.027	0.84	BMI %	-0.002	0.36	0.006	0.61	6
ZnT8A	-0.17	0.29				0.007		11
ZnT8A	-0.2	0.2	BMI %	-0.003	0.19	0.018	0.232	17
Zinc category (+ ,-)	-0.12	0.23				0.01		34
Zinc category (+ ,-)	-0.13	0.21	BMI %	-0.003	0.22	0.02	0.255	39
Insulin dose	-0.03	0.83				0.0003		13
Insulin dose	-0.03	0.825	BMI %	-0.002	0.37	0.0059	0.63	17
Number of positive antibodies		0.1114				0.0430	0.1114	0
0	0	0						
1	0.2215	0.206						
2	-0.02	0.893						
3	-0.114	0.458						
4	-0.129	0.526						
Number of positive antibodies		0.2522	BMI %	-0.0022	0.3004	0.0376	0.2772	0
0	0	0						
1	0.142	0.439						
2	-0.042	0.788						
3	-0.142	0.375						
4	-0.163	0.43						

Table 9 Continued

Number of positive antibodies (continuous)	-0.07860	0.0421				0.0237	0.0421	0
Number of positive antibodies (continuous)	-0.07640	0.0538	BMI %	-0.00269	0.1933	0.0277	0.0968	
Number of positive antibodies class1(0,≥1)	-0.029	0.843				0.0002		0
Number of positive antibodies class1(0, ≥1)	-0.0644	0.6656	BMI %	-0.0022	0.3015	0.0068	0.5688	0
Number of positive antibodies class2(0-1, ≥2)	-0.213773	0.0273				0.0278		0
Number of positive antibodies class2(0-1, ≥2)	-0.187670	0.0585		-0.00206	0.3115	0.0269	0.1038	0
Number of positive antibodies class3(0,1,2, ≥3)		0.0570				0.0429	0.0570	0
0	0	0						
1	0.221	0.204						
2	-0.021	0.893						
≥3	-0.116	0.44						
Number of positive antibodies class3(0,1,2, ≥3)		0.1472	BMI %	-0.00226	0.2967	0.0375	0.1770	0
0	0	0						
1	0.1417	0.438						
2	-0.042	0.787						
≥3	-0.145	0.352						

Table 9 provided the results for the univariate regression and univariate regression with BMI percentile adjustment of log (adiponectin).

P-value: In the univariate regression analysis, number of positive antibodies (continuous), number of positive antibodies class2 and number of positive antibodies class3 were significant for predicting log (adiponectin) with p-values of 0.042, 0.027 and 0.057. With the addition of BMI percentile to the model, the p-values for number of positive antibodies (continuous), number of positive antibodies class2 and class3 increased to 0.054, 0.058 and 0.147.

β coefficients : The β coefficients for number of positive antibodies (continuous), number of positive antibodies class2 and class3 indicated the negative linear relationship with log(adiponectin) before and after BMI percentile adjustment.

R^2: In the univariate analysis of number of positive antibodies (continuous), number of positive antibodies class2 and class3, the R^2 values were very small, revealing the variation explained from those variables were very low, only from 2 to 5 percent. With the addition of BMI percentile to the models, the R^2 were still very small.

Covariate adjustment variable: BMI percentile was not significant for predicting the log (adiponectin).

Table 10. Univariate regression with C-peptide, glucose of log (adiponectin)

Independent Var1	β	P-value	Independent Var2	β	P-value	R^2	Pr > F	N of missing
Glucose	0.00005	0.923				0.00006		12
C-peptide	-0.005	0.83				0.0003		9
C-peptide/glucose	-2.74	0.41				0.0045		21
C-peptide	-0.009	0.74	**Glucose**	0.0001	0.85	0.001	0.93	21
C-peptide	-0.009	0.73	**Glucose(<120, >=120)**	0.0004	0.996	0.0007	0.94	21

Table 10 provided the results for the univariate regression analysis when glucose and C-peptide were treated as predictors of log (adiponectin).

P-value: None of independent variables was significant.

3.4.2 Simple regression of log(leptin)

Table 11. Univariate regression and univariate regression with age adjustment of log (leptin)

Independent Var	β	P-value	Adjusted Var	β	P-value	R^2	Pr > F	N of missing
BMI %	0.012	<.0001				0.095		20
BMI %	0.012	<.0001	Age	0.0044	0.0015	0.153	<.0001	20
BMI z-score	0.4	<.0001				0.14		20
BMI z-score	0.4	<.0001	Age	0.0044	0.0011	0.197	<.0001	20
Central obesity	0.64	<.0001				0.122		44
Central obesity	0.63	<.0001	Age	0.00408	0.006	0.172	<.0001	44
Waist	0.024	<.0001				0.15		41
Waist	0.026	0.0003	Age	-0.0009	0.66	0.152	<.0001	41
Height	0.008	0.0037				0.053		18
Height	0.003	0.742	Age	0.00278	0.525	0.056	0.0121	18
Waist/height	3.977	0.0006				0.088		44
Waist/height	4.272	0.0002	Age	0.0047	0.0016	0.156	<.0001	44
HbA1c	0.053	0.5075				0.0029		23
HbA1c	0.14	0.0882	Age	0.00497	0.0007	0.08	0.003	23
Cholesterol	-0.0004	0.8561				0.00022		21
Cholesterol	0.00071	0.75	Age	0.00484	0.0009	0.07	0.004	21
LDL	0.004	0.1849				0.019		85
LDL	0.004	0.2351	Age	0.00641	0.0013	0.13	0.0023	85
HDL	-0.0017	0.7657				0.00059		21
HDL	0.0013	0.8211	Age	0.00482	0.001	0.07	0.004	21
DQ2/DQ8		0.8629				0.0047		15
X	0	0						
DQ2	0.148	0.45						
DQ2/DQ8 class	0.05	0.813						
DQ8	0.123	0.5101						
DQ2/DQ8		0.9299	Age	0.0043	0.0023	0.0628	0.0386	15
X	0	0						
DQ2	0.11	0.563						
DQ2/DQ8 class	0.0503	0.8050						
DQ8	0.1036	0.5688						
Triglycerides	-0.000038	0.9755				0.000006		21
Triglycerides	0.00036	0.76	Age	0.00481	0.0009	0.07	0.004	21
Percentile for diastolic	0.00015	0.96				0.000016		41

Table 11 Continued

blood pressure								
Percentile for diastolic blood pressure	0.0049	0.1827	Age	0.0046	0.0051	0.058	0.0197	41
Percentile for systolic blood pressure	0.0015	0.553				0.0026		41
Percentile for systolic blood pressure	0.00388	0.1430	Age	0.0044	0.0051	0.06	0.016	41

Table 11 provided the results for the univariate regression and univariate regression with age adjustment of log (leptin).

P-value: In the univariate regression analysis, BMI percentile, BMI z-score, central obesity waist, height and waist/height ratios were significant for predicting log (leptin). When the covariate of age was added to the models, those variables were still significant except height, due to the high correlation between age and height.

β coefficients: The β coefficients of BMI percentile, BMI z-score , central obesity, waist , height and waist/height ratios in univariate regression models were all positive, revealing the positive linear relationship with log (leptin).

R^2: The R^2 of the univariate regression models of BMI percentile, BMI z-score , central obesity , waist , height and waist/height ratios were very small, demonstrating that the variation explanation from those variables were very low, no more than 5 percent. After age was adjusted, the effect of predicting variation increased by nearly 10 percent, and ranged from 15 to 18 percent.

Covariate adjustment variable: Age was significant for predicting log (leptin). However, in the model of waist and height, age reduced its significant importance because of high correlations between age and height and age and waist. Age had positive linear relationship with log (leptin), indicating that when age increased, log (leptin) also increased.

Other variables: When age was added as a covariate, it had an influence on the relationships between HbA1c and log (leptin), percentile for diastolic blood pressure and log (leptin) and percentile for systolic blood pressure and log (leptin). Although p-values became smaller, none reached statistical significance.

Table 12. Univariate regression and univariate regression with BMI percentile adjustment of log (leptin)

Independent Var	β	P-value	Adjusted Var	β	P-value	R^2	Pr > F	N of missing
IA2	-0.135	0.25				0.0083		15
IA2	-.0414	0.7251	BMI %	0.012	0.0002	0.095	0.0005	20
IAA	0.059	0.4			0.014			125
IAA	0.072	0.2727	BMI %	0.0147	0.0023	0.199	0.0061	126
ICA	-0.0056	0.21			0.0099			15
ICA	-0.0055	0.2	BMI %	0.012	<0.0001	0.1	0.0002	20
GAD	0.152	0.47			0.0033			15
GAD	0.39	0.064	BMI %	0.014	<0.0001	0.115	<0.0001	20
ZnT8A	-0.492	0.052			0.025			23
ZnT8A	-0.35	0.167	BMI %	0.012	0.0004	0.11	0.0002	28
Zinc category (+ ,-)	0.0142	0.93			0.00006			44
Zinc category (+ ,-)	0.123	0.43	BMI %	0.0153	<0.0001	0.122	0.0003	48
Insulin dose	0.914	0.0001				0.099		27
Insulin dose	0.782	0.0006	BMI %	0.0114	0.0003	0.176	<.0001	30
Number of positive antibodies		0.4085				0.0252	0.4085	15
0	0	0						
1	0.08	0.772						
2	0.276	0.259						
3	-0.019	0.937						
4	0.053	0.8651						
Number of positive antibodies		0.6659	BMI %	0.012201	0.0003	0.1090	0.0039	20
0	0	0						
1	0.251	0.3705						
2	0.347	0.145						
3	0.2038	0.396						
4	0.22872	0.4529						
Number of positive	-0.027	0.652				0.0013		15

Table 12 Continued

antibodies (continuous)								
Number of positive antibodies (continuous)	0.024	0.687	BMI %	0.0125	<0.0001	0.0957	0.0005	20
Number of positive antibodies class1(0, ≥1)	0.1075	0.6363				0.0014	0.6363	15
Number of positive antibodies class1(0, ≥1)	0.274	0.2173	BMI %	0.013019	<.0001	0.1038	0.0002	20
Number of positive antibodies class2(0-1, ≥2)	0.0631	0.6815				0.0011		15
Number of positive antibodies class2(0-1, ≥2)	0.11663	0.4402		0.012294	<.0001	0.0983	0.0004	20
Number of positive antibodies class3(0,1,2, ≥3)		0.2714				0.0247	0.2714	15
0	0	0						
1	0.08	0.77						
2	0.276	0.258						
≥3	-0.00596	0.9799						
Number of positive antibodies class3(0,1,2, ≥3)		0.4976	BMI %	0.012220	0.0003	0.1089	0.0016	20
0	0	0						
1	0.252	0.368						
2	0.347	0.144						
≥3	0.2086	0.3743						

Table 12 provided the statistical information about the univariate regression and univariate regression with BMI percentile adjustment of log (leptin).

P-value: In the univariate regression analysis, ZnT8A and insulin dose were significant for predicting log (leptin). When age was added into the model, insulin dose was still significant but ZnT8A became non-significant.

β coefficients: The β coefficient for insulin dose revealed positive linear relationship with log (leptin) when age was adjusted or not.

R^2: The R^2 was very small, demonstrating that the variation explained from insulin dose was very low(9.9%). When BMI percentile included in the model, the R^2 increased to 17.6%.

Covariate adjustment variable: BMI percentile was significant for predicting log (leptin) and had positive linear relationship with log (leptin).

Table 13. Simple regression with C-peptide, glucose of log (leptin)

Independent Var1	β	P-value	Independent Var2	β	P-value	R2	Pr > F	N of missing
Glucose	-0.0017	0.054				0.025		27
C-peptide	0.115	0.0053				0.05		22
C-peptide/ glucose	18.65	0.0002				0.092		34
C-peptide	0.11	0.0076	**Glucose**	-0.002	0.07	0.07	0.0061	34
C-peptide	0.12	0.004	**Glucose(<120, >=120)**	-0.34	0.0114	0.09	0.0013	34

Table 13 provided the results of simple regression with C-peptide and glucose of log (leptin).

P-value: All the predictors of glucose and C-peptide were significant for predicting log (leptin).

β coefficients: The β coefficient of glucose showed a negative linear relationship between glucose and log (leptin). The β coefficients of other variables were all positive, revealing the positive linear relationship between the other variables and log (leptin).

R^2: The R^2 were very small, from 2% to 9%.

3.4.3 Simple regression of log(adiponectin/leptin)

Table 14. Univariate regression and univariate regression with age adjustment of log (adiponectin/leptin)

Independent Var	B	P-value	Adjusted Var	β	P-value	R^2	Pr > F	N of missing
BMI %	-0.0123	0.0013				0.06576		20
BMI %	-0.0121	0.0007	Age	-0.0077	<.0001	0.19177	<.0001	20
BMI z-score	-0.4163	<.0001				0.10385		20
BMI z-score	-0.4137	<.0001	Age	-0.0077	<.0001	0.22991	<.0001	20
Central obesity	-0.7005	0.0002				0.10454		44
Central obesity	-0.6795	0.0001	Age	-0.0071	<.0001	0.21373	<.0001	44
Waist	-0.0324	<.0001				0.19948		41
Waist	-0.0298	0.0003	Age	-0.0011	0.6373	0.20085	<.0001	41
Height	-0.0139	<.0001				0.10894		18
Height	0.00176	0.8614	Age	-0.0083	0.1015	0.12438	<.0001	18
Waist/height	-4.5058	0.001				0.08115		44
Waist/height	-4.9918	0.0001	Age	-0.0078	<.0001	0.21432	<.0001	44
HbA1c	0.00293	0.9758				6E-06		23
HbA1c	-0.1358	0.1525	Age	-0.008	<.0001	0.13293	<.0001	23
Cholesterol	0.00109	0.6854				0.00108		21
Cholesterol	-0.0007	0.7895	Age	-0.0076	<.0001	0.1255	<.0001	21
LDL	-0.0068	0.0624				0.03892		85
LDL	-0.0058	0.0752	Age	-0.01	<.0001	0.24045	<.0001	85
HDL	0.00478	0.4801				0.00329		21
HDL	0.00012	0.9848	Age	-0.0076	<.0001	0.12509	<.0001	21
DQ2/DQ8		0.9149				0.0033	0.9149	15
X	0	0						
DQ2	-0.1552	0.506						
DQ2/DQ8 class	-0.044	0.859						
DQ8	-0.0566	0.7988						
DQ2/DQ8		0.9765	Age	-0.0073	<.0001	0.1256	0.0003	15
X	0	0						
DQ2	-0.09	0.68						
DQ2/DQ8 class	-0.045	0.85						
DQ8	-0.02316	0.9117						
Triglycerides	0.00063	0.6648				0.00124		21

Table 14 Continued

Triglycerides	7.5E-06	0.9957	Age	-0.0076	<.0001	0.12508	<.0001	21
Percentile for diastolic blood pressure	0.00347	0.3852				0.00572		41
Percentile for diastolic blood pressure	-0.0038	0.3762	Age	-0.0071	0.0003	0.10112	0.0009	41
Percentile for systolic blood pressure	0.00165	0.5944				0.00215		41
Percentile for systolic blood pressure	-0.002	0.5218	Age	-0.0067	0.0003	0.09855	0.0011	41

Table 14 provided the results of the univariate regression and univariate regression with age adjustment of log (adiponectin/leptin).

P-value: In the univariate regression, BMI percentile, BMI z-score, central obesity, waist, height and waist/height ratios were significant for predicting log (adiponectin/leptin). When age was added into the model, those variables were still significant except height, due to the high correlation between age and height.

β coefficients: The β coefficients of BMI percentile, BMI z-score , central obesity, waist, height and waist/height ratios in univariate regression models were negative, revealing a negative linear relationship between those variables and log (adiponectin/leptin).

R^2: In the univariate analysis, the R^2 indicated that the variation explained from those variables were from 6% to 20%. After the addition of age into the model, the percent of variation explained in the dependent variable increased from 20% to 23%.

Covariate adjustment variable: Age was significant for predicting log (adiponectin/leptin). However, with the addition of waist and height, age became non-significant because of high correlations between age and height and age and waist. Age had negative linear relationship with log (adiponectin/leptin), indicating that when age increased, log (adiponectin/leptin) decreased.

Table 15. Univariate regression and univariate regression with BMI percentile adjustment of log (adiponectin/leptin)

Independent Var	β	P-value	Adjusted Var	β	P-value	R^2	Pr > F	N of missing
IA2	0.116	0.4092				0.00432		15
IA2	0.03527	0.8058	BMI %	-0.0121	0.0019	0.06614	0.0055	20
IAA	0.00751	0.9386				0.00013		125
IAA	-0.0039	0.9668	BMI %	-0.0179	0.0082	0.14255	0.0291	126
ICA	0.00447	0.4003				0.00448		15
ICA	0.0046	0.3816	BMI %	-0.0123	0.0012	0.07047	0.0039	20
GAD	-0.0878	0.7261				0.00078		15
GAD	-0.3143	0.2218	BMI %	-0.0134	0.0006	0.07492	0.0027	20
ZnT8A	0.47839	0.1107				0.01687		23
ZnT8A	0.32146	0.2929	BMI %	-0.0127	0.0018	0.08359	0.0019	28
Zinc category (+ ,-)	-0.0656	0.7259				0.00096		44
Zinc category (+ ,-)	-0.1842	0.3258	BMI %	-0.0165	0.0003	0.10061	0.0014	48
Insulin dose	-0.9383	0.0007				0.07551		27
Insulin dose	-0.8274	0.0027	BMI %	-0.011	0.0036	0.12854	<.0001	30
Number of positive antibodies		0.6149				0.0170	0.6149	15
0	0	0						
1	0.1286	0.697						
2	-0.243	0.4						
3	-0.103	0.72						
4	-0.218629	0.5574						
Number of positive antibodies		0.6492	BMI %	-0.0127	0.0019	0.0811	0.0262	20
0	0	0						
1	-0.09	0.789						
2	-0.32	0.268						
3	-0.334	0.254						
4	-0.4	0.2806						
Number of positive antibodies (continuous)	-0.058	0.42				0.004		15
Number of positive antibodies (continuous)	-0.104	0.15	BMI %	-0.0132	0.0006	0.0785	0.002	20
Number of positive	-0.128	0.6352				0.0014	0.6532	15

Table 15 Continued

antibodies class1(0, ≥1)								
Number of positive antibodies class1(0, ≥1)	-0.307436	0.2564	BMI %	-0.013	0.0007	0.0737	0.0030	20
Number of positive antibodies class2(0-1, ≥2)	-0.2523	0.1664				0.0121	0.1664	15
Number of positive antibodies class2(0-1, ≥2)	-0.282	0.1249	BMI %	-0.012342	0.0011	0.0802	0.0017	20
Number of positive antibodies class3(0,1,2, ≥3)		0.4715				0.0160	0.4715	15
0	0	0						
1	0.129	0.697						
2	-0.243	0.403						
≥3	-0.123637	0.6608						
Number of positive antibodies class3(0,1,2, ≥3)		0.4882	BMI %	-0.01273	0.0017	0.0807	0.0128	20
0	-0.093	0.786						
1	-0.32	0.266						
2	-0.32	0.266						
≥3	-0.347	0.2258						

Table 15 provided the results of the univariate regression and univariate regression with BMI percentile adjustment of log (adiponectin/leptin).

P-value: In the univariate regression analysis, only insulin dose was significant for predicting log (adiponectin/leptin). After age was adjusted, insulin dose was still significant.

β coefficients: The β coefficient of insulin dose in univariate regression model was negative, revealing the negative linear relationship between insulin dose and log (adiponectin/leptin).

R^2: The R^2 was small, demonstrating that the variation explanation from insulin dose was 7.5%. When BMI percentile was added into the model, the effect of predicting variation of insulin dose increased to 12.8%.

Covariate adjustment variable: BMI percentile was significant for predicting log (adiponectin/leptin) and had a negative linear relationship with log (adiponectin/leptin).

Table 16. Simple regression with C-peptide, glucose of log (adiponectin/leptin)

Independent Var1	β	p-value	Independent Var2	β	p-value	R2	Pr > F	N of missing
Glucose	0.002	0.0562				0.02475		27
C-peptide	-0.1251	0.0107				0.04233		22
C-peptide/ glucose	-22.252	0.0002				0.09371		34
C-peptide	-0.1251	0.0111	**Glucose**	0.00196	0.0581	0.06896	0.0072	34
C-peptide	-0.1353	0.0059	**Glucose(<120, >=120)**	0.38423	0.0153	0.084	0.0023	34

Table 16 provided the results of simple regression with C-peptide and glucose of log (adiponectin/leptin).

P-value: All of the glucose and C-peptide variables were significant predictors of log (adiponectin/leptin).

β coefficients: Glucose had a positive β coefficient, revealing the positive linear relationship between glucose and log (adiponectin/leptin). The β coefficients of the other predictors were all negative, revealing a negative relationship with log (adiponectin/leptin).

R^2: The R^2 were very small, from 2% to 10%.

3.4.4 Comparison of univariate regression results

From **Table 17**, summarized the result of the univariate regression models

Number of positive antibodies classes: For log (leptin) and log (adiponectin/leptin), the number of positive antibody level was not significant as a predictor. When the outcome variable was log (adiponectin), the number of positive antibody level was significant. The β coefficient was negative, which revealed when the number of positive antibodies level increased, log (adiponectin) decreased.

Waist, height and waist/height ratio: All the three variables were significant predictors for the three outcomes. For log (leptin), waist, height and waist/height had positive β coefficients. For log (adiponectin) and log (adiponectin/leptin), waist, height and waist/height had negative β coefficients.

The remaining variables: The remaining variables were significant only for log (leptin) and log (adiponectin/leptin) and their associations were in opposite directions as indicated by sign of the β coefficients.

Table 17. Comparison of univariate regression results

Significant predictor	β coefficient sign for log(adiponectin)	β coefficient sign for log(leptin)	β coefficient sign for log(adiponectin/leptin)
Waist	−	+	−
Height	−	+	−
Waist/height	−	+	−
Number of positive antibodies (continuous)	−	Not significant	Not significant
Number of positive antibodies class2(0-1, ≥2)	−	Not significant	Not significant
Number of positive antibodies class3(0,1,2, ≥3)	−	Not significant	Not significant
BMI %	Not significant	+	−
BMI z score	Not significant	+	−
Central obesity	Not significant	+	−
ZnT8A	Not significant	−	Not significant
Insulin dose	Not significant	+	−
Glucose	Not significant	−	+
C-peptide	Not significant	+	−
C-peptide/ glucose	Not significant	+	−

3.5 MULTIVARIATE LINEAR REGRESSION

3.5.1 Independent variables selection procedures for multivariate regression models

To select the independent variables of the multivariate regression models, two selection procedures were performed in parallel and compared: manual, and a combination automatic + manual selection procedure. All multivariate regression models were fit using PROC GLM in SAS 9.3.

Manual selection procedure:

An initial model was run including all non-correlated variables and one variable from each of the five highly correlated groups (**Table 7**). Each of the variables from the five highly correlated groups was chosen randomly for inclusion in the initial model. This approach was designed to decrease collinearity resulting from inclusion of more than one variable from a given highly correlated group. For example, in the highly correlated group 1, BMI percentile was used as a first candidate and the other variables in group 1 were left out. All other non-correlated variables which did not belong to the highly correlated groups were added into the initial model simultaneously.

Individual predictors in the initial model were considered for exclusion if p-value >0.05, except for BMI percentile in the log(adiponectin) model as this specific relationship was of interest. The individual variable associated with the highest p-value was then excluded, and the model with remaining variables was refit in the next iteration, and the process was repeated as long as the removal of a specific variable did not reverse the significance of variables remaining in the model. For example, if one predictor was excluded with other previously significant variables changed to be nonsignificant, then the variable should be kept in the model.

If some of the remaining variables in the fitted model were chosen from highly correlated groups, other variables in the same groups were substituted into the model and the results were compared. The variable was kept in the model if it had lowest individual p-value compared to the other variables in the same highly correlated group. The final model was that which included any variables significant at the 0.05 level following this selection procedure, as well as the most significant highly correlated variable within a group. For example, if LDL was tested to be significant, cholesterol would also have been tested in a separate model with the other previously selected variables (based on the $p<0.05$ criterion). If the model including cholesterol had lower p-value compared to the model including LDL (cholesterol and LDL were in the same highly correlated variable group), then cholesterol would be selected instead of LDL in the final model.

Automatic + Manual selection procedure:

For this alternative variable selection approach, the independent variables of the initial model included all non-correlated variables and one variable from each of the five highly correlated groups, similar to the manual selection procedure. However, a preliminary round of variable selection was performed by SAS automatically using a stepwise selection criteria (slentry=0.25 slstay=0.15 in SAS code). Once the procedure was completed, the selection was modified manually. For example, if some of the selected predictors were chosen from correlated groups, other variables in the same groups were later substituted for them and the model was refit, similar to the process described above. And using the same manual selection procedure, the variable in the highly correlated group was kept in the model if it had lowest individual p-value. In addition, if the automatic procedure removed BMI percentile in the log(adiponectin) model, then it would be added back (as this specific relationship between BMI percentile and

log(adiponectin) was of interest). The resulting model after applying this selection protocol was deemed the final model.

3.5.2 Final models of log (adiponectin)

Table 18. Multivariate linear regression models of log (adiponectin)

Model	Predictors		β coefficient	DF	p-value(overall/individual)	N of predictors	N of observations	Root MSE	R^2	Adjusted R2	AIC	BIC
1					0.0003	6	139	0.496	0.21	0.154	-44.55	-182
	BMI %		0.0026	1	0.3466							
	Age		-0.0024	1	0.0159							
	Waist %	<25%	-*	2	0.0006							
		25%-75%	0.067									
		>75%	-0.466									
	Gender		0.1288	1	0.1579							
	Number of positive antibodies class2(0-1,≥2)		-0.28	1	0.0063							
	DQ2/DQ8	X	-	3	0.1920							
		DQ2	0.115									
		DQ2/DQ8	0.027									
		DQ8	0.234									
2					0.0005	6	139	0.498	0.20	0.145	-43.07	-181
	BMI %		0.0014	1	0.5990							
	Age		-0.0022	1	0.0278							
	Waist %	<25%	-	2	0.0007							
		25%-75%	0.077									
		>75%	-0.457									
	BMI %		0.1099	1	0.2277							
	Number of positive antibodies Class3(0,1,2, ≥3)		-0.1118	1	0.0134							
	DQ2/DQ8	X	-	3	0.2180							
		DQ2	0.098									

Table 18 Continued

		DQ2/DQ8	0.028									
		DQ8	0.227									
3					0.0017	6	139	0.5	0.21	0.14	-39.21	-175.55
	BMI %		0.00254	1	0.3832							
	Age		-0.0024	1	0.0184							
	Waist %	<25%	-	2	0.0010							
		25%-75%	0.063									
		>75%	-0.46									
	Gender		0.12271	1	0.1974							
	Number of positive antibodies	0	-	4	0.0918							
		1	0.0999									
		2	-0.187									
		3	-0.242									
		4	-0.19									
	DQ2/DQ8	X	-	3	0.2145							
		DQ2	0.1048									
		DQ2/DQ8	0.0252									
		DQ8	0.2287									
4					0.0007	6	139	0.497	0.196	0.14	-42.3	-179.7
	BMI %		0.00144	1	0.605							
	Age		-0.0022	1	0.032							
	Waist %	<25%	-	2	0.0007							
		25%-75%	0.081									
		>75%	-0.45									
	Gender		0.098	1	0.282							
	Number of positive antibodies (continuous)		-0.095	1	0.0206							
	DQ2/DQ8	X	-	3	0.2274							
		DQ2	0.092									
		DQ2/DQ8	0.0265									
		DQ8	0.224									
5					<.0001	3	144	0.497	0.17	0.14	-50.6	-194.24
	age		-0.0026	1	0.0063							
	Waist %	<25%	-	2	0.0008							
		25%-75%	0.142									

Table 18 Continued

		>75%	-0.331								
	Number of positive antibodies class2(0-1,≥2)		-0.2852	1	0.0040						

*Reference group

Five final models of log (adiponectin) were presented in **Table 18**.

Models 1 to 4 indicated the consistent result with the previous univariate regression result.

Model 1:

P-value: The results of univariate regression (**Table 8**) indicated number of positive antibodies class2 had the p-value of 0.0273.After adding BMI percentile, the p-value was 0.0585, close to the significant level of 0.05. And the results of multivariate regression model 1showed the p-value for number of positive antibodies class2 was 0.0063 when the other variables (including BMI percentile) were included.

Model 2:

P-value: The results of univariate regression indicated number of positive antibodies class3 had the p-value of 0.057, close to the significant level of 0.05. After BMI percentile was included in the model, the p-value was 0.1472. And the results of multivariate regression model 2 showed the p-value of number of positive antibodies class3 was 0.0134 when the other variables (including BMI percentile) were included.

Model 3:

P-value: When number of positive antibodies was treated as a categorical variable and when BMI percentile was adjusted, in both the multivariate and univariate regression models, number of positive antibodies was not significant for predicting log (adiponectin).

Model 4:

P-value: In the univariate regression, when number of positive antibodies was treated as a continuous variable, it was a significant predictor of log (adiponectin), with a p-value of 0.0421. The p-value increased to 0.0538 after BMI percentile was adjusted. And in the multivariate regression model 4, it was also significant with a p-value of 0.0206 when other variables (including BMI percentile) were included.

Models 1 to 4:

β coefficients : The β coefficients for the number of positive antibodies classes was negative, indicating that subjects with a greater number of positive antibodies had higher log (adiponectin) level.

Waist percentile and age were also significant for predicting log (adiponectin). There was a negative linear relationship between age and log (adiponectin). Individuals in the highest waist percentile group (>75%) had lower log (adiponectin) levels and those in the 25-75% group had higher log (adiponectin) levels compared to individuals in the lowest waist group(<25%).

Model 5:

Mean squared error root (MSE root), R^2 Adjusted R^2, Akaike information criterion (AIC) and Bayesian information criterion (BIC) of the five models were also presented in **Table 18**.

The five models had similar MSE root, R^2, adjusted R^2, AIC and BIC values. Model 5 was selected by the stepwise criteria in SAS and had the smallest AIC and BIC and did not include BMI percentile. The other four models helped to reveal a relationship of interest between number of positive antibodies and log (adiponectin) when the other variables (including BMI percentile) were included.

3.5.3 Final models of log (leptin)

Table 19. Multivariate linear regression models of log (leptin)

Model	Predictors		Beta coefficient	DF	p-value(overall/individual)	N of predictors	N of observations	Root MSE	R2	Adjusted R2	AIC	BIC
6					<.0001	10	122	0.61	0.49	0.44	15.48	-103.4
	BMI z-score		0.478	1	<.0001							
	C-peptide		0.1156	1	0.0037							
	Age		0.0024	1	0.1071							
	Gender		0.616	1	<0.0001							
	DQ2/DQ8	X	-	3	0.3439							
		DQ2	0.121									
		DQ2/DQ8	0.298									
		DQ8	0.231									
	Insulin dose		0.369	1	0.1008							
	HbA1c		0.199	1	0.0169							
	Glucose		-0.0011	1	0.189							
	ICA		-0.0057	1	0.1133							
	GAD		0.4639	1	0.02							
7					<.0001	6	106	0.63	0.48	0.45	15.96	-89.05
	BMI z-score		0.3294	1	0.0016							
	C-peptide		0.10987	1	0.0059							
	Central obesity		0.38531	1	0.0331							
	Gender		0.54905	1	<.0001							
	Glucose		-0.0012	1	0.1735							
	Insulin dose adjusted by HbA1c		0.16144	1	0.0002							

Two models were presented in **Table 19**.

The final two models of log (leptin) revealed that number of positive antibody was not significant for predicting log (leptin).

In model 6, BMI z-score, C-peptide, gender, HbA1c, and GAD were significant. All these variables had a positive linear relationship with log (leptin). In model 7, BMI z-score, C-

peptide, central obesity, gender, and insulin dose adjusted by HbA1c were significant for predicting log (leptin) and all these variables had a positive linear relationship with log (leptin). Model 6 and 7 had similar predictors. The two models had similar findings with the univariate regressions (**Table 17)**.

Comparing the AIC, BIC, R^2 and adjusted R^2 of the two models, model 6 and 7 had similar AIC, R^2 and adjusted R^2 except BIC. The smaller number of observations might be a reason for the larger BIC of model 7. However, the two models showed similar significant predictors for predicting log (leptin).

3.5.4 Final models of log (adiponectin/leptin)

Table 20. Multivariate linear regression models of log (adiponectin/leptin)

Model	Predictors		Beta coefficient	DF	p-value(overall/ individual)	Number of predictors	Number of observations	Root MSE	R2	Adjusted R2	AIC	BIC
8					<.0001	5	115	0.78	0.4	0.367	66.36	-47.74
	BMI z-score		-0.228	1	0.1067							
	Insulin dose adjusted by HbA1c		-0.137	1	0.0046							
	Gender		-0.407	1	0.0073							
	Age		-0.0074	1	<.0001							
	Waist %	<25%	-	2	0.0017							
		25%-75%	0.07									
		>75%	-0.953									
9	HbA1c		-0.3288	1	0.0048	6	111	0.83	0.33	0.2884	78.08	-31.99
	Glucose		0.00273	1	0.0147							
	C-peptide		-0.1216	1	0.0191							
	Waist/height		-4.3144	1	0.0256							
	Gender		-0.455	1	0.0073							
	BMI z-score		-0.2487	1	0.1093							

Two models were identified for log (adiponectin/leptin) and shown in **Table 20**. The final two models indicated that number of positive antibody was not a significant predictor of log (adiponectin/leptin).

In model 8, insulin dose adjusted by HbA1c, gender, age and waist percentile were significant and all these variables except waist percentile had a negative linear relationship with log (adiponectin/leptin). Individuals in the highest waist percentile group (>75%) had lower log (adiponectin/leptin) levels and those in the 25-75% group had higher log (adiponectin/leptin) levels compared to individuals in the lowest waist group (<25%). In model 9, HbA1c, glucose, C-peptide, waist/height and gender were significant for predicting log (adiponectin/leptin) and only glucose had a positive linear relationship with log (adiponectin/leptin).

Comparing the AIC, BIC, R^2 and adjusted R^2 of the two models, model 8 had higher R^2, higher adjusted R^2, smaller MSE root and smaller AIC and BIC. This indicated that model 8 fit better. The two models showed similar significant independent variables for predicting log (adiponectin/leptin).

3.5.5 Results of multivariate regression models

The final multivariate regression models gave consistent results with the univariate regression results (**Table 17)**. For log (adiponectin), waist percentile, number of positive antibodies and age were significant predictors. When number of positive antibodies or age increased, log (adiponectin) level decreased. Individuals in the highest waist percentile group (>75%) had lower log (adiponectin) levels and those in the 25-75% group had higher log (adiponectin) levels compared to individuals in the lowest waist group (<25%). For log (leptin), BMI z-score, C-peptide, gender, HbA1c, central obesity, gender, and insulin dose adjusted by

HbA1c were significant predictors. For log (adiponectin/leptin), the significant predictors were gender, age, waist percentile, HbA1c, glucose, C-peptide and waist/height ratio.

3.6 TEST OF REGRESSION MODEL ASSUMPTIONS

3.6.1 Existence

For each specific combination of the predictors, log (adiponectin), log (leptin) and log (adiponectin/leptin) had normal distributions, according to **Figure 1 and Table 2**.

3.6.2 Independence

Log (adiponectin), log (leptin) and log (adiponectin/leptin) were randomly distributed.

3.6.3 Linearity

The partial regression plot of residuals versus each predictor with adjustment for all other predictors indicated if any nonlinearity was present in the relationship between outcome variable and each predictor. For log (adiponectin), log (leptin) and log (adiponectin/leptin), those plots between continuous predictors and the outcomes did not indicate a clear departure from linearity.

3.6.3.1 Linearity testing for log (adiponectin)

The partial regression plots generally showed a linear relationship between the continuous predictors and the log (adiponectin). However there was variability as indicated by a noticeable amount of scatter around the regression line. (**Figure 2 to 6**).

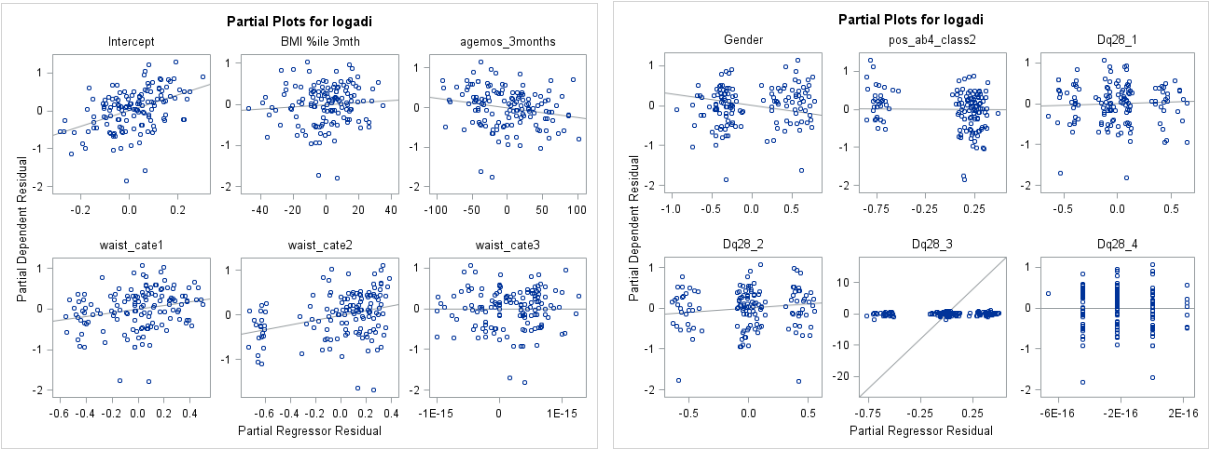


Figure 2. Partial regression residual plot for model 1

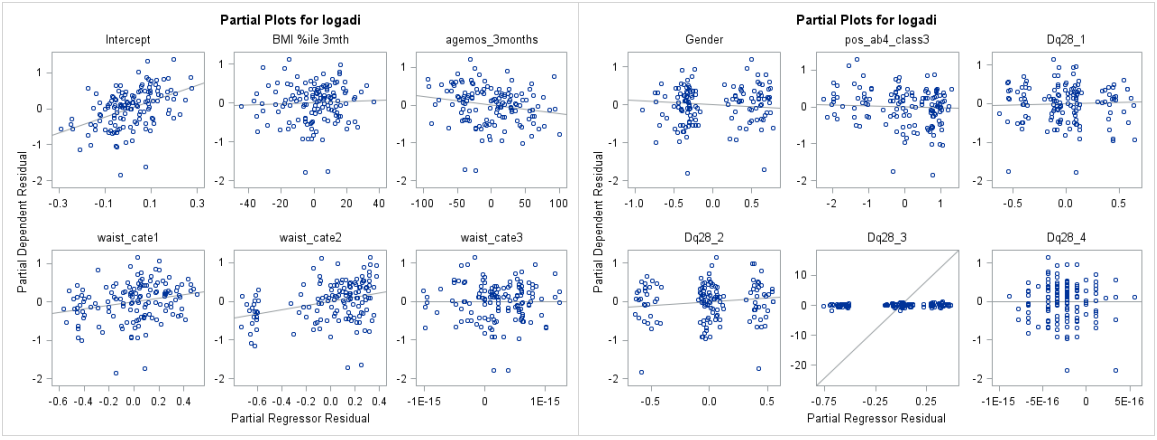


Figure 3. Partial regression residual plot for model 2

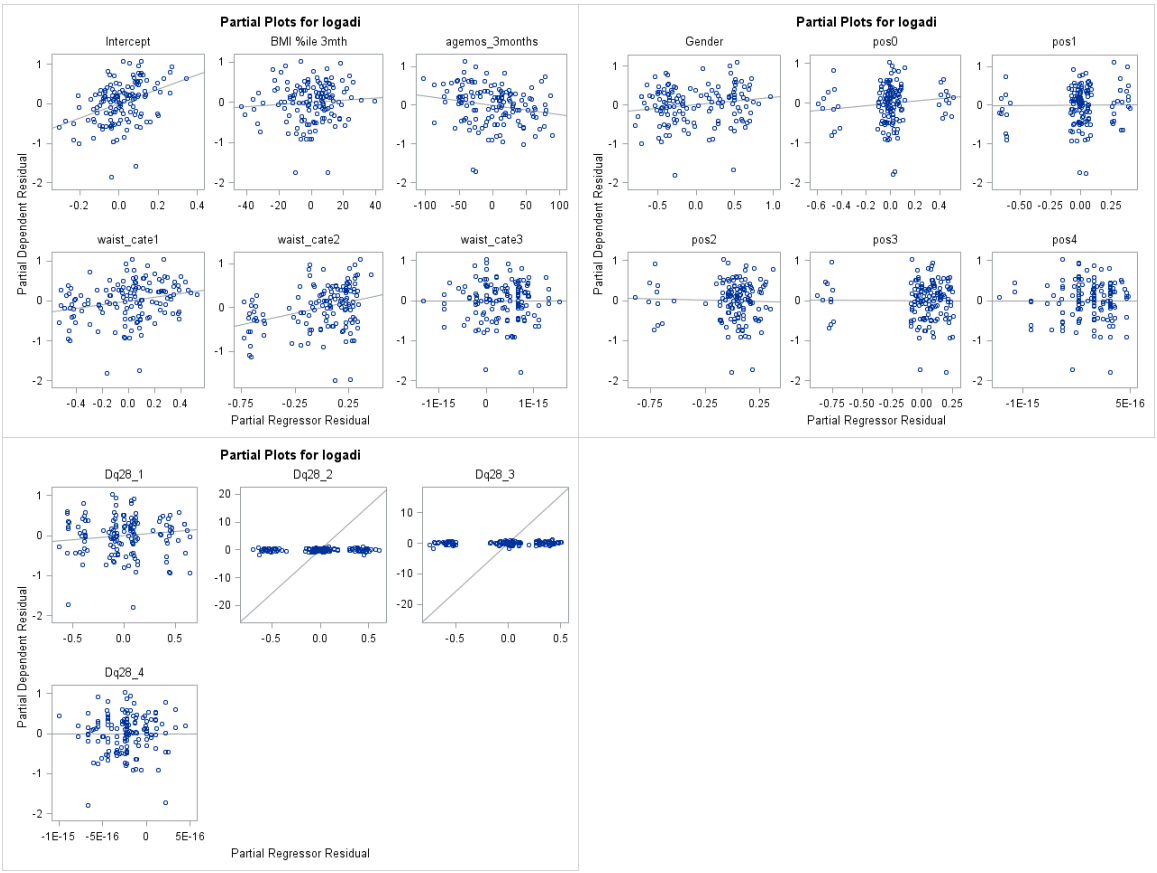


Figure 4. Partial regression residual plot for model 3

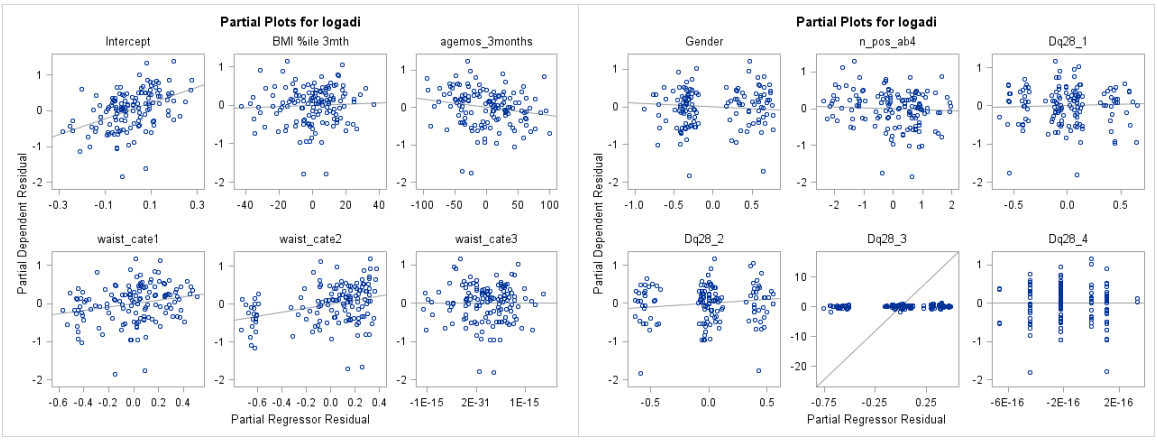


Figure 5. Partial regression residual plot for model 4

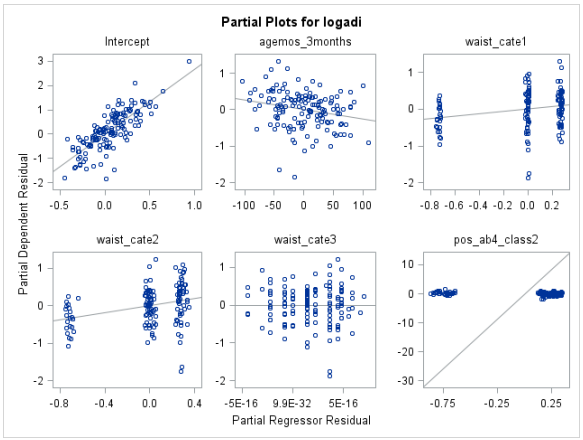


Figure 6. Partial regression residual plot for model 5

3.6.3.2 Linearity testing for log (leptin)

The partial regression plots generally showed a linear relationship between the continuous predictors and the log (leptin). However there was variability as indicated by a noticeable amount of scatter around the regression line. (**Figure 7 to 8**).

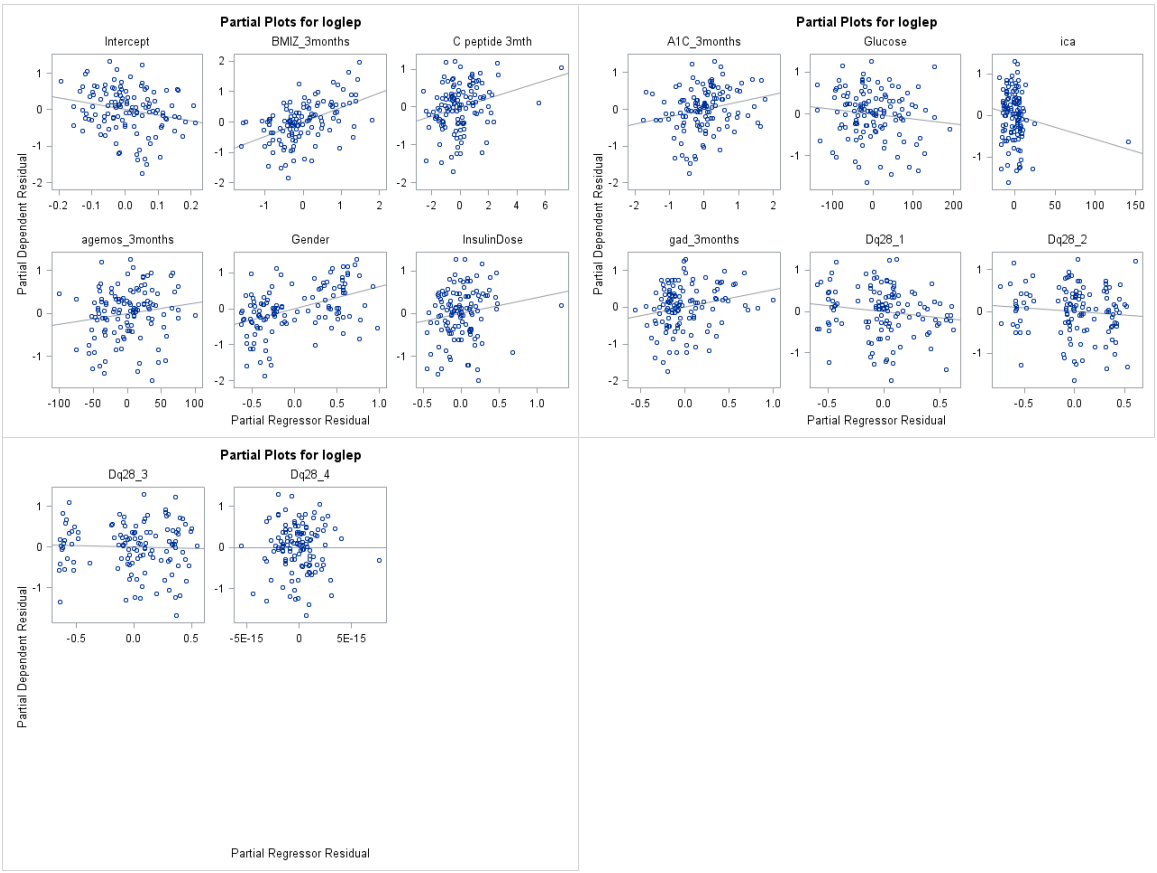


Figure 7. Partial regression residual plot for model 6

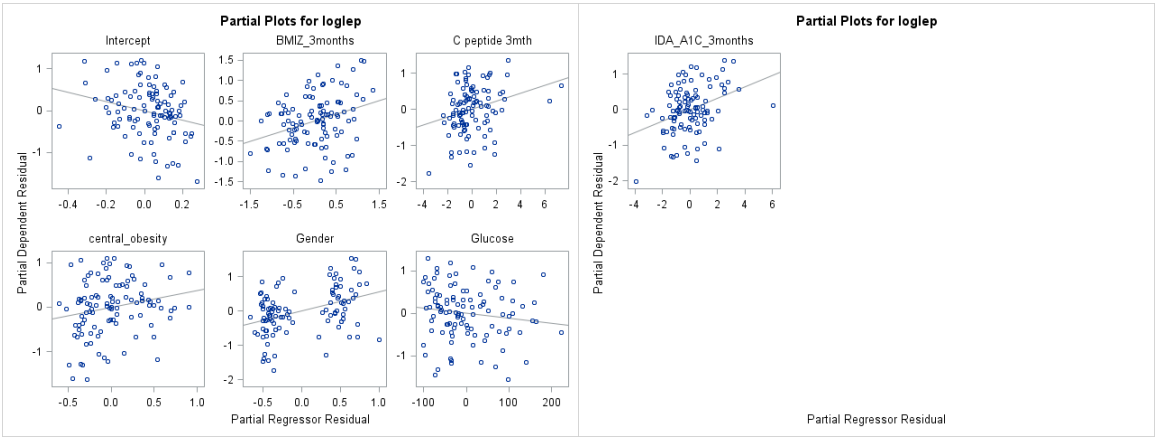


Figure 8. Partial regression residual plot for model 7

3.6.3.3 Linearity testing for log (adiponectin/leptin)

The partial regression plots generally showed a linear relationship between the continuous predictors and the log (adiponectin/leptin). However there was variability as indicated by a noticeable amount of scatter around the regression line. (**Figure 9 to 10**).

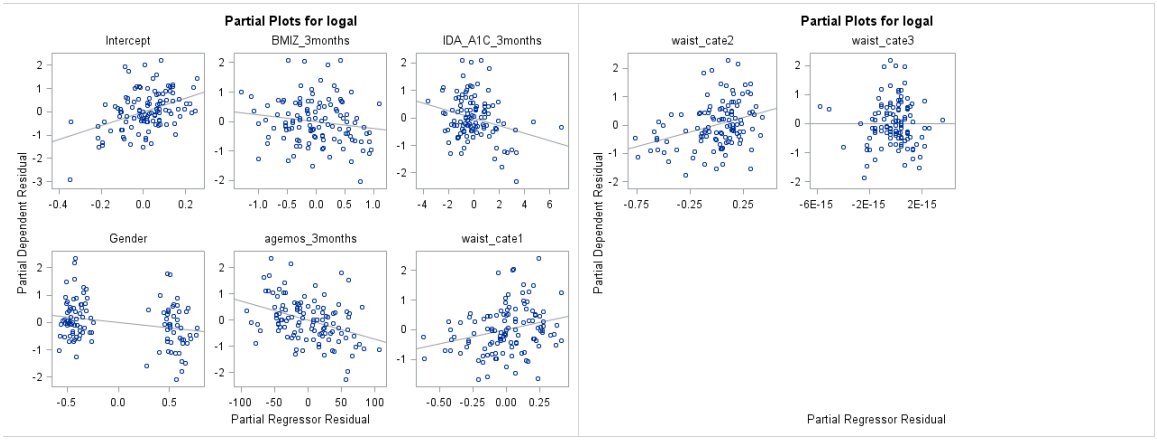


Figure 9. Partial regression residual plot for model 8

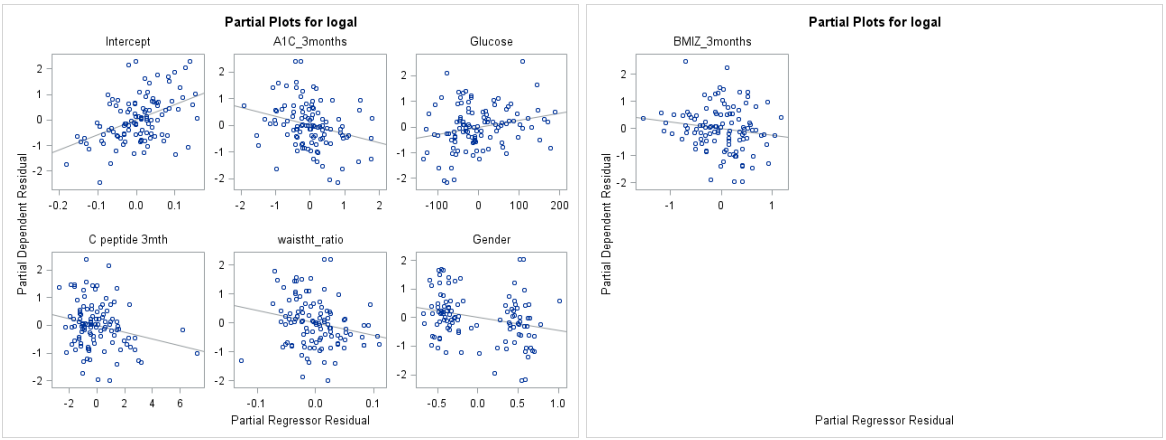


Figure 10. Partial regression residual plot for model 9

3.6.4 Homoscedasticity

The homoscedasticity could be tested by looking if the variance of outcome variables were the same for any fixed combination of predictors. The two dimensional plots could help to test the homoscedaticity problem.

There were two plots corresponding to each model. The first was plot between the residuals and the predicted outcomes. If the pattern was randomly distributed, the homoscedasticity assumption was fulfilled. The second plot was between the outcomes and the predicted outcomes. If a linear relationship was displayed, then the homoscedasticity assumption was fulfilled.

From the following plots (**Figure 12, Figure 14, Figure 16, Figure 18, Figure 20, Figure 22, Figure 24, Figure 26, Figure 28**) of all nine models, the residuals were all randomly distributed versus the predicted outcomes. The positive linear relationships between the outcomes and the predicted outcomes were clearly displayed from the scatter plots of outcomes versus predicted outcomes of model 1 to 9(**Figure 11, Figure 13, Figure 15, Figure 17, Figure 19, Figure 21, Figure 23, Figure 25, Figure 27)**.

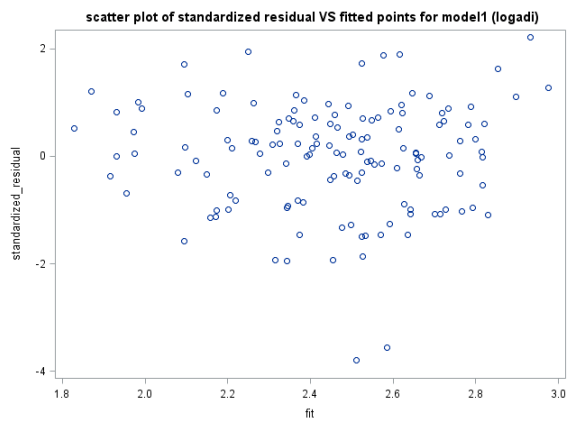


Figure 11. Model 1: Scatter plot of standardized residuals versus fitted points

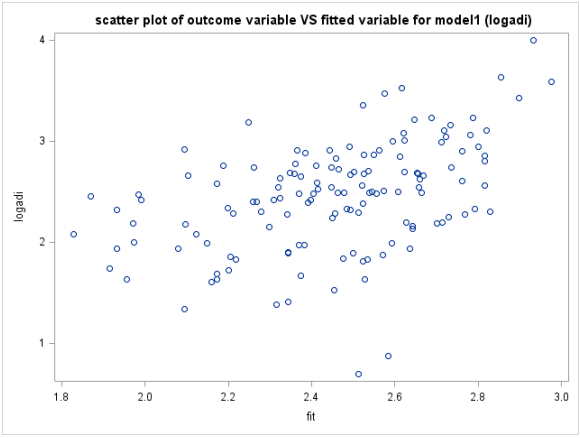


Figure 12. Model 1: Scatter plot of outcome variables versus fitted points

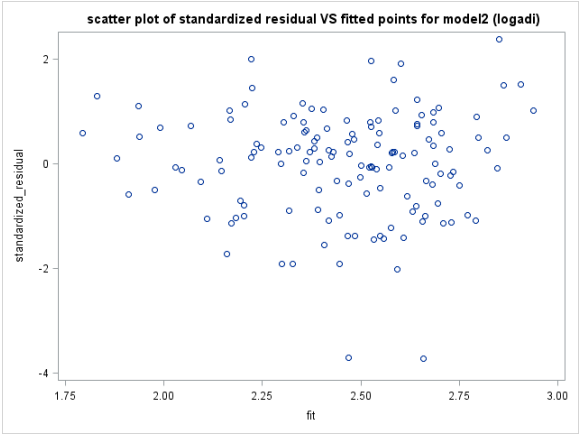


Figure 13. Model 2: Scatter plot of standardized residuals versus fitted points

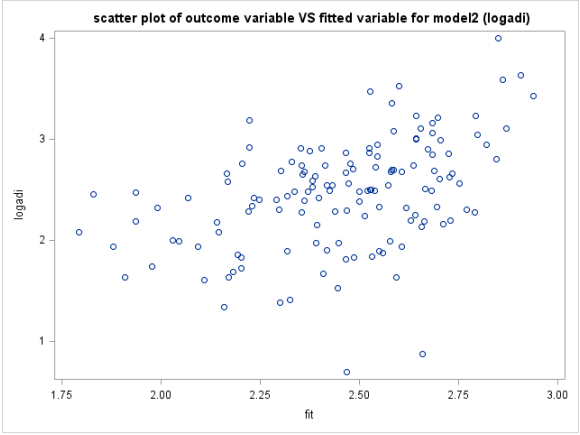


Figure 14. Model 2: Scatter plot of outcome variables versus fitted points

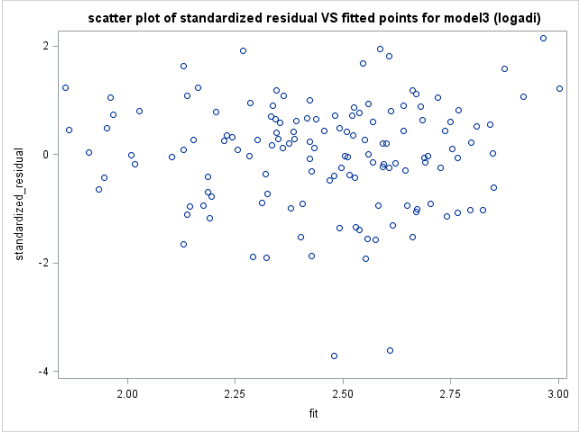


Figure 15. Model 3: Scatter plot of standardized residuals versus fitted points

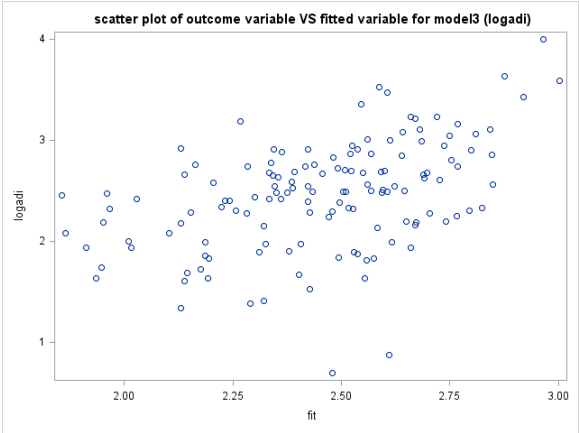


Figure 16. Model 3: Scatter plot of outcome variables versus fitted points

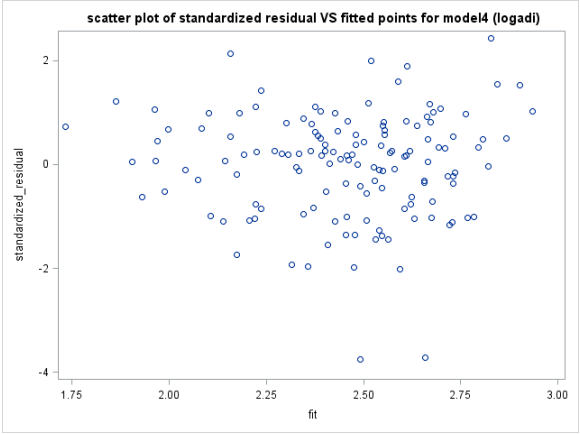


Figure 17. Model 4: Scatter plot of standardized residuals versus fitted points

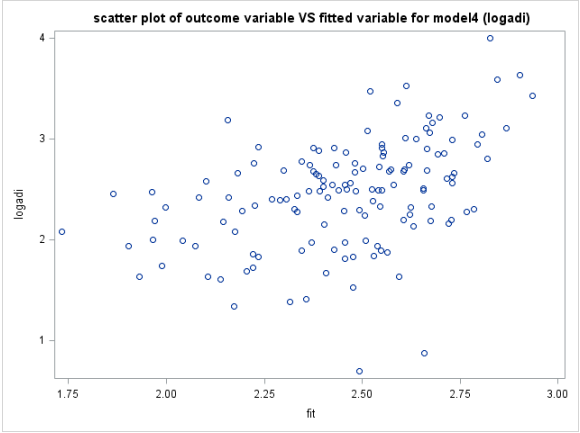


Figure 18. Model 4: The scatter plot of outcome variables versus fitted points

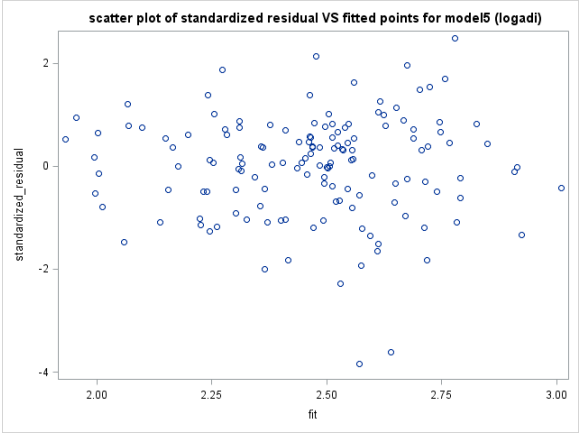


Figure 19. Model 5: Scatter plot of standardized residuals versus fitted points

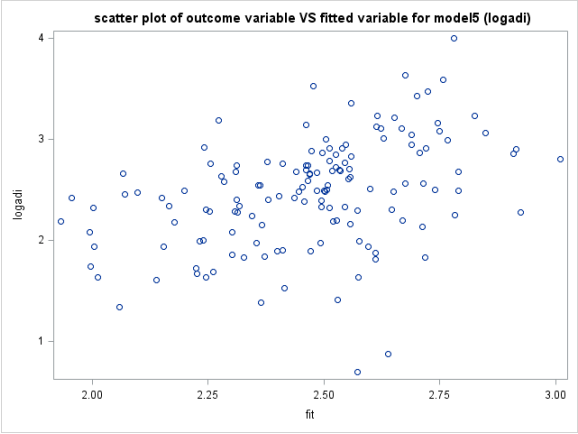


Figure 20. Model 5: Scatter plot of outcome variables versus fitted points

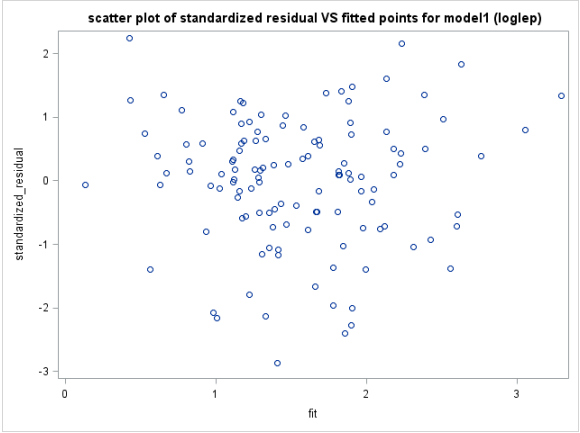


Figure 21. Model 6: Scatter plot of standardized residuals versus fitted points

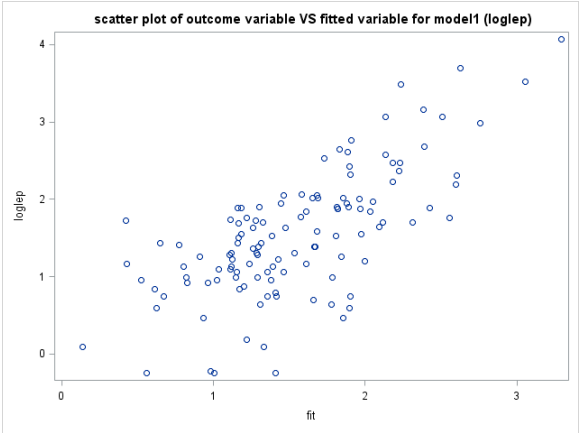


Figure 22. Model 6: Scatter plot of outcome variables versus fitted points

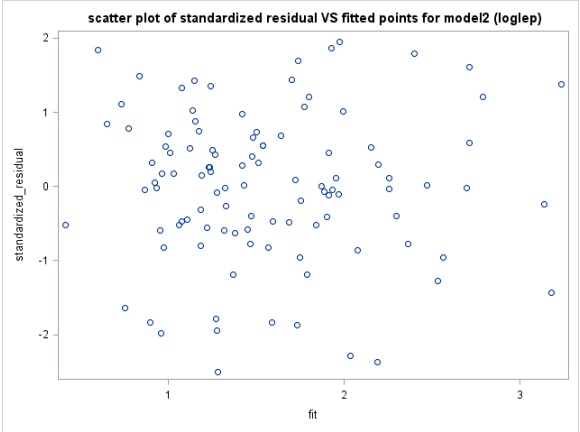


Figure 23. Model 7: Scatter plot of standardized residuals versus fitted points

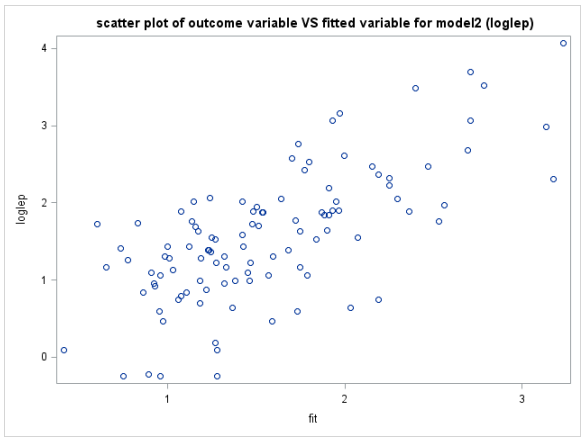


Figure 24.Model 7: Scatter plot of outcome variables versus fitted points

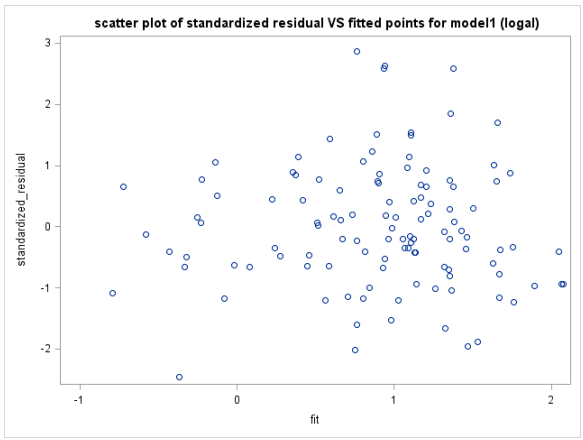


Figure 25.Model 8: Scatter plot of standardized residuals versus fitted points

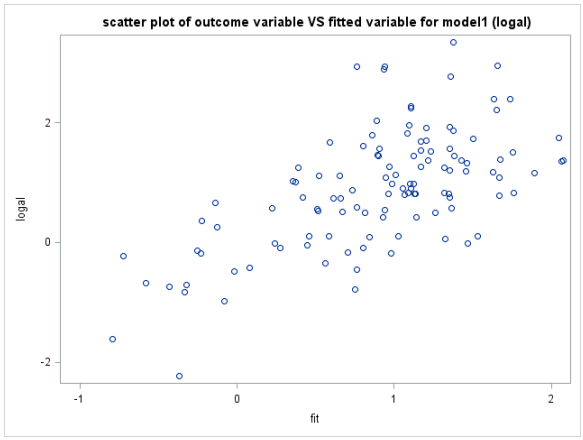


Figure 26. Model 8: Scatter plot of outcome variables versus fitted points

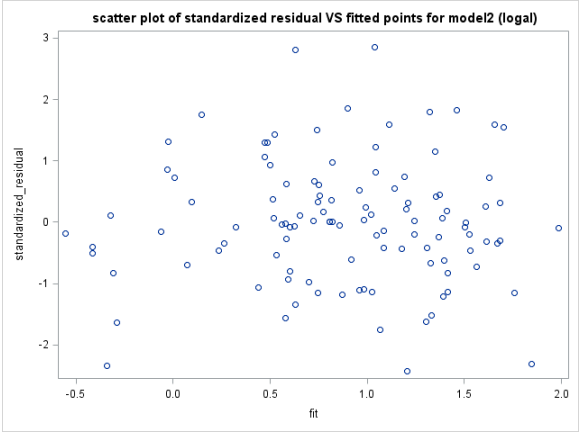


Figure 27. Model 9: Scatter plot of standardized residuals versus fitted points

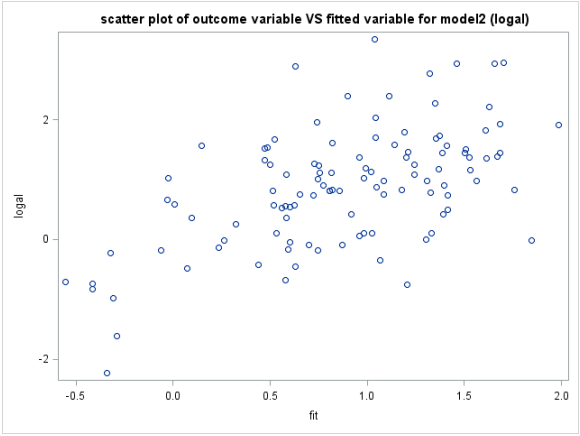


Figure 28. Model 9: Scatter plot of outcome variables versus fitted points

3.6.5 Normality

For any fixed combination of predictors, the outcome variables had normal distributions. The normality could be tested by plotting the residuals. One dimensional histogram and the QQ plot could reveal the normality of the residuals and helped to test if the outcome variables had normal distributions.

The histogram and QQ plots (**Figure 29-37**) of the residuals indicated that the residuals were normally distributed, comparing with the standard normal distribution. The p-values of

Goodness-of-Fit Tests for normal distribution by Kolmogorov-Smirnov tests were all greater than 0.25, the normality assumption of all nine models were satisfied.

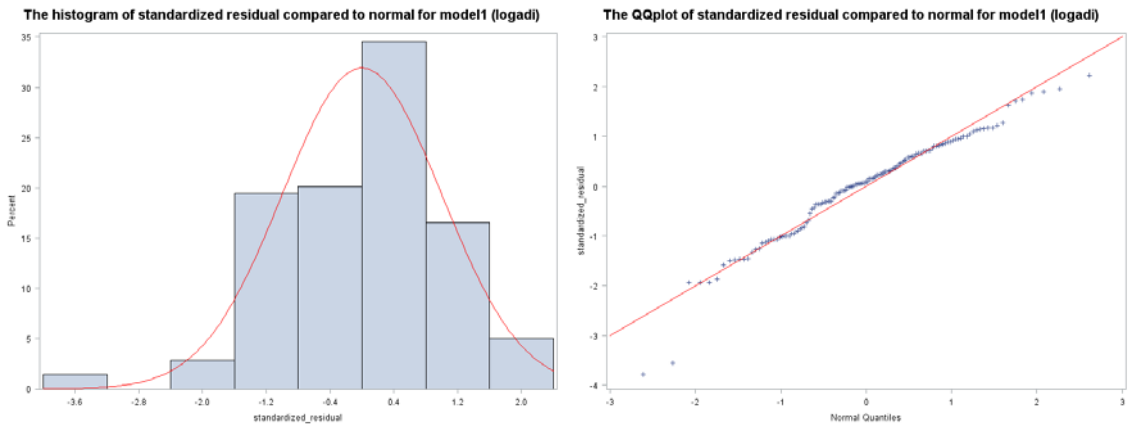


Figure 29. Histogram and QQ plot of standardized residual versus normal distributions for model 1

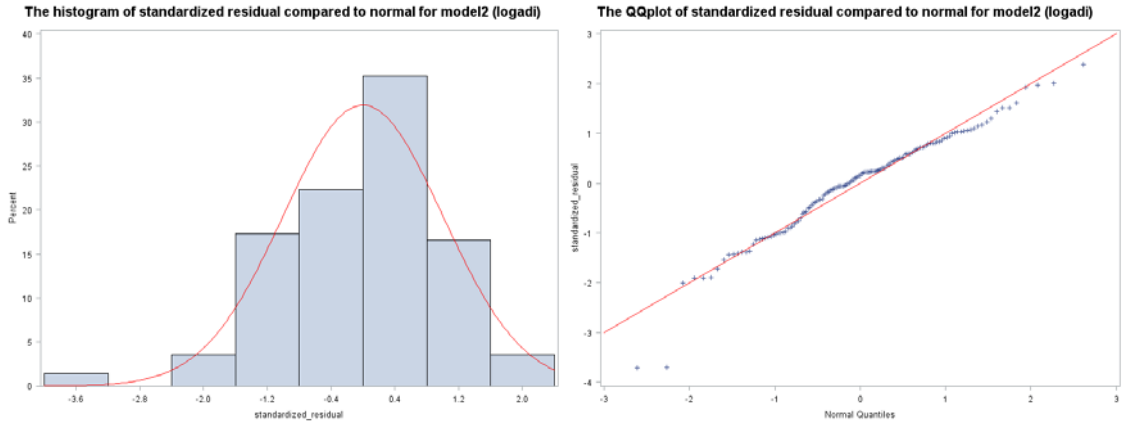


Figure 30. Histogram and QQ plot of standardized residual versus normal distributions for model 2

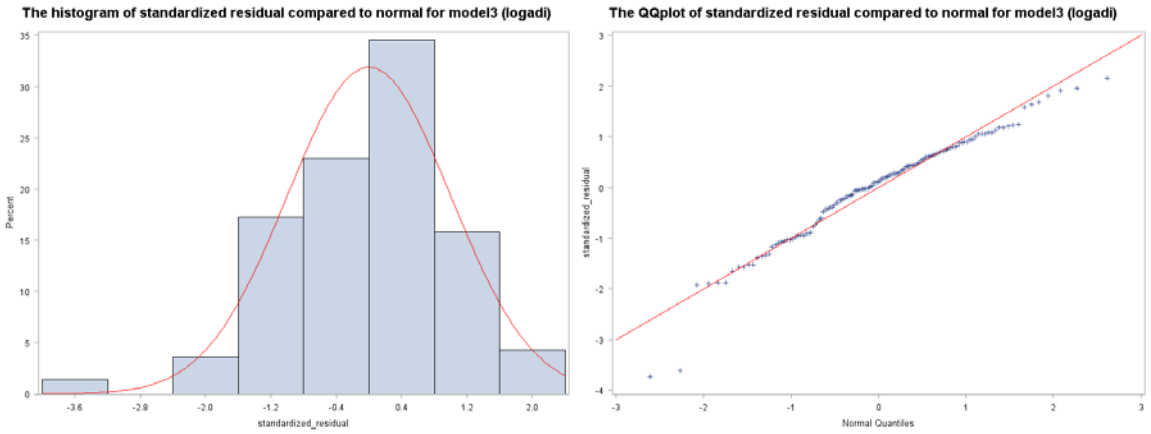


Figure 31. Histogram and QQ plot of standardized residual versus normal distributions for model 3

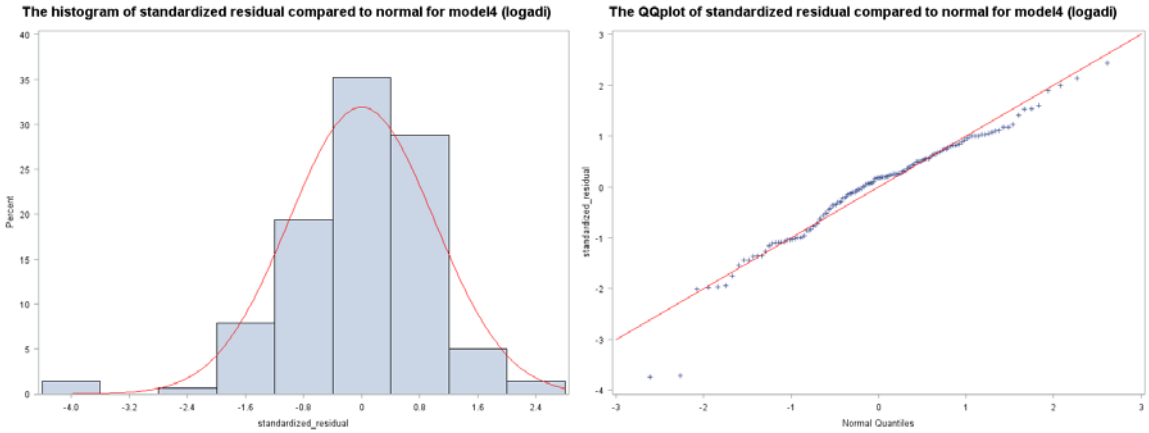


Figure 32. Histogram and QQ plot of standardized residual versus normal distributions for model 4

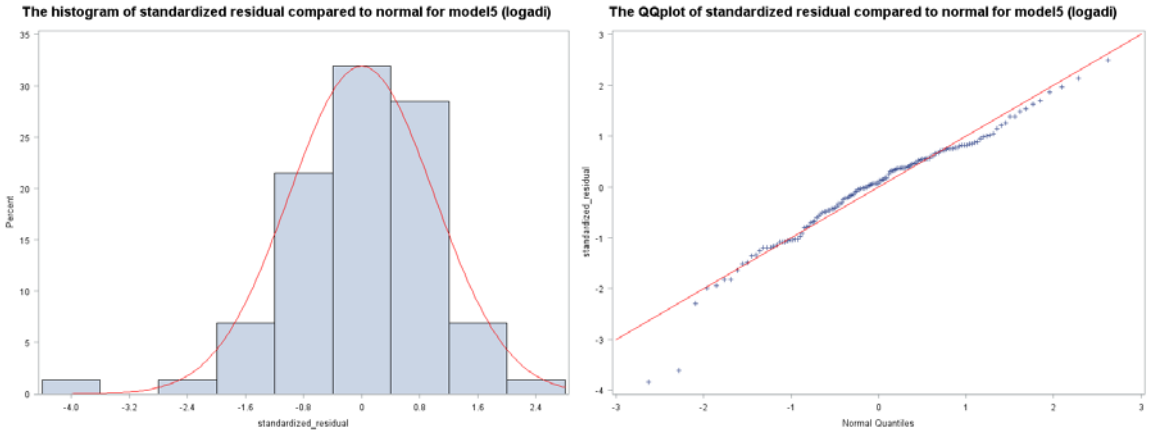


Figure 33. Histogram and QQ plot of standardized residual versus normal distributions for model 5

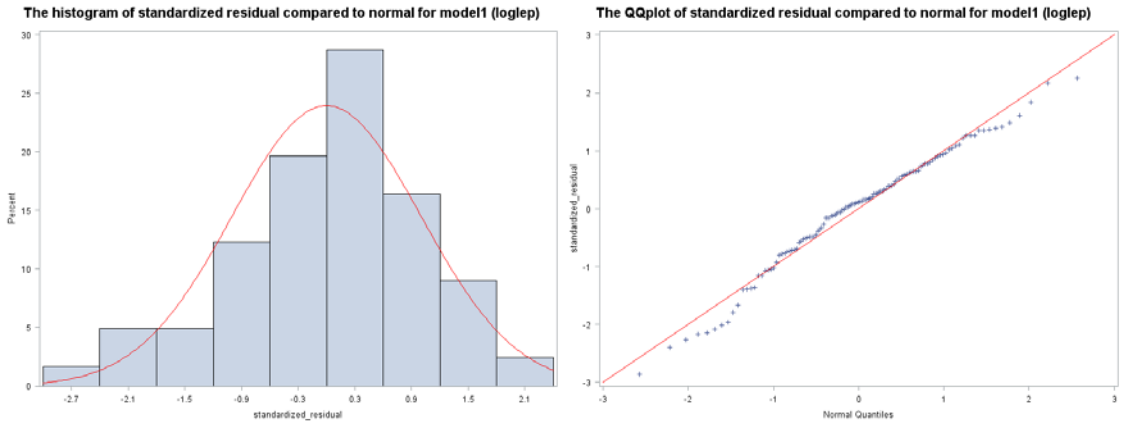


Figure 34. The histogram and QQ plot of standardized residual versus normal distributions based on model 6

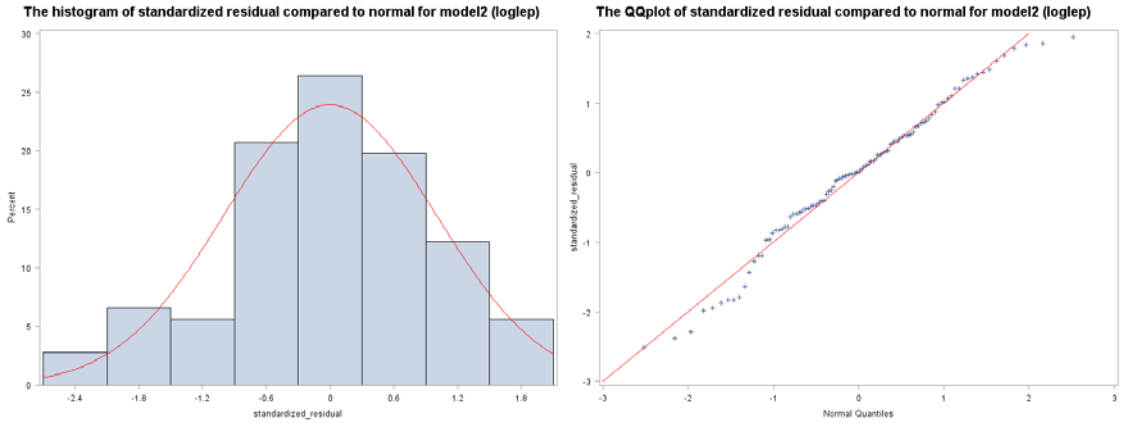


Figure 35. Histogram and QQ plot of standardized residual versus normal distributions for model 7

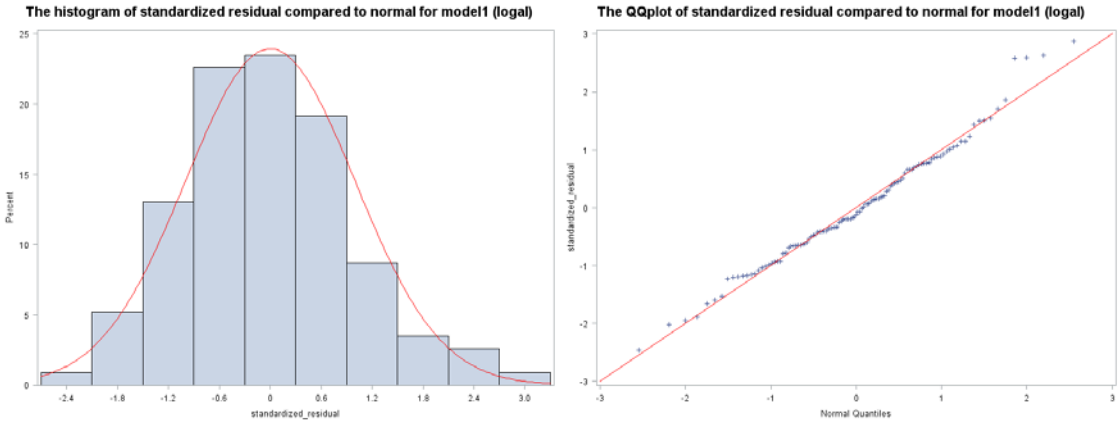


Figure 36. Histogram and QQ plot of standardized residual versus normal distributions for model 8

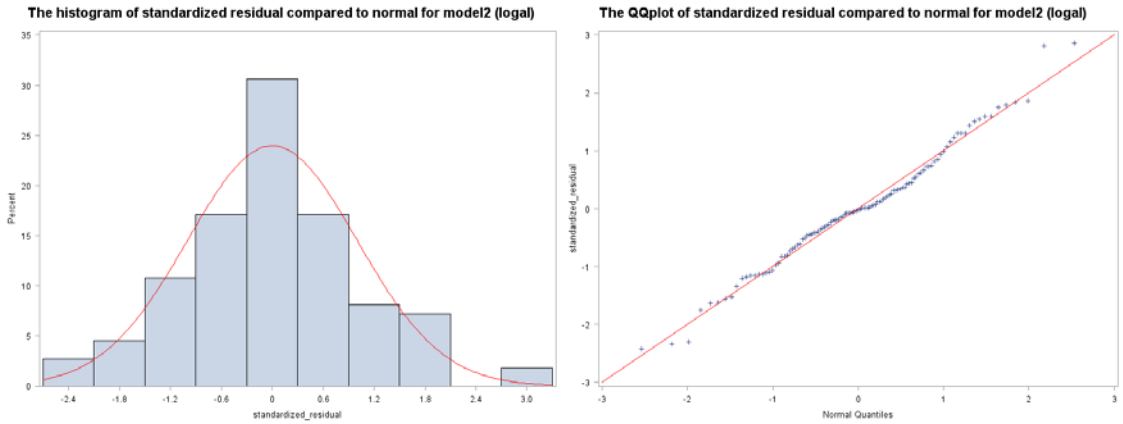
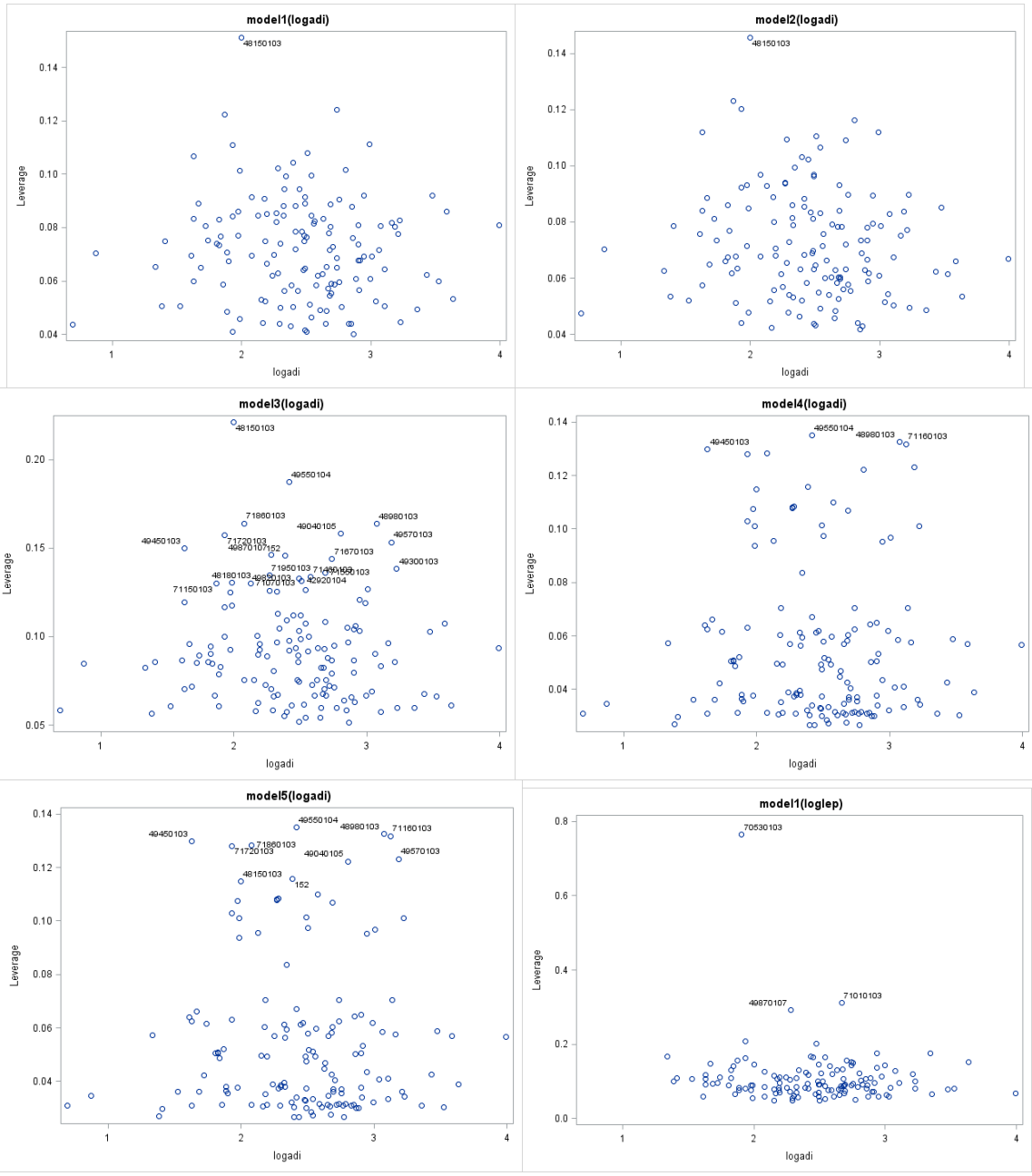


Figure 37. Histogram and QQ plot of standardized residual versus normal distributions for model 9

3.6.6 Leverage and influence points diagnostics

3.6.6.1 Leverage points

The leverage points were outliers in the predictor space, it could be clarified by using the criteria $h_i > 2(k+1)/n$, where k= number of predictors in the model, n = observation numbers. The following plots (**Figure 38**) showed the leverage points labeled with patient numbers for all nine models. For model 3 and 5, there were more than 10 leverage points. For the other models, the leverage points were no more than 5, these observations should be checked to detect if there were some unusual records or tests.


model1(logadi)
48150103
Leverage
logadi
model2(logadi)
48150103
Leverage
logadi
model3(logadi)
48150103
49550104
71860103
48980103
49040105
49570103
49450103
71720103
49870107152
71670103
49300103
71950103
48180103
71150103
42920104
Leverage
logadi
model4(logadi)
49550104
48980103
71160103
49450103
Leverage
logadi
model5(logadi)
49550104
48980103
71160103
49450103
71860103
71720103
49040105
49570103
48150103
152
Leverage
logadi
model1(loglep)
70530103
71010103
49870107
Leverage
logadi

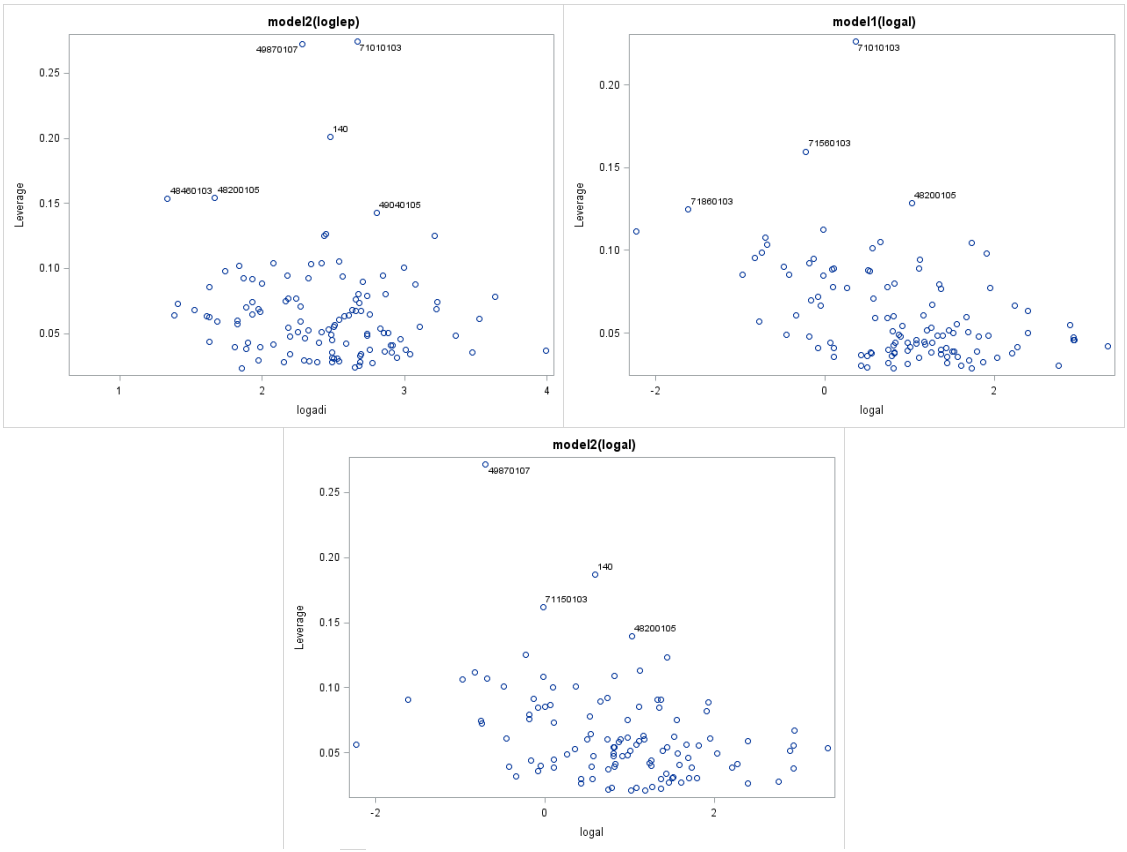
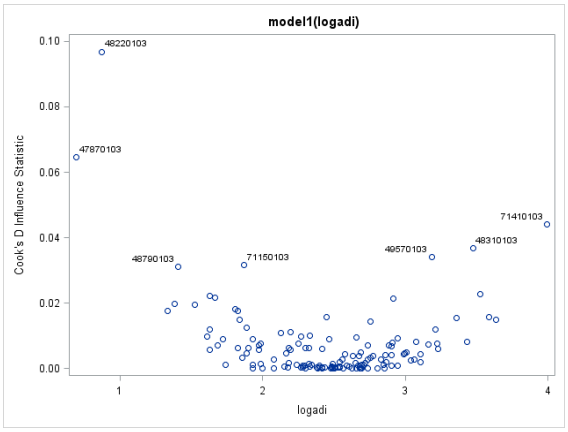


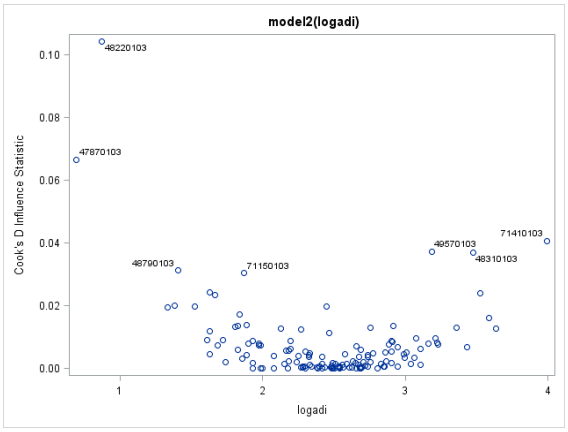
Figure 38. Leverage versus outcome variables for models 1to 9

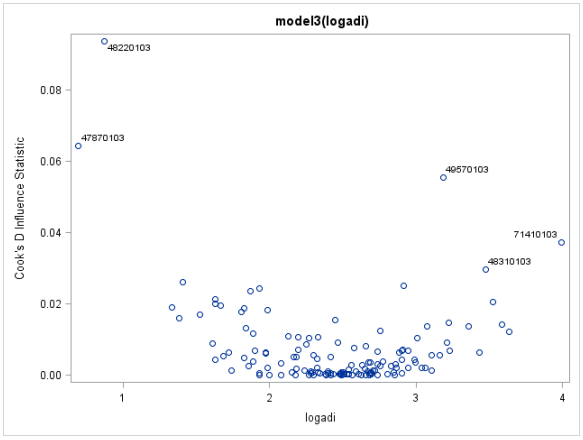
3.6.6.2 Influential points

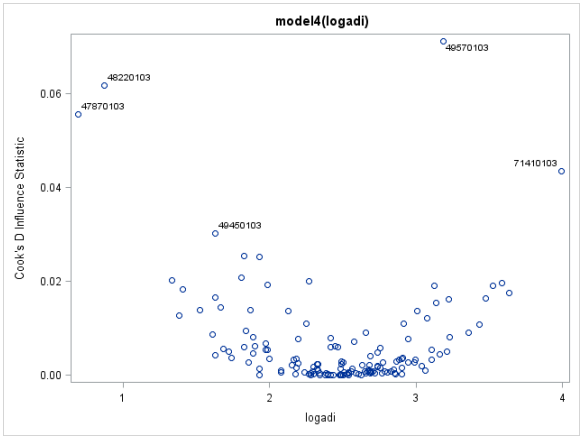
Cook's distance was a summary measure of actual influence, it helped to classify the problematic points. We used the criteria (Cook'D >4/n) to detect the problematic points.

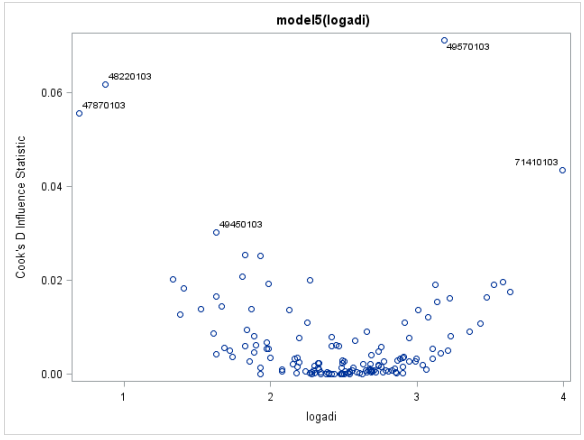
The following plots in **Figure 39** revealed the influences labeled with patient numbers for all nine models. For each model, there were more than 5 influential points, these observations should be checked to detect if there were some unusual records or tests.

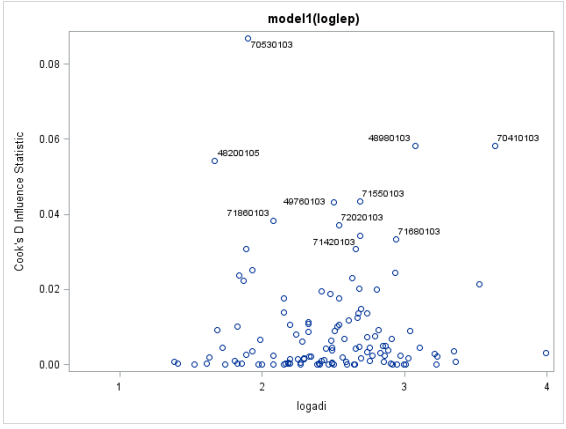

model1(logadi)
Cook's D Influence Statistic
logadi
48220103
47870103
71410103
48310103
49570103
48790103
71150103


model2(logadi)
Cook's D Influence Statistic
logadi
48220103
47870103
71410103
49570103
48310103
48790103
71150103


model3(logadi)
Cook's D Influence Statistic
logadi
48220103
47870103
49570103
71410103
48310103


model4(logadi)
Cook's D Influence Statistic
logadi
49570103
48220103
47870103
71410103
49450103


model5(logadi)
Cook's D Influence Statistic
logadi
49570103
48220103
47870103
71410103
49450103


model1(loglep)
Cook's D Influence Statistic
logadi
70530103
48980103
70410103
48200105
71550103
49760103
71860103
72020103
71680103
71420103

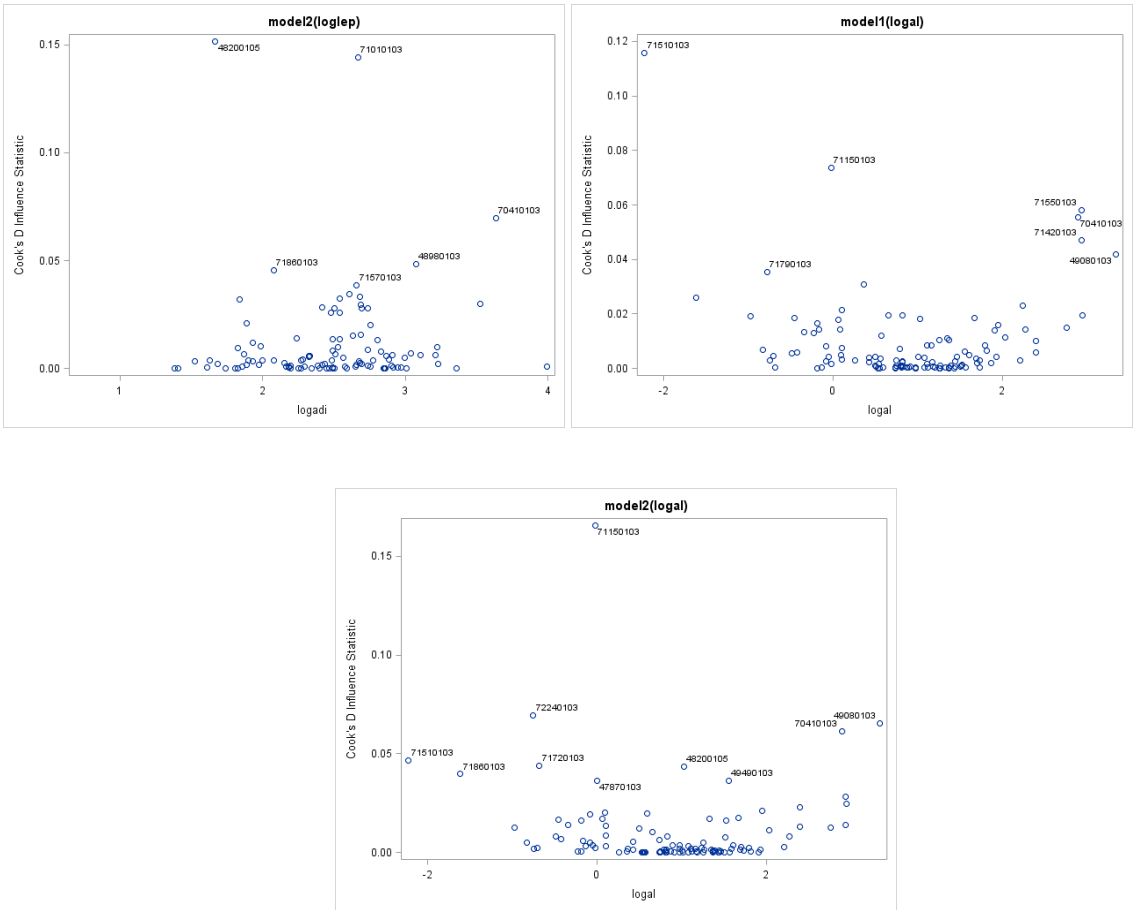


Figure 39. Cook's Distance versus outcome variables for models 1 to 9

3.6.7 Collinearity

The variance inflation factor (VIF) quantified the severity of multicollinearity in the regression analysis. It provided an index that measured how much the variance of an estimated regression coefficient was increased because of collinearity.

A rule of thumb was that if VIF > 10 then multicollinearity was high. From the following **Table 21 to 23**, all those VIFs for the predictors in the final models were no more than 2.3, which revealed that no collinearity problems existed.

Table 21.VIFs for models 1 to 5

Vifs for models of Log(adiponectin)						
Model1	**BMI %**	**Age**	**Waist%**	**Gender**	**Number of positive antibodies class2(0-1,≥2)**	**DQ2/DQ8**
VIF	1.74	1.02	1.73	1.08	1.02	1.05
Model2	**BMI %**	**Age**	**Waist%**	**Gender**	**Number of positive antibodies class3 (0,1,2,≥3)**	**DQ2/DQ8**
VIF	1.78	1.01	1.74	1.07	1.02	1.05
Model3/4	**BMI %**	**Age**	**Waist%**	**Gender**	**Number of positive antibodies(continuous)**	**DQ2/DQ8**
VIF	1.78	1.01	1.74	1.07	1.03	1.05
Model5	**Age**	**Waist%**	**Number of positive antibodies class2(0-1,≥2)**			
VIF	1.01	1	1.01			

Table 22.VIFs for models 6 to 7

VIFs for models of Log(Leptin)										
Model1	**BMI z-score**	**C-peptide**	**Age**	**Gender**	**Insulin Dose**	**HbA1c**	**Glucose**	**ICA**	**GAD**	**DQ2/DQ8**
VIF	1.21	1.34	1.34	1.16	1.35	1.38	1.31	1.05	1.17	1.09
Model2	**BMI z-score**	**C-peptide**	**Central obesity**	**Gender**	**Glucose**	**Insulin dose adjusted by HbA1c**				
VIF	1.65	1.15	1.66	1.09	1.07	1.21				

Table 23.VIFs for model 8 to 9

Vifs for models of Log(Adiponectin-leptin ratio)						
Model1	**BMI z-score**	**Insulin dose adjusted by HbA1c**	**Gender**	**Age**	**Waist%**	
VIF	2.17	1.03	1.03	1.01	2.18	
Model2	**HbA1c**	**Glucose**	**C-peptide**	**Waist/height**	**Gender**	**BMI z- score**
VIF	1.25	1.14	1.15	2.18	1.09 7	2.22

4.0 DISCUSSION AND CONCLUSION

This study found that adiponectin had different significant predictors compared to leptin and adiponectin/leptin ratio. However, there were some factors in common.

The number of positive antibodies was statistically significant only for predicting adiponectin. It was significant, irrespective of adjustment by BMI percentile ($p<0.05$). The β coefficient revealed those subjects with greater numbers of positive antibodies had lower adiponectin levels. Additionally, waist percentile and age were significant predictors of adiponectin. Age had a negative (inverse) linear relationship with adiponectin. Individuals in the highest waist percentile group (>75%) had lower adiponectin levels and those in the 25-75% group had higher adiponectin levels compared to individuals in the lowest waist group (<25%).

For leptin, BMI z-score, central obesity, C-peptide, gender, HbA1c, GAD, and insulin dose adjusted by HbA1c were significant. These predictors all had positive linear relationships with leptin.

For adiponectin/leptin ratio, waist percentile, waist/height ratio, insulin dose adjusted by HbA1c, HbA1c, gender, age, glucose and C-peptide were significant predictors. All of these predictors had negative (inverse) linear relationships with adiponectin/leptin ratio. Individuals in the highest waist percentile group (>75%) had lower adiponectin levels and those in the 25-75% group had higher adiponectin levels compared to individuals in the lowest waist group (<25%).

These results were different from the conclusion in our previously published study: those subjects with the greatest number of positive autoantibodies had higher adiponectin, lower leptin, and higher adiponectin/leptin ratios than those with lower numbers of positive antibodies. A possible explanation may be that the subjects between the two studies were different: first, the previous study was conducted from 1990 to 2000 and the current study enrolled a more recent cohort from 2004 to 2008. The subjects of our current study were heavier with a median BMI percentile of 78.4 [IRQ: 16.6 - 99.7] in contrast to subjects from the previous study with a median BMI percentile of 62.1 [IRQ: 44.2-78.1]. Second, the design of the former study matched individuals by race, age, gender, and year of diagnosis. In the current analysis, over 94% were Caucasian and race was not considered as a predictor. The contrast in results between the two studies was reasonable considering the differences in the two study cohorts.

To confirm the findings of this study, further exploration of the data is warranted including examining interactions among various factors. In this data set there were a limited number of subjects with complete information for IAA and LDL. As a result, the regression models could not adequately evaluate the relationship with our outcome measures. Further data collection and analysis including these two predictors should be considered.

Public health Significance:

Adiponectin, leptin and the ratio of adiponectin to leptin each demonstrated their own unique predictors within this population of T1 diabetic children. As cited earlier, adiponectin is a protein produced by adipocyte cells and possesses potent insulin sensitizing and anti-inflammatory properties [16]. Adiponectin protects against development of T2D and atherosclerosis in animal models [17]. Also higher circulating levels of adiponectin are associated with a lower risk of T2D and coronary heart disease in prospective studies [18].

Therefore, it is reasonable to investigate the correlates and predictors of adiponectin in this group of children with newly diagnosed T1D. The number of positive antibodies was significantly related to the prediction of adiponectin with or without adjustment by BMI percentile. The regression coefficient indicated those subjects with greater number of positive antibodies had lower adiponectin levels. Moreover, waist percentile was also an important predictor and had an inverse linear relationship with adiponectin. The identification of potential modifiable risk factors in children with this condition would be high priority.

APPENDIX: SAS PROGRAM FOR REGRESSIONS

```
* for adiponectin;
* stepwise to find the multi variables;
proc glmselect data=a.natalie0529_01;
class waist_cate Dq2_dq8_b central_obesity n_pos_ab4 ;
model logadi= bmipct_3months bmiz_3months cpeptide_beckerlab_3months
central_obesity waistht_ratio agemos_3months gender
n_pos_ab4 Dq2_dq8_b  insulindose a1c_3months
cholesterol_heinz_lab_3months ldl hdl_heinz_lab_3months
Waist_cate IDA_A1C_3months IDA_A1C_cate glucose
triglyceride_heinz_lab_3months p_dbp_score p_sbp_score
ica gad_3months ia2_3months /selection=stepwise slentry=0.25 slstay=0.15;
run;
*model1;
proc glm data=a.natalie0529_01;
class waist_cate dq2_dq8_b;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
pos_ab4_class2 dq2_dq8_b /solution ss3;
run;
proc glmselect data=a.natalie0529_01;
class waist_cate dq2_dq8_b/ ref=first;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
pos_ab4_class2 dq2_dq8_b / selection=none stop=none stats=all;
run;
*plots for model1;
proc glm data=a.natalie0529_01;
class waist_cate dq2_dq8_b;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
pos_ab4_class2 dq2_dq8_b /solution ss3;
output out=a.adi1
predicted=fit residual=resid
rstudent=studentized_resid;
run;
data a.adi1_1;
set a.adi1;
standardized_residual=resid/0.48;
run;
ods graphics on;
ods graphics off;
proc univariate data=a.adi1_1 ;
var standardized_residual;
title " The histogram of standardized residual compared to normal for model1
(logadi) ";
histogram standardized_residual / normal(mu=0 sigma=1 color=red) ;run;
proc univariate data=a.adi1_1 ;
```

```
var standardized_residual;
title " The QQplot of standardized residual compared to normal for model1
(logadi) ";
qqplot standardized_residual/ normal(mu=0 sigma=1  color=red) ;run;
proc sgplot data=a.adi1_1;
title " scatter plot of standardized residual VS fitted points for model1
(logadi)";
scatter x= fit y=standardized_residual;
run;
proc sgplot data=a.adi1_1;
title " scatter plot of outcome variable VS fitted variable for model1
(logadi)";
scatter x= fit y=logadi;
run;
*model2;
proc glmselect data=a.natalie0529_01;
class waist_cate dq2_dq8_b/ref=first;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
pos_ab4_class3 dq2_dq8_b / selection=none stop=none stats=all;run;
proc glm data=a.natalie0529_01;
class waist_cate dq2_dq8_b;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
pos_ab4_class3 dq2_dq8_b /solution ss3;
output out=a.adi2
predicted=fit residual=resid
rstudent=studentized_resid;run;
data a.adi2_1;
set a.adi2;
standardized_residual=resid/0.48;
run;
ods graphics on;
proc univariate data=a.adi2_1 ;
var standardized_residual;
title " The histogram of standardized residual compared to normal for model2
(logadi) ";
histogram standardized_residual / normal(mu=0 sigma=1 color=red) ;run;
proc univariate data=a.adi2_1 ;
var standardized_residual;
title " The QQplot of standardized residual compared to normal for model2
(logadi) ";
qqplot standardized_residual/ normal(mu=0 sigma=1  color=red);run;
proc sgplot data=a.adi2_1;
title " scatter plot of standardized residual VS fitted points for model2
(logadi)";
scatter x= fit y=standardized_residual;run;
proc sgplot data=a.adi2_1;
title " scatter plot of outcome variable VS fitted variable for model2
(logadi)";
scatter x= fit y=logadi;run;

proc glm data=a.natalie0529_01;
class waist_cate dq2_dq8_b;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
pos_ab4_class3 dq2_dq8_b /solution ss3; run;
proc glmselect data=a.natalie0529_01;
class waist_cate dq2_dq8_b;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
```

```
pos_ab4_class3 dq2_dq8_b / selection=none stop=none stats=all;run;
* model 3;
proc glm data=a.natalie0529_01;
class waist_cate dq2_dq8_b n_pos_ab4;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
n_pos_ab4 dq2_dq8_b /solution ss3;
output out=a.adi3
predicted=fit residual=resid
rstudent=studentized_resid;run;
proc univariate data=a.adi3 ;
var resid;
histogram resid / normal ;run;
data a.adi3_1;
set a.adi3;
standardized_residual=resid/0.48;
run;
proc univariate data=a.adi3_1 ;
var standardized_residual;
title " The histogram of standardized residual compared to normal for model3
(logadi) ";
histogram standardized_residual / normal(mu=0 sigma=1 color=red) ;run;
proc univariate data=a.adi3_1 ;
var standardized_residual;
title " The QQplot of standardized residual compared to normal for model3
(logadi) ";
qqplot standardized_residual/ normal(mu=0 sigma=1  color=red) ;run;
proc sgplot data=a.adi3_1;
title " scatter plot of standardized residual VS fitted points for model3
(logadi)";
scatter x= fit y=standardized_residual;run;
proc sgplot data=a.adi3_1;
title " scatter plot of outcome variable VS fitted variable for model3
(logadi)";
scatter x= fit y=logadi;run;
proc glmselect data=a.natalie0529_01;
class waist_cate dq2_dq8_b n_pos_ab4/ref=first;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
n_pos_ab4 dq2_dq8_b / selection=none stop=none stats=all;run;
* model 4;
proc glmselect data=a.natalie0529_01;
class waist_cate dq2_dq8_b /ref=first;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
n_pos_ab4 dq2_dq8_b / selection=none stop=none stats=all;run;
proc glm  data=a.natalie0529_01;
 class waist_cate dq2_dq8_b  ;
model logadi=  bmipct_3months agemos_3months  waist_cate   gender
n_pos_ab4 dq2_dq8_b;run;
proc glm data=a.natalie0529_01;
class waist_cate dq2_dq8_b ;
model logadi=  bmipct_3months agemos_3months  waist_cate   gender
n_pos_ab4 dq2_dq8_b /solution ss3;
output out=a.adi4
predicted=fit residual=resid
rstudent=studentized_resid;run;
proc univariate data=a.adi4 ;
var resid;
histogram resid / normal ;run;
```

```
data a.adi4_1;
set a.adi4;
standardized_residual=resid/0.48;
run;
proc univariate data=a.adi4_1 ;
var standardized_residual;
title " The histogram of standardized residual compared to normal for model4
(logadi) ";
histogram standardized_residual / normal(mu=0 sigma=1 color=red) ;run;
proc univariate data=a.adi4_1 ;
var standardized_residual;
title " The QQplot of standardized residual compared to normal for model4
(logadi) ";
qqplot standardized_residual/ normal(mu=0 sigma=1  color=red) ;run;
proc sgplot data=a.adi4_1;
title " scatter plot of standardized residual VS fitted points for model4
(logadi)";
scatter x= fit y=standardized_residual;
run;
proc sgplot data=a.adi4_1;
title " scatter plot of outcome variable VS fitted variable for model4
(logadi)";
scatter x= fit y=logadi;
run;
proc glm data=a.natalie0529_01;
class waist_cate Dq2_dq8_b n_pos_ab4;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
n_pos_ab4 Dq2_dq8_b/solution ss3;  run;
proc glmselect data=a.natalie0529_01;
class waist_cate dq2_dq8_b n_pos_ab4;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
n_pos_ab4 dq2_dq8_b / selection=none stop=none stats=all;run;
*model 5;
proc glmselect data=a.natalie0529_01;
class waist_cate pos_ab4_class2/ref=first;
model logadi= agemos_3months waist_cate pos_ab4_class2/ selection=none
stop=none stats=all;run;
proc glm data=a.natalie0529_01;
class waist_cate ;
model logadi= agemos_3months waist pos_ab4_class2/solution ss3 ;
output out=a.adi5
predicted=fit residual=resid
rstudent=studentized_resid;run;
proc univariate data=a.adi5 ;
var resid;
histogram resid / normal ;run;
data a.adi5_1;
set a.adi5;
standardized_residual=resid/0.489;run;

proc univariate data=a.adi5_1 ;
var standardized_residual;
title " The histogram of standardized residual compared to normal for model5
(logadi) ";
histogram standardized_residual / normal(mu=0 sigma=1 color=red) ;run;
proc univariate data=a.adi5_1 ;
var standardized_residual;
```

```
title " The QQplot of standardized residual compared to normal for model5
(logadi) ";
qqplot standardized_residual/ normal(mu=0 sigma=1  color=red) ;run;
proc sgplot data=a.adi5_1;
title " scatter plot of standardized residual VS fitted points for model5
(logadi)";
scatter x= fit y=standardized_residual;
run;
proc sgplot data=a.adi5_1;
title " scatter plot of outcome variable VS fitted variable for model5
(logadi)";
scatter x= fit y=logadi;
run;
* test the linearity;
proc glm data=a.natalie0529_01;
class waist_cate dq2_dq8_b;
model logadi= bmipct_3months agemos_3months  waist_cate   gender
pos_ab4_class2 dq2_dq8_b /solution ss3 ; run;
title " partial regression residual plot for model1(logadi)";
proc reg data=a.natalie0529_01;
model logadi= bmipct_3months agemos_3months  waist_cate1 waist_cate2
waist_cate3 gender pos_ab4_class2
Dq28_1 Dq28_2 Dq28_3 Dq28_4/ partial r influence ;
id PID;
run;
title " partial regression residual plot for model2(logadi)";
proc reg data=a.natalie0529_01;
model logadi=bmipct_3months agemos_3months  waist_cate1 waist_cate2
waist_cate3 gender pos_ab4_class3
Dq28_1 Dq28_2 Dq28_3 Dq28_4/ partial;
id PID;
run;
title " partial regression residual plot for model3(logadi)";
proc reg data=a.natalie0529_01;
model logadi= bmipct_3months agemos_3months  waist_cate1 waist_cate2
waist_cate3 gender pos0 pos1 pos2 pos3 pos4
Dq28_1 Dq28_2 Dq28_3 Dq28_4/ partial;
id PID;
run;
title " partial regression residual plot for model4(logadi)";
proc reg data=a.natalie0529_01;
model logadi= bmipct_3months agemos_3months  waist_cate1 waist_cate2
waist_cate3 gender  n_pos_ab4
Dq28_1 Dq28_2 Dq28_3 Dq28_4/ partial;
id PID;
run;
title " partial regression residual plot for model5(logadi)";
proc reg data=a.natalie0529_01;
model logadi=agemos_3months  waist_cate1 waist_cate2 waist_cate3
pos_ab4_class2/ partial;
run;
* influencial points;
* model 1;
proc reg data=a.natalie0529_01;
model logadi= bmipct_3months agemos_3months  waist_cate1 waist_cate2
waist_cate3  gender  pos_ab4_class2
Dq28_1 Dq28_2 Dq28_3 Dq28_4/ r influence ;  run;
```

```
ods graphics on;
proc reg data=a.natalie0529_01;
model logadi=bmipct_3months agemos_3months  waist_cate1 waist_cate2
waist_cate3 gender  pos_ab4_class2
Dq28_1 Dq28_2 Dq28_3 Dq28_4/ partial influence ;
output out= a.infadi1 r=residual rstudent=sdr h=lev cookD= cook;
run;
data a.infadi1a;
set a.infadi1;
standardized_residual=residual/0.48;
run;
data a.infadi1_1;
set a.infadi1a;
if lev> 0.1295 then PID1=PID;
else PID1=.;
if standardized_residual>= 3 then PID2=PID;
else PID2=.;
if cook>= 0.029 then PID3=PID;
else PID3=.;
run;
proc sgplot data=a.infadi1_1;
title " model1(logadi)";
scatter x= logadi y=lev/ datalabel=PID1 ;
format PID1 8.0;run;
proc sgplot data=a.infadi1_1;
title " model1(logadi)";
scatter x= logadi y=standardized_residual/ datalabel=PID2 ;format PID2
8.0;run;
proc sgplot data=a.infadi1_1;title " model1(logadi)";
scatter x= logadi y=cook/ datalabel=PID3 ;format PID3 8.0;run;
* model 2;
proc reg data=a.natalie0529_01;
model logadi= bmipct_3months agemos_3months  waist_cate1 waist_cate2
waist_cate3   gender  pos_ab4_class3
Dq28_1 Dq28_2 Dq28_3 Dq28_4/ partial influence ;
output out= a.infadi2 r=residual rstudent=sdr h=lev cookD= cook;
run;
data a.infadi2_1;
set a.infadi2;
if lev> 0.1295 then PID1=PID;
else PID1=.;
if sdr>= 3 then PID2=PID;
else PID2=.;
if cook>= 0.029 then PID3=PID;
else PID3=.;
run;
proc sgplot data=a.infadi2_1;
title " model2(logadi)";
scatter x= logadi y=lev/ datalabel=PID1 ;
format PID1 8.0;run;
proc sgplot data=a.infadi2_1;
title " model2(logadi)";
scatter x= logadi y=sdr/ datalabel=PID2 ;format PID2 8.0;run;
proc sgplot data=a.infadi2_1;title " model2(logadi)";
scatter x= logadi y=cook/ datalabel=PID3 ;format PID3 8.0;run;
proc graphics on;
* model 3;
```

```
proc reg data=a.natalie0529_01;
model logadi= bmipct_3months agemos_3months  waist_cate1 waist_cate2
waist_cate3   gender  pos0 pos1 pos2 pos3 pos4
Dq28_1 Dq28_2 Dq28_3 Dq28_4/ partial influence ;
output out= a.infadi3 r=residual rstudent=sdr h=lev cookD= cook;
run;
data a.infadi3_1;
set a.infadi3;
if lev> 0.1295 then PID1=PID;
else PID1=.;
if sdr>= 3 then PID2=PID;
else PID2=.;
if cook>= 0.029 then PID3=PID;
else PID3=.;
run;
proc sgplot data=a.infadi3_1;
title " model3(logadi)";
scatter x= logadi y=lev/ datalabel=PID1 ;
format PID1 8.0;run;
proc sgplot data=a.infadi3_1;
title " model3(logadi)";
scatter x= logadi y=sdr/ datalabel=PID2 ;format PID2 8.0;run;
proc sgplot data=a.infadi3_1;title " model3(logadi)";
scatter x= logadi y=cook/ datalabel=PID3 ;format PID3 8.0;run;
* model 4;
proc reg data=a.natalie0529_01;
model logadi= bmipct_3months agemos_3months  waist_cate1 waist_cate2
waist_cate3   gender  n_pos_ab4
Dq28_1 Dq28_2 Dq28_3 Dq28_4/ partial influence ;
output out= a.infadi3 r=residual rstudent=sdr h=lev cookD= cook;
run;
data a.infadi4_1;
set a.infadi4;
if lev> 0.1295 then PID1=PID;
else PID1=.;
if sdr>= 3 then PID2=PID;
else PID2=.;
if cook>= 0.029 then PID3=PID;
else PID3=.;
run;
proc sgplot data=a.infadi4_1;
title " model4(logadi)";
scatter x= logadi y=lev/ datalabel=PID1 ;
format PID1 8.0;run;
proc sgplot data=a.infadi4_1;
title " model4(logadi)";
scatter x= logadi y=sdr/ datalabel=PID2 ;format PID2 8.0;run;
proc sgplot data=a.infadi4_1;title " model4(logadi)";
scatter x= logadi y=cook/ datalabel=PID3 ;format PID3 8.0;run;

* model 5;
proc reg data=a.natalie0529_01;
model logadi= agemos_3months  waist_cate1 waist_cate2 waist_cate3
pos0 pos1 pos2 pos3 pos4/ partial influence vif;
output out= a.infadi5 r=residual rstudent=sdr h=lev cookD= cook;
run;
data a.infadi5_1;
```

```
set a.infadi5;
if lev> 0.1111 then PID1=PID;
else PID1=.;
if sdr>= 3 then PID2=PID;
else PID2=.;
if cook>= 0.0278 then PID3=PID;
else PID3=.;
run;
proc sgplot data=a.infadi5_1;
title " model5(logadi)";
scatter x= logadi y=lev/ datalabel=PID1 ;
format PID1 8.0;run;
proc sgplot data=a.infadi5_1;
title " model5(logadi)";
scatter x= logadi y=sdr/ datalabel=PID2 ;format PID2 8.0;run;
proc sgplot data=a.infadi5_1;title " model5(logadi)";
scatter x= logadi y=cook/ datalabel=PID3 ;format PID3 8.0;run;
* vif ;
* model1;
proc reg data=a.natalie0529_01;
model logadi=bmipct_3months agemos_3months  waist_cate  gender
pos_ab4_class2 dq2_dq8_b/ vif;  run;
* model2;
proc reg data=a.natalie0529_01;
model logadi= bmipct_3months agemos_3months  waist_cate  gender
pos_ab4_class3 dq2_dq8_b/ vif;  run;
* model3/4;
proc reg data=a.natalie0529_01;
model logadi= bmipct_3months agemos_3months  waist_cate  gender
n_pos_ab4 dq2_dq8_b/ vif;  run;
* model5;
proc reg data=a.natalie0529_01;
model logadi= agemos_3months waist_cate
pos_ab4_class2/vif ;run;
```

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