

PREDICTION OF INSULIN RESISTANCE BY STATISTICAL TOOL MARS

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## ABSTRACT

### PREDICTION OF INSULIN RESISTANCE BY STATISTICAL TOOL MARS

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Recently, following the rise in *obesity* prevalence, the incidence of *type 2 diabetes* rose remarkably. *Diabetes* is a serious disorder, accompanied by increased risk of developing heart disease, kidney failure, and new cases of blindness. Dietary habits are strongly related to *type 2 diabetes*. We sought to observe how *dietary protein* and *glycemic index patterns*, *weight change* and/or other predictors we selected relate to *insulin resistance* change.

First, we applied *multiple linear regression*, and then statistical tool *Multivariate Adaptive Regression Splines (MARS)* to a clinical data set. Refining the settings, we selected an *optimal model*. It constituted a good prediction for our problem.

According to our results, *weight change* strongly relates to *insulin resistance* change. Moreover, *weight change* and baseline *insulin resistance* are highly interacting with each other. Together, they have a strong effect on the model performance. Similarly, we observed an *interaction* between *weight change* and *dietary protein content*. *Weight change* and *dietary protein* jointly relate to *insulin resistance* change. Yet we could not detect any relationship between dietary *glycemic index* and *insulin resistance* change. The thesis ends with a conclusion and an outlook to future studies.

Keywords: *insulin resistance*, *weight loss*, *dietary protein* and *glycemic index*, *MARS*, *multiple linear regression*.

## ÖZ

### İSTATİSTİKSEL ARAÇ MARS İLE İNSÜLİN DUYARLILIĞI TAHMİNİ

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Son zamanlarda, artan *obezite* yaygınlığını takiben, *tip-2 diyabet* görülme sıklığı dikkate değer bir biçimde artmıştır. *Diyabet*, artan kalp krizi, böbrek yetmezliği ve sonradan oluşan körlük riskinin eşlik ettiği ciddi bir hastalıktır. Beslenme alışkanlığı *tip 2 diyabet* ile oldukça ilgilidir. Biz, *besinsel protein* ve *glisemik index* içeriklerinin, *kilo değişiminin* ve/veya seçtiğimiz diğer öngörücü değişkenlerin *insülin direnci* değişimine nasıl etki ettiğini gözlemlemeyi amaçladık.

Klinik bir veri setine önce *çoklu linear regresyon*, sonra da *MARS*'ı uyguladık. Ayarları iyileştirerek, en uygun modeli seçtik. Bu model problemimiz için iyi bir tahmin oluşturdu.

Sonuçlarımıza göre, *kilo değişimi insülin direnci* değişimiyle güçlü bir şekilde ilişki gösteriyor. Ayrıca, *kilo değişimi* ve temel *insülin direnci* değeri birbiriyle yüksek derecede etkileşimli. Bunlar, beraber, model performansı üzerinde güçlü bir etki gösteriyor. Benzer şekilde, *kilo değişimi* ve *besinsel protein* miktarının da bir etkileşimini gözlemledik. *Kilo değişimi* ve *besinsel protein* birlikte *insülin direnci* değişimiyle ilişki göstermekte. *Besinsel glisemik indeks* ve *insülin direnci* değişimi arasında bir ilişki saptayamadık.

Anahtar Kelimeler: *insülin direnci*, *kilo değişimi*, *besinsel protein* ve *glisemik indeks*, *MARS*, *çoklu doğrusal regresyon*.

*In the memory of my dear friend, Yener Yemliha Tuncel...*



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## LIST OF ABBREVIATIONS

BMI: Body Mass Index  
CID: Clinical Investigation Day  
DBP: Diastolic Blood Pressure  
DIOGenes: The Diet, Obesity, and Genes  
FAs: Fatty Acids  
GCV: Generalized Cross Validation  
GI: Glycemic Index  
HDL: High-Density Lipoprotein  
HGI: High Glycemic Index  
GL: Glycemic Load  
HP: High Protein  
HP/HGI: High Protein/High Glycemic Index  
HP/LGI: High Protein /Low Glycemic Index  
HOMA-IR: Homaostasis Model Assessment –Insulin Resistance  
LCD: Low Calorie Diet  
LDL: Low-Density Lipoprotein  
LGI Low Glycemic Index  
LP: Low Protein  
LP/HGI: Low Protein/High Glycemic Index  
LP/LGI: Low Protein/Low Glycemic Index  
MARS: Multivariate Adaptive Regression Splines  
MSE: Mean Squared Error  
MUFA: Mono Unsaturated Fatty Acids  
PUFA: Poly Unsaturated Fatty Acids  
OGTT: Oral Glucose Tolerance Test  
RSS: Residual Sum of Squares  
SAD: Sagittal Abdominal Diameter  
SBP: Systolic Blood Pressure  
SFAs: Saturated Fatty Acids  
UFAs: Unsaturated Fatty Acids

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## CHAPTER 1

### INTRODUCTION

*Obesity*, an excessive fat accumulation in the body, is related to a number of chronic diseases such as cancer, cardiovascular disease, and diabetes [1]. The prevalence of *obesity* dramatically increased during last decades [2]. Together with that increase, the prevalence of *type 2 diabetes* rose remarkably. *Type 2 diabetes* is 50 to 100 times more frequent in obese subjects and most of *type 2 diabetes* patients are obese or overweight [3]. *Type 2 diabetes* is a disease caused by impaired production and/or ineffective use of insulin, a hormone responsible for blood glucose control [3]. *Type 2 diabetes* is related to life threatening disorders such as kidney failure [4].

Dietary habits are closely linked to the risk of developing both *obesity* and *diabetes* [2]. Contemporary dietary habits of humans are remarkably different from the estimated dietary habits of their ancient ancestors [5]. Energy that human body needs to achieve vital functions and physical activities as well as to manage body temperature can be provided by a mixture of three types of dietary macronutrients; carbohydrate, protein, and fat [5]. Modern humans consume more fat and less protein than their ancestors [5].

Weight gain, the major cause of *obesity*, can dramatically increase the risk of developing *type 2 diabetes* [2]. *Weight loss* is the most widely used prevention approach to *type 2 diabetes*. Even a *weight loss* of 5-10%, regarded as a modest degree, can reduce *insulin resistance* and provide a better blood glucose management. The most successful way to lose weight is a calorie restricted diet [4].

Many scientific researches investigate the relationship between dietary *glycemic index*, dietary *protein* [6], weight management, and *insulin resistance* [7] [8]. Some of them demonstrate that low *glycemic index (LGI)* diets affect postprandial blood insulin favourably, while some of them report no significant relationship. Therefore, this issue remains controversial [7] [9].

*Insulin resistance* is a strong predictor of *type 2 diabetes* [10]. By observing *insulin resistance level*, scientists can establish new prevention approaches to *type 2 diabetes*, and manage insulin dosage adjustment in *type 1 diabetes* patients [11].

The scientific research project, the Diet, Obesity, and Genes (DIOGenes) study, was carried out in eight European countries (The Netherlands, Denmark, United Kingdom, Greece, Spain, Germany, Bulgaria and Czech Republic). Among other

topics, DIOGenes investigated the effects of *ad libitum* dietary macronutrient patterns, regarding protein and *glycemic index*, on weight regain and *insulin resistance*. The main goal was to separate the effects of weight reduction (8 weeks) from dietary effects of 26 weeks dietary intervention to overcome weaknesses of former studies [12]. Formerly, in the concept of DIOGenes study, Goyenechea et al. performed a *multiple linear regression* to the clinical data set, in order to observe the relationship between *weight change*, *dietary protein content*, *glycemic index* and *insulin resistance* change [13]. They selected the patients, who lost the largest amount of their weight during low calorie diet were selected to use for the model construction. They used the *weight loss* during dietary intervention, *protein content* and *glycemic index* dietary patterns, baseline *insulin resistance* level and centre type, as the predictors.

*Multiple linear regression* is a *parametric regression* approach which assumes linear relationships between variables [14]. However, fitting an equation to a data with complex behaviour may cause unwanted results. Although the *regression* equation fits well to some parts of the data, it fails to fit in other parts. In such cases, in order to make better estimates, the data should be partitioned into regions and different *regression* equations should be used for different regions. This approach is called *piecewise regression* [15]. *Multivariate Adaptive Regression Splines (MARS)* is a *nonparametric regression* method. It partitions the input space into intervals and computes a different *regression* equation for each of them [14]. It forms *piecewise linear regression model* by using surrogates of predictors called *basis functions* [16]. We proposed that it may perform well on our data.

In the context of this study, we *pre-processed* the raw data in accordance with a formerly published study within the scope of DIGenes research project [46]. After *pre-processing* the data, we applied first *multiple linear regression* and then *MARS* using the same variables. Having changed the settings, we observed how the model performance of *MARS* changes and tried to find a good approximation for our data. We used SPSS 15.0 and *MARS* for Windows (Version 7, Salford Systems, San Diego, California).

We aimed to observe the possible underlying relationships between *insulin resistance* change and the predictors we selected, especially the *dietary protein* and *glycemic index patterns*. Moreover, we aimed to observe the performance of *MARS* model on the current data. We wanted to find out if *MARS* constitutes a good approximation for the current data. To achieve this purpose, we observed how the model performance changes as the *MARS* parameters were altered.

The following chapter, Literature Review, is focused on the medical and mathematical basis of the study. We started with the medical background, provided some basic information about the basic terms such as *insulin sensitivity*, *insulin resistance*, *pre-diabetes*, *diabetes*, *diabetes types*, and *metabolic syndrome*; mentioned the current methods for assessing *insulin resistance*. In the context of



mathematical background, we explained *statistical learning, parametric and nonparametric regression, regression splines*, and model performance. In the Methods section, we introduced *MARS* tool and its methodology. We proceeded with the Application section where we detailed the data description, data preparation and the applications. We explained our results in the Result section, and discussed our results in the Conclusion and Outlook section.



## CHAPTER 2

### LITERATURE REVIEW

#### 2.1 MEDICAL BACKGROUND

##### 2.1.1. Insulin Sensitivity and Insulin Resistance

After eating, the digestive system breaks down dietary carbohydrates into glucose. As a consequence, blood glucose rises. Increased blood glucose triggers beta cells in the pancreas to release insulin, a hormone regulating blood glucose [17], fat, and protein metabolisms in the body [18]. Insulin plays a key role in glucose metabolism: it mediates glucose uptake in muscle and fat cells, glucose storage in muscle and liver cells, and reduces glucose production in liver cells [17]. Initially, insulin binds to its specific cell-surface receptors on its target cells. A number of signals are generated and a variety of metabolic effects promoting the storage of nutrients in the target cells are triggered [11].

The efficiency of insulin to trigger the regulatory mechanisms in its target cells and thereby reduce increased blood glucose is called *insulin sensitivity*. Due to factors such as excess weight, *obesity* and sedentary lifestyle, the *insulin sensitivity* level of target cells can decrease significantly [11]. As a result, these cells lose their ability to establish the normal biological response to a given level of blood glucose [4]. This situation is called *insulin resistance* [11]. In case of insulin resistance, when blood glucose rises, muscle and fat cells do not respond adequately to insulin. To compensate for high blood glucose, the pancreas produces more insulin [17]. As a result blood insulin rises (*hyperinsulinemia*), but blood glucose becomes barely normal [19]. Usually insulin resistance is considered as a relative deficiency of insulin while a consecutive fate of beta-cells leads to an absolute deficiency of insulin and thereby to diabetes. Excess blood glucose is related to *pre-diabetes*, diabetes, and other serious diseases [17]. *Type 2 diabetes* patients have high blood insulin unless they are in a progressed stage [20].

*Insulin resistance* is related to *type 2 diabetes*, *obesity*, hypertension, cardiovascular disease, dyslipidemia polycystic ovary syndrome, nonalcoholic fatty liver disease, and chronic kidney disease [17] [20]. *Insulin resistance* does not exist in every individual having these disorders, or vice versa. However, *insulin resistance* usually emerges long before these disorders [17] [20]. It is a

strong predictor of *type 2 diabetes* [10] [11] [21] and cardiovascular disease [21]. Detecting *insulin resistance* of non-diabetic individuals is crucial, since it can be used to assess the risk of developing diabetes [11] [20]. Moreover, cheap treatments of *insulin resistance* exist and are able to delay or prevent the possible consequences of *insulin resistance* [20]. By measuring *insulin sensitivity*, scientists can establish new treatment approaches to improve glucose metabolism to prevent *pre-diabetes* and type 1 or *type 2 diabetes* and more accurate insulin dosage adjustment in type 1 diabetes patients [11].

### **2.1.2. Pre-diabetes, Diabetes and Metabolic Syndrome**

To compensate for the insulin resistance, the pancreas secretes more insulin. Increased blood insulin manages to dispose intracellular glucose and thus blood glucose remains relatively normal. With time, as the individual becomes more *insulin resistant*, fasting blood glucose and glucose tolerance become impaired [22]. Chronic excessive blood glucose causes demise of beta cells. Insulin production and secretion decreases, *pre-diabetes* occurs [17] [18]. When a person without *diabetes* has blood glucose higher than normal, the risk of developing *type 2 diabetes* increases. This situation is called *pre-diabetes* [23].

People with *pre-diabetes* can delay or sometimes prevent developing *type 2 diabetes* by using precautionary measures such as losing weight and enhancing physical activity [23]. Characteristics of *pre-diabetes* are *IFG* (Fasting plasma glucose levels between 100 mg/dL [5.6 mmol/L] and 125 mg/dL [6.9 mmol/L]) or impaired glucose tolerance (*IGT*) (2-h OGTT values between 140 mg/dL [7.8 mmol/L] and 199 mg/dL [11.0 mmol/L]) [24] [25]. *Pre-diabetes* is accompanied by *insulin resistance*, and can be detected by increased serum triglycerides, decreased *HDL* levels, increased fasting and postprandial serum glucose and insulin levels. The variability of blood pressure in overweight individuals with *pre-diabetes* is abnormal [22].

Table 1 Criteria for diagnosis of *diabetes* [25]

A1C $\geq$ 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG $\geq$ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L).
*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

Diabetes is a chronic disorder, seen in 347 million people worldwide [27]. People with *diabetes* have hyperglycemia, increased blood glucose. An individual with a fasting blood glucose greater than or equal to 7.0 mmol/L has *diabetes* [27]. *Diabetes* enhances the risk of developing heart disease [27], kidney failure, and new cases of blindness (retinopathy) [23]. Three main types of *diabetes* are type 1, *type 2* and gestational diabetes [27].

Type 1 diabetes arises when the pancreas cannot produce sufficient amount of insulin [27], because the immune system destroys beta cells [23]. The causes of type 1 *diabetes* are still not clearly known [27]. Genetic, autoimmune and environmental factors may play a role for developing type 1 diabetes [23]. Excessive urine production, *weight loss*, vision changes, constant thirst, hunger and tiredness are common symptoms of type 1 diabetes [27].

90% of *diabetes* is of *type 2*. *Type 2 diabetes* occurs when the body fails to use the insulin effectively [23]. It is the condition most obviously linked to *insulin*

*resistance* [20]. *Type 2 diabetes* usually begins as *pre-diabetes* [23]. Being overweight and sedentary lifestyle are main causes of it. Although the symptoms of type 1 and *type 2 diabetes* are similar, the diagnosis of *type 2 diabetes* is more difficult, since the symptoms are usually less apparent [27]. Lowering blood glucose is a treatment approach to *diabetes* [23].

Symptoms such as increased urine volume, and glycosuria are usually present in *type 2 diabetes*. Therefore, they are useful for diagnosis. According to World Health organization diabetes can be detected early by blood testing [23] [28]. A1C test, fasting plasma glucose (FPG) and 2-h Oral Glucose Tolerance Test (OGTT) can be used to diagnose *type 2 diabetes* [17] [28]. 2-h OGTT or fasting blood glucose value can be used in epidemiological studies [28]. For middle aged and *obese/overweight* individuals it is appropriate to use fasting blood glucose for the diagnosis. However, while detecting the prevalence in overall population, sometimes the results of fasting and 2-h OGTT glucose concentrations may be conflicting [28].

The oral glucose tolerance test (OGTT) is widely used for the detection of glucose intolerance and *type 2 diabetes*. OGTT is a test to determine how fast glucose is removed from the blood. During OGTT, fasting, postprandial 0, 30, 60, and 120 min blood glucose levels get measured. For the postprandial measurements standard oral glucose load (75 g) is applied [19]. If impaired glucose tolerance exists, blood glucose levels increase suddenly and continuously and at 2h OGTT after reaching up a peak value, plasma glucose levels do not go down below 140 mg/dL [19].

Sedentary lifestyle, 140/90 mmHg or higher blood pressure, HDL level lower than 35 mg/dL, triglyceride level above 250 mg/dL, *pre-diabetes* (*IFG* or *IGT*) are some of the mentioned risk factors for diabetes according to National Diabetes Information Clearinghouse's 2012 report. *Obese/overweight* adults older than 45 years old are in high risk group for *diabetes*. BMI is a measure which can be used to decide whether an individual is normal, *obese*, and *overweight*. Even if BMI of an individual falls into a normal range, the location of fat on the body is noteworthy for development of *diabetes*. An increased waist circumference enhances the risk of developing *type 2 diabetes* [23].

*Insulin resistance syndrome*, also called *metabolic syndrome*, is a cluster of three of the following features: large waist circumference (40 inches or more for men and 35 inches or more for women), high blood triglycerides (150 mg/dL or above) or low blood HDL levels (for men below 40 mg/dL, for women and below 50 mg/dL), high blood pressure (130/85 or above) and hyperinsulinemia [17] [20].

### 2.1.3. Assessing Insulin Sensitivity and Insulin Resistance

Different methods are present for *insulin resistance* assessment [19]. The typical characteristics of *insulin resistance* are decreasing *insulin sensitivity* of target tissues, increased levels of fasting and/or postprandial blood glucose and blood insulin [22]. Therefore, blood tests such as the A1C test, the fasting plasma glucose test (FPG) and the oral glucose tolerance test (OGTT) can be used for diagnosis of *insulin resistance* [17]. If an individual has blood glucose greater than 200 mg/dL 2h after 75 g glucose load, the patient is diagnosed as diabetic. If the blood glucose is between 140 and 199 mg/dL, the patient has *pre-diabetes* [11].

Fasting blood insulin is highly correlated with *insulin resistance* [20]. In an individual without diabetes, it is possible to estimate *insulin resistance* by an insulin assay after an overnight fast [19].  $1 / (\text{fasting insulin})$  is a measure for *insulin sensitivity*. As the degree of *insulin resistance* increase, fasting blood insulin rises, accordingly  $1/\text{fasting insulin}$  value decreases [19]. Blood insulin measurements are not standardized. As a result false positive results may be present; therefore, this approach is limited for *insulin resistance* detection [19]. Assessing the changes in blood glucose levels of the same individuals in different time points with same methods can overcome this problem [19].

**Table 2** Methods to measure *insulin resistance* [19]

1 Various methods to measure insulin resistance			
Method	Comments	Advantages	Disadvantages
Hyperinsulinemic euglycemic glucose clamp	Gold standard method for quantifying insulin sensitivity	Direct measure of insulin under steady-state conditions	Laborious, involves intra venous infusion of insulin, frequent blood sampling
Oral glucose tolerance test	Clinically used to detect glucose intolerance	Helps in estimating other surrogate indices	Useful for glucose tolerance but not for IR
Fasting insulin	Most practical method to measure IR	Detects insulin resistance before clinical disease appears	Lack of standardization of the insulin assay procedure
Glucose/insulin ratio (G/I ratio)	comparable to insulin sensitivity measured by the FSIVGTTT	Highly sensitive & specific for insulin sensitivity	Does not aptly reveal the physiology of insulin sensitivity
Insulinogenic index (IGI)	index of $\beta$ -cell function $\delta I (0-30 \text{ min}) / \delta G (0-30 \text{ min})$	Measure of first-phase insulin response to glucose challenge	Not broadly validated
Homeostasis model assessment	Assesses inherent $\beta$ -cell function and insulin sensitivity $HOMA-IR = (G \times I) / 22.5$	Simple, minimally invasive, predicts fasting steady-state G and I levels	Insulin sensitivity in subjects treated with insulin needs further validation
Quantitative insulin sensitivity check index (QUICKI)	Mathematical transformation of FBG and insulin $QUICKI = 1 / [\log (I \mu U/mL) + \log (G \text{ mg/dL})]$	Consistent, precise index of insulin sensitivity, minimally invasive	Normal range to be established for each laboratory due to significant inter laboratory variations in insulin assay
Minimal model analysis of frequently sampled intravenous glucose tolerance test	Indirect measure of insulin sensitivity/resistance	Analysis using the computer program MINMOD	Multiple blood sampling
Glucose insulin (GI) product	Index of whole-body insulin sensitivity		
Fasting insulin resistance index	$(\text{fasting } G \times \text{fasting } I) / 25$		

The most accurate test to measure *insulin resistance* is the euglycemic clamp technique (Table 2) [11] [17]. Amount of glucose infused in a particular time

reflects the degree of *insulin resistance*. This constitutes the main principle of this technique. However, this method is too complicated and difficult. Therefore, it is only appropriate for some scientific researches but not useful for common use [17] [20]. In addition, euglycemic clamp does not reflect dynamic conditions such as postprandial states. Therefore, more applicable surrogate markers of *insulin resistance* are required [19].

In 1985, a mathematical model, named *Homeostasis Model Assessment: insulin resistance (HOMA-IR)*, was developed [29]. It estimates *insulin resistance* using fasting plasma glucose and insulin concentrations. The formula to calculate *HOMA-IR* score is: fasting serum insulin ( $\mu\text{U/ml}$ )  $\times$  fasting plasma glucose ( $\text{mmol/l}$ )/22.5 [29]. Higher *HOMA* scores denote higher *insulin resistance* [10] [29]. Since *HOMA* estimates are strongly correlated with the estimates acquired by euglycaemic clamp technique, it can be used as a surrogate marker of *insulin resistance* [10] [29]. This method is widely used as a cheap and simple method [10].

#### **2.1.4. Risk Factors for Insulin Resistance**

Most important causes of *insulin resistance* (reducers of *insulin sensitivity*) are excess weight or *obesity* [11] [17] [18]. World Health Organization defines excess weight (overweight) as BMI greater than or equal to 25 and *obesity* as BMI greater than or equal to 30 [27]. However, *insulin resistance* is more remarkably related to abdominal *obesity* independent of body weight [17] [20]. Waist circumference and waist-to-hip ratio are two main measurements of abdominal *obesity* [17] [20]. Large waist circumference causes *insulin resistance*, cardiovascular disease, high blood pressure and cholesterol by triggering the release of some hormones [17].

Diet composition affects *insulin resistance* and risk of *type 2 diabetes* [21]. Excess caloric intake causes excess weight, large waist circumference, and *obesity* [30].

Low calorie diet even for a couple of days induces *insulin sensitivity* increase even before remarkable *weight loss*. *Weight loss* triggers the further reduction of *insulin resistance*. A scientific research focusing on *obese* (mean BMI= 36.4  $\text{kg/m}^2$ ) but *non-diabetic* woman illustrated that significant improvements are achieved when 15% of the weight is lost (they were still obese with mean BMI= 30.5  $\text{kg/m}^2$ ). However, even a small amount of weight regain cause blood insulin increase to the baseline level [20].

Different carbohydrate content in a diet is called *glycemic load (GL)* [19]. *Glycemic index* is a measure of carbohydrate quality [30], which reflects how much the *glycemic load* increase postprandial blood glucose in proportion to same amount of white bread or glucose [19]. In other words it measures how rapid the



body uses carbohydrates as glucose [19] [30]. Low *glycemic index* (LGI) diets cause insulin and glucose responses decrease. Compared to a (HGI) diet, a low *glycemic index* diet reduces blood insulin and *insulin resistance* levels. A high *glycemic index* diet triggers the release of postprandial counter-regulatory hormones and free fatty acids (FFAs). Increase of FFAs is strongly related to diminished *insulin sensitivity* in muscles. Release of FFAs stimulates the programmed cell death of beta cells in liver and thereby inhibits the insulin production. Moreover, in *type 2 diabetes* patient's body, FFA-stimulated insulin secretion is defective [18].

High *glycemic index* diet accelerates fasting substantially [30], increase blood glucose and blood insulin [19]. High *protein* and low *glycemic index* diets induce faster *weight loss*; reduce postprandial blood glucose and insulin [30].

*Sagittal abdominal diameter (SAD)* is another important anthropometric measurement for *insulin resistance*. According to Risérus et al., *SAD* is more significantly correlated with *insulin sensitivity* compared to other anthropometric measurements such as BMI, waist circumference and waist-to-hip ratio [21].

Hypertension is also related to *insulin resistance*, but the mechanism is unclear. One half of the hypertension patients have increased blood insulin [20]. Subjects with *pre-diabetes* have abnormal variability of 24 hour blood pressure [22].

Physical exercise enhances glucose burn by more muscles, it helps blood glucose regulation. Furthermore, after physical exercise, muscle cells are reported to become more *insulin sensitive* [17].

*Insulin resistance* can accompany *IFG* levels. *IFG* raises the extensity of small dense *LDL* particles [19]. *IFG* is associated with high triglyceride and low *HDL* levels, hypertension, large waist circumference and *obesity* [24].

Some other *insulin resistance risk factors* are certain diseases, hormones, age, smoking, sleeping problems and ethnicity [17].

## **2.2. MATHEMATICAL BACKGROUND**

### **2.2.1. Learning**

Supervised learning is the task of predicting a variable (named as target or output variable) using a number of other variables, by learning form a set of examples (named as predictor or input variables) [31].

Two types of prediction methods are: *regression* and classification. Supervised learning is called *regression* when the outcome measurement is quantitative; classification when the outcome measurement is qualitative [31].

The aim of *statistical learning* is to maximize the accuracy of predictions. A model may have a maximized performance on a set of a training data [32], achieving zero training error [14], but it may fail to predict new unseen observations. In that case, the model memorizes the training data set instead of learning and generalizing from it. This problem is named as *overfitting* [32].

A statistical model is based on assumptions and by giving order to the data allows us to make decisions and understand events [33]. The goal is to find a good approximation function, based on the relationship between target and predictor variables [31].

### 2.2.2. Parametric and Non-Parametric Regression

Detecting the relationships between target variable and predictor variables can be hard for researchers. Predictive modeling technique can be used to solve this problem, but it requires some hypotheses on the function of each candidate predictor and which *interactions* should be considered between them. For instance linear *regression*, which is an example of *parametric regression*, is based on the assumption of a linear relationship between the target variable and the predictor variables [14]. On the contrary, *nonparametric regression* allows the *regression* function to be driven directly from data instead of making such an assumption [14]. For instance *regression spline* approach does not require the researcher to specify the operational form of each candidate variable. Instead, it lets the data determine such functional relationships [34].

The following model equations set examples to *nonlinear regression* [15]:

$$y = ax + b,$$

$$y = a_1x^2 + a_2x + c,$$

$$y = m \sin(b_1x) + n \cos(b_2x),$$

where  $y$  and  $x$  are the target and the predictor variables, and  $a, b, a_1, a_2x, c, m, b_1, n, b_2$  are coefficients, also called the parameters of the *regression*. *Parametric regression* uses data to estimate the parameters of a *regression*. It tends to use expressions with a small number of parameters, whereas *nonparametric regression* does not consider the number of parameters, just aims to acquire the trends from the data. That is the main difference between *parametric* and *nonparametric regression*. Formerly, a minimum number of parameters used to have computational benefits. Today, computer technology is well developed, and using a large number of parameters is not impractical any more. Therefore, the priority should be given to the effectiveness, instead of the number of parameters [15].

### 2.2.3. Linear Regression

It is helpful to firstly understand *linear regression models* in order to then understand *nonlinear regression models* [35]. When the target variable is an affine linear function of parameters, the *regression* is called *linear regression* [15]. *Linear models* constitute estimates for the  $\beta$  parameters [35].

In a *simple linear regression*, the output variable is related to only one predictor variable. The expected value of a random target variable,  $Y$  is as follows [36]:

$$E Y / x = \beta_0 + \beta_1 x.$$

For each observation of  $Y$  the model can be represented as [36]:

$$Y = \beta_0 + \beta_1 x + \varepsilon,$$

where  $\beta_0$  and  $\beta_1$  are *regression coefficients* and  $\varepsilon$  is the random error term [36].

A *linear model*, including more than one predictor, is called a *multiple linear regression model*. A *multiple linear regression model* has the following form [36]:

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k + \varepsilon.$$

Given a vector of predictor variables,  $X^T = X_1, X_2, \dots, X_p$  to predict the output  $Y$  we use the model [31]:

$$\hat{Y} = \hat{\beta}_0 + \sum_{j=1}^p X_j \hat{\beta}_j.$$

### 2.2.4. Regression Splines

*Regression splines* use linear combinations of *piecewise polynomial basis functions*, which are combined in *knots* [34]. *Spline functions* are structurally connected piecewise smooth functions such as *polynomial splines*. Generally, *splines* fit the data locally, though there are exceptions [37].

### 2.2.5. Performance of a Regression Model

For models with a numerical target variable, model performance is evaluated generally by an accuracy measure which reflects the discrepancy between the actual value and the estimate of that value [15] [16]. The most widely used accuracy measure to assess model performance is a function of model residuals, called *Root Mean Squared Error (RMSE)*. Model residuals equals to observations minus predictions. The *Mean Squared Error (MSE)* is calculated by squaring the residuals and summing them. The *RMSE* is then calculated by taking the square root of the *MSE* to express it in the same units of the original data [15] [16]:

$$MSE[\hat{m}(x)] = E[(\hat{m}(x) - m(x))^2],$$

where  $\hat{m}(x)$  stands for an estimate calculated by the *regression* equation, and  $m(x)$  the actual value of that estimate [15].

There is a relationship between bias, variance and MSE [15]:

$$MSE[\hat{m}(x)] = (\text{Bias}[\hat{m}(x)])^2 + \text{Var}[\hat{m}(x)].$$

*Coefficient of determination ( $R^2$ )* is another widely used model performance metric.  $R^2$  constitutes a measure of correlation, not accuracy. It can be thought as a proportion of the information in the data explained by the model. The denominator of that proportion is sample variance of the outcome. Therefore,  $R^2$  depends on the variation in the outcome [16].

## CHAPTER 3

### METHODS

#### 3.1. Introduction to MARS

*MARS*, developed by Jerome Friedman in 1991, is an adaptive *regression* procedure suitable for high-dimensional problems [31] [38]. *MARS* is a combination of *stepwise linear regression* and *spline/tree* model [39]. It constitutes a set of coefficients and *basis functions* using the data as the only source of information, without any assumption about the functional relationship between the target variable and the response variables [14]. It automatically selects the candidate predictor variables and random relationships between them [34]. *MARS* is suitable for multi dimensional *regression* data, since it avoids the curse of dimensionality by partitioning the input space into intervals with its own *regression* equation [14]. *MARS* method uses internal algorithms to determine how many intervals to use for the model. No analytical equation can be used for that purpose. Researcher can detect the appropriate value by trying different values and re-sampling [16].

#### 3.2. Methodology of MARS

*MARS* does not use the predictors directly. Instead, it uses some surrogate features which are functions usually of one or two predictors at a time. By breaking the predictor into two groups, it constructs two versions of a predictor. For each group, it models linear relationships between the target and the predictor variables. Using the candidate features of a predictor, a *linear regression model* is created and all the data points are regarded as a candidate cut point. The predictor and cut point with the smallest error is chosen to be used for the model [16]. To estimate the slopes and intercepts, the new features are added to a *basic linear regression*. A *piecewise linear regression model* emerges as new features enter the *basic linear regression model* [16].

*Knot* marks the end of one region of data and the beginning of another, where the behaviour of the function changes. *MARS* algorithm searches and detects the *knots*. This detection is based on the data, where the classical *regression spline* approach distributes the *knots* evenly. *MARS* uses as little *knots* as possible. It adds a *knot* only when it is necessary to describe the relationships between two variables [42].

*MARS* uses a model building strategy similar to that of *stepwise linear regression* [31]. Instead of using the predictor itself, it uses surrogate features called *basis functions* to express the intervals having different functional forms [31] [44].

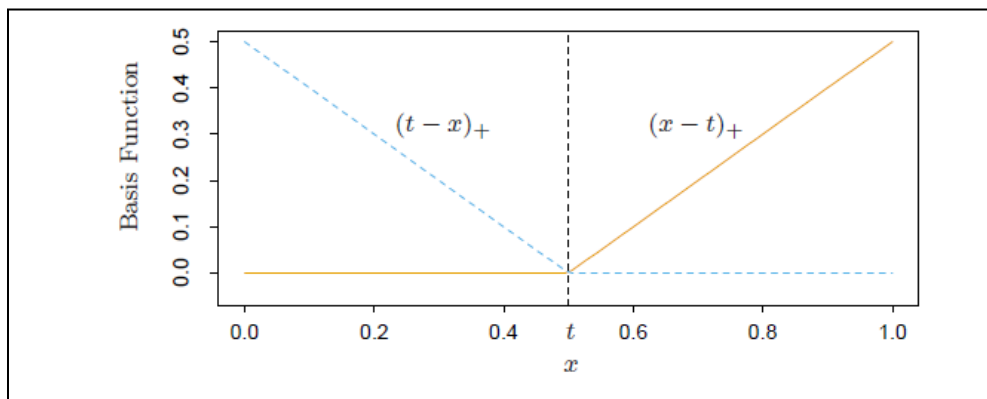
*Basis functions* constitute the transformed versions of the variables [40]. *Basis functions* in one dimension have the form [31]:

$$x - t_+ = \begin{cases} x - t, & \text{if } x > t, \\ 0, & \text{otherwise,} \end{cases} \quad t - x_+ = \begin{cases} t - x, & \text{if } x < t, \\ 0, & \text{otherwise.} \end{cases}$$

Here  $t$  represents a *knot* [41]. The “+” refers to positive part [31]. The functions above are piecewise linear truncated functions. They are together called *reflected pairs* [41]. The collection of candidate *basis functions* for a *MARS* model is [31]:

$$C = (X_j - t)_+, (t - X_j)_+ \in x_{1j}, x_{2j}, \dots, x_{Nj}, j = 1, 2, \dots, p,$$

where  $N$  corresponds to the number of observations and  $p$  to the dimension of the input space [41]. For an illustration we refer to Figure 1. If all predictor values are distinct, the number of *maximum basis functions* is  $2Np$  [31] [41].



**Figure 1** An example of *basis functions*  $x - 0.5_+$  and  $0.5 - x_+$

The form of *MARS* model is as follows [31]:

$$f(X) = \beta_0 + \sum_{m=1}^M \beta_m h_m(X),$$

where  $h_m(X)$  represents a *basis function* included in  $C$  or a product of more than one such functions and  $\beta_m$  are estimated coefficients by minimizing *RSS* through *linear regression* [31].

Afterwards, products of *basis functions* can be added to the model as well. The form of such terms can be represented as [31]:

$$\hat{\beta}_{m+1} h_a(X) \cdot (X_j - t)_+ + \hat{\beta}_{m+2} h_a(X) \cdot (t - X_j)_+,$$

where  $h_a(X)$  represents one of the *reflected pairs* that are considered to be added to the model at that particular time [31].

*MARS* method is composed of a forward and a backward stage [42] [43]. The forward stage aims to produce and *basis functions*, larger than optimal number to deliberately *overfit* the training data [43]. The model starts by the constant function  $h_0 \quad X = 1$  [31]. *Basis function* pairs that give the largest *RSS* decrease in the model are progressively and recursively added [39], until the model reaches a user specified *maximum basis functions* [44]. Then, by backward stage *MARS* eliminates *basis functions*, which contributes less to the training error [31] [39] [42] selectively and iteratively one by one to choose the most generalizable approximation [43]. This pruning process aims to limit the complexity of the model by reducing the number of its *basis functions*, since like most of the *nonparametric* methods, *MARS* is generally adaptive and flexible, which may generate *overfitting* unless counteracting preventions are applied [14].

In data mining, the model quality is assessed usually by partitioning data into training and test tests. However, when the data set is small, holding out a subset of the data (usually, one-half to one-third of the data) may cause some representative data to be excluded from the training set. In addition, performing testing on a small data set may cause some sensitiveness to the random variation. Therefore misleading goodness of fit results may occur. An alternative approach to assess how well the model will predict unseen objects is cross validation [40]. In fact, the balance between the accuracy and complexity of the model is achieved by an index, called Generalized Cross Validation (*GCV*) [39]. *GCV* is an approximation to the cross validation term, which averages a weighted prediction error over the entire data set by using each data point as the testing set [40]. To determine the contribution of the features on the model performance, how much the error rate is decreased when each predictor variable is added into the model is estimated. *GCV* statistics is used for this purpose. *GCV* produces a refined error estimate rather than the apparent error rate. By default, the number of terms to remove is automatically determined using *GCV* [16]. *MARS* finds the *optimal model*, using the *GCV* value. The *optimal model* chosen at the end of the backward pruning process [31]. It is the one with the lowest *GCV* measure [31] [40]:

$$GCV(\mu) := \frac{\sum_{i=1}^N (y_i - \hat{f}_\mu(x_i))^2}{(1 - M(\mu) / N)^2},$$

where  $M(\mu)$  represents the effective parameters, which is the summation of the number of term used in the model and the number of parameters used to estimate the *knot* places in the model [31]. The degree of features added to the model and the number of retained terms constitute the tuning parameters of the *MARS* model [16].

*MARS* has several advantages including automatic feature selection [16], being able to perform rapidly [43]. It does not require much *pre-processing* such as predictor filtering or data transformations [16]. It can handle multi-valued categorical inputs and missing values naturally [38]. Correlated predictors can complicate the model interpretation but do not affect model performance [16].

*MARS* can handle categorical variables, considering all possible binary combinations of the categories as two different groups. These binary combinations are used to create a pair of *basis functions* and treat it as any other [31].

Each *basis function* of *MARS* operates in a specific region of the predictor space, constructs piecewise linear models for the local relationships and is set to zero out of their localization [16] [31]. A useful option sets an upper limit on the order of *interaction*. For instance, allowing at most two-way *interactions* eases the interpretations remarkably [31]. When the upper limit of *interactions* are set to 1, the model becomes additive and interprets clearly how each predictor relates individually to the outcome without considering the other predictors [16] [31].

To try every candidate *knot*, for a predictor with  $N$  observations, *linear regression models* with  $O(N)$  operations are needed to be performed. *MARS* appears to use totally  $O(N^2)$  operations, but it does not. It starts trying the rightmost candidate *knot* and move from right to left trying one *knot* at a time. In each move, the *basis functions* differ by a constant over the right part, by zero over the left part. Therefore, after each move the fit is updates  $O(1)$  times and *MARS* uses totally  $O(N)$  operations [31].

Smoothing or complexity of a model in *MARS* can be determined by the number of *basis functions* [31]. As the model becomes more complex, the variance tends to increase as well where the squared bias tends to decrease [31]. As model complexity increases, the training error decreases but as the training error becomes too small, the generalization ability decreases, and the model becomes *overfit* to the training data [31]. The generalization performance of a learning method is a measure of its prediction capability on test data and the quality of the model [31].

The modeler can set some parameters of *MARS*, to investigate different models, in order to find the *optimal model*. One of the major parameters is the *maximum basis functions* [40] [45]. Each iteration of forward step adds 2 *basis functions* to the model. Therefore, this setting also specifies the number of forward steps *MARS* will iterate [45]. The optimum *maximum number of basis functions* mainly on the data size. For larger data sizes, it should be greater. By default, it is set to 15. The best way of detecting the optimal setting for *maximum basis functions* is trial and error [40].



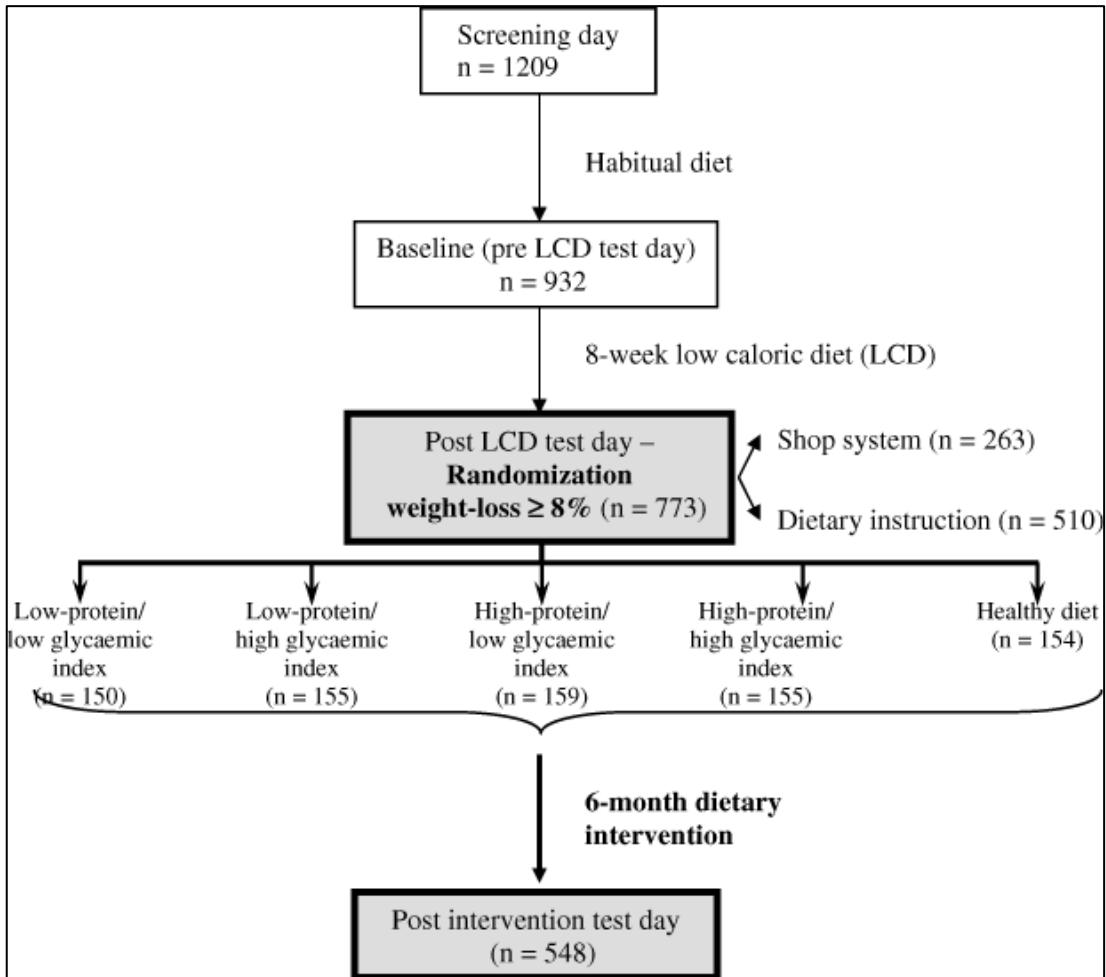
Another major parameter of *MARS* which the modeler can specify, is the *maximum interactions*. By default it is set to 1, which does not consider any of the *interactions* between the predictors. It is called *main effect model*. However, the *main affect model* may not constitute a good fit to the data. The optimal setting should also be detected by trial and error approach. If the *GCV* value of the model decreases when the *interactions* are allowed, then that model should be preferred. If there is no improvement in *GCV* value, the *interactions* should not be included. To obtain an *optimal model*, *MARS* favours adding new variables. However, there is a parameter, *penalty on added variables*, which can be modified by the modeler, to exclude highly correlated variables from the model [40].

The parameter, *minimum observations between knots*, is set to 0 by default. It can be set to a positive integer, but if it is not altered, *MARS* automatically handles it, considering the sample size and model complexity. If the modeler sets it to 1, *MARS* becomes more locally adaptive, since it considers a *knot* at any value [45].

### **3.3. Application of Multiple Linear Regression and MARS on the Real World Data Set**

#### **3.3.1. Data Collection Procedure**

The dietary intervention and clinical analysis of DIOGenes [13] was composed of two research periods; low calorie diet (LCD) and dietary intervention. Initially, 932 volunteers (312 male and 620 female) from 891 families with at least one obese or overweight parent ( $BMI \geq 27 \text{ kg/m}^2$ ) attended a low-calorie diet for 8 weeks with the goal to lose at least 8% of their body weight. The volunteers achieving that goal (773 volunteers) were randomized to 5 dietary groups: high protein/high *glycemic index* (HP/HGI), low protein/low *glycemic index* (LP/LGI), high protein/low *glycemic index* (HP/LGI), low protein/high *glycemic index* (LP/HGI) as well as a control group, providing the measures of national dietary guidelines. All diets were non-energy restricted (*ad libitum*) but low in fat (25–30% of energy from fat). In one centre type (shopping centre), 263 volunteers were given all food free, while in the other centre type 510 got dietary instructions only. 548 volunteers managed to finish the dietary intervention period while the others dropped out [13].



**Figure 2** Schematic overview of *DIOGenes* [13]

There were three main investigation days of the study: pre-LCD (baseline), post-LCD (randomization) and post-intervention (cf. Figure 2) [13].

### 3.3.2. Data Description and Pre-processing Details

Data set was composed of 7 variables:  $X_1$  (centre type),  $X_2$  (drop-out),  $X_3$  (*dietary GI*),  $X_4$  (*dietary protein*),  $X_5$  (*weight change*),  $X_6$  (baseline *HOMA-IR*), and  $Y$  (*HOMA-IR* change). We used  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$ , and  $X_6$  as predictors, and  $Y$  as the target variable (Table 3). While  $X_1$ ,  $X_2$ ,  $X_3$  and  $X_4$  are categorical variables,  $X_5$  and  $X_6$  and  $Y$  are continuous.

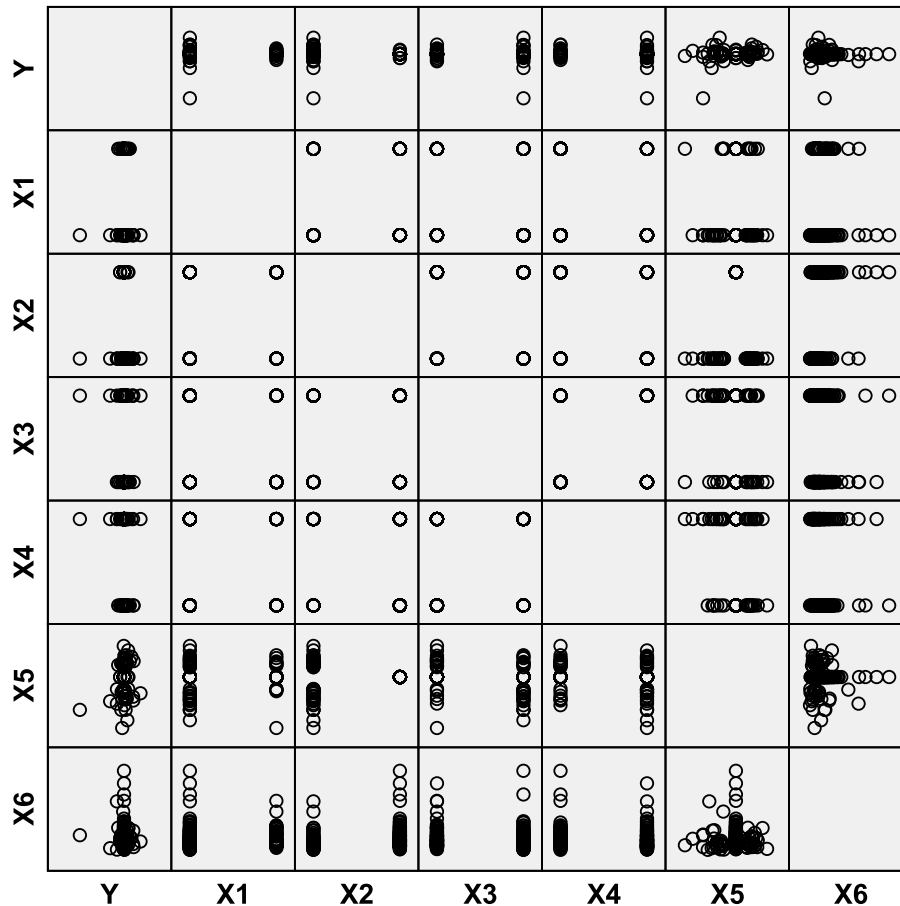
**Table 3** The variables included in the data set

$Y$	<i>HOMA-IR</i> change	<i>HOMA-IR</i> change during dietary intervention $I0 * G0 / 135$ (SI units)
$X_1$	Center type	center type: 1="not shopping center", 2="shopping center"
$X_2$	Drop-out	drop-out: 0 = "no drop-out after the LCD", 1 = "drop-out after the LCD"
$X_3$	<i>Dietary GI pattern</i>	low <i>glycemic index</i> diet: 0 = "no", 1 = "yes"
$X_4$	<i>Dietary protein pattern</i>	high <i>protein</i> diet: 0 = "no", 1 = "yes"
$X_5$	<i>Weight change</i>	<i>weight change</i> during dietary intervention
$X_6$	Baseline <i>HOMA-IR</i>	<i>HOMA-IR</i> , calculated after low calorie diet (before dietary intervention)

The labels for  $X_3$  are “1” and “0”. They reflect the low *GI* and high *GI*, respectively. Similarly for,  $X_4$  labels “1” and “0” represent *high protein* and *low protein dietary patterns*, respectively.  $X_5$  corresponds to *weight change* during dietary intervention. During low calorie diet, the participants attended the same commercially available diet. On the other hand, in different centre types there was a difference regarding the application of dietary intervention. In shopping center 263 volunteers got all food free, while 510 volunteers, in the other type of research centre, got dietary instructions only. Label 2 is used for shopping centre, and 1 for the other centre type. Furthermore,  $X_2$  reflects withdraw or completion; label 1 corresponds to drop-out while 0 corresponds to completion [13].

Since we used raw data, some *pre-processing* was needed before the model construction. We followed the *pre-processing* procedure of a formerly published study within the scope of DIOGenes [46]. We selected only the patients with the most successful *weight loss* (at least 10% per cent of their initial weight) [13]. Missing values which are due to withdraw from the study are not considered as randomly missing, since withdraw can be related to a lower adherence to the particular diet type [13] [46]. Such missing values are assumed to be the same as the value before dietary intervention [46]. Therefore, the changes of such values (weight and *HOMA-IR*) during dietary intervention were recorded as 0 [13]. The missing values except for the ones resulting from withdraw, assumed to be missing at random. They are consequences of 3 facts: Some of the blood samples

got lost; some of them were in a small amount to perform the analysis and some of the measurements were failed [46]. Such missing values are excluded from the analysis.



**Figure 3** Scatter plot matrix based on the data set after *pre-processing*

According to the scatter plot matrix (cf. Figure 3), the output values of the group 1 of  $X_1$  (center type) is more dispersed, whereas the output values of group 2 is aggregated in a smaller area. It makes sense because patients in group 2 had the food for free whereas the other group had dietary instructions only. It may have caused some difference between the individuals.

Similarly, output values for the individuals in group 0 of  $X_2$  (drop-out) are more dispersed, while the output values of group 1 are aggregated in a smaller area. It is because we filled the missing values caused by drop out by 0.

For the output values for the individuals in group 1 of both  $X_3$  (*low glycemic index*) and  $X_4$  (*high protein content*) are marginally dispersed. On the contrary, the output values for the individuals in group 0 of each variable are gathered in a small interval.

The values of  $X_5$  and  $X_6$  (*weight change* and *baseline HOMA-IR* value, respectively), but their  $Y$  values are close, except of some dispersal.

### 3.3.3. Application of Multiple Linear Regression

Initially, we performed *multiple linear regression* using all of the predictors. Afterwards, we conducted *multiple linear models* excluding first dietary *protein content*, then *glycemic index* variables.

### 3.3.4. Application of MARS

First, we included all the variables to the model and adjusted the *maximum interactions* by trial and error (restricting by 1, 2, 3, 4 and then 5, respectively), and *maximum basis functions*. We left the other parameters as default. We found the *optimal model* considering the *GCV* value.

### 3.3.5. Initial Models

Using all the variables, we observed the *optimal models* for different level of *maximum interactions*. Initially, we used the default setting for *maximum interactions*, 1, to observe the main models. Then, enhancing the *maximum interactions* by 1 in each iteration we observed the *GCV* values of each *optimal model*, for corresponding settings.

Since none of the first *optimal models* included  $X_3$ , we excluded  $X_3$  and repeated the same procedure.

### 3.3.6. Observing How MARS Parameters Affect the Model Performance

To illustrate the effect of *maximum basis functions* on the model performance, we started with the default setting of *maximum basis functions*, 15, and increased the setting by 5, in each application. We limited *maximum interactions* by 2, and left all the other parameters as default. We observed both *adjusted- $R^2$*  and *GCV* values of the *optimal models*.

To achieve a clearer interpretation, we limited the *maximum interactions* by 2. Changing the *minimum observations between knots* parameter, and adjusting the *maximum basis functions*, we observed how the performance of the *optimal model* alters.



## CHAPTER 4

### RESULTS

#### 4.1. Multiple Linear Regression

*Multiple linear regression model* we achieved when we used all the predictors had an *adjusted-R<sup>2</sup>* of 0.026 and an *R<sup>2</sup>* value of 0.056. The *adjusted-R<sup>2</sup>* value of the *multiple linear model* we constructed without using *protein content* as a predictor was 0.030, and the *R<sup>2</sup>* value was 0.055. The *adjusted-R<sup>2</sup>* value of the *multiple linear model* we constructed without using *glycemic index* as a predictor was 0.031, and the *R<sup>2</sup>* value was 0.055. There are only slight differences between the *adjusted-R<sup>2</sup>* values of those models (see Appendix C).

Formerly, Goyenechea et al. performed *multiple linear regression* to the data [13]. The *multiple linear regression models* excluding *glycemic index* and *protein content* dietary patterns has *R<sup>2</sup>* values of 0.14, and 0.17, respectively [13]. Performances of the *linear models* which we conducted are different than that of the model formerly conducted, because of the differences in data *pre-processing*.

#### 4.2. Performance of the Initial MARS Models and the Effect of Maximum Interactions on the Performance of Optimal Models

We detected the *optimal models* for each *maximum interaction* setting, by trying different *maximum basis functions*. As we increased *maximum interactions*, *GCV* values tended to decrease, while naive and *adjusted-R<sup>2</sup>* values tended to increase, except of a reverse tendency when *maximum interactions* increased to 4. We found the *optimal model* with the lowest *GCV* value, when we set *maximum interactions* to 5, and *maximum basis functions* to 53, It had a *GCV* value of 0.58, an *adjusted-R<sup>2</sup>* value of 0.78, and an *R<sup>2</sup>* value of 0.79 (cf. Table 4).

**Table 4** *Optimal models* for different *maximum interaction* settings

<i>Maximum interactions</i>	<i>Maximum number of basis functions</i>	<i>R<sup>2</sup></i>	<i>Adjusted-R<sup>2</sup></i>	<i>GCV</i>	<i>Variables appeared in the final model</i>
no interactions	20	0.15	0.13	1.84	<i>X<sub>5</sub>, X<sub>6</sub></i>
2-ways	55	0.71	0.61	0.92	<i>X<sub>5</sub>, X<sub>6</sub></i>
3-ways	76	0.75	0.74	0.77	<i>X<sub>2</sub>, X<sub>4</sub>, X<sub>5</sub>, X<sub>6</sub></i>
4-ways	55	0.65	0.63	1.02	<i>X<sub>2</sub>, X<sub>5</sub>, X<sub>6</sub></i>
5-ways	53	0.79*	0.78	0.58	<i>X<sub>1</sub>, X<sub>2</sub>, X<sub>4</sub>, X<sub>5</sub>, X<sub>6</sub></i>

The predictor variable  $X_1$  appeared only when maximum 5-way *interactions* are allowed. Furthermore,  $X_3$  (*dietary glycemic index*) did not appear in any of the models (cf. Table 4), which means it does not have any contribution to the model. All the other variables appeared at least in one of the *optimal models*. Therefore, we took  $X_3$  out and repeated the same procedure.

### 4.3. Optimal Models for Dietary Protein

Excluding the  $X_3$  variable, we observed the *final models*, following the same steps. Again, for each *maximum interactions* level, we detected *optimal models* by changing *maximum basis functions*. The model with the lowest *GCV* value, and the highest  $R^2$  value emerged, when we set the *maximum interactions* parameter to 5 and adjusted the *maximum basis functions* parameter by trial and error. Table 5 shows the performance of *optimal models* for different *maximum interactions*. When we allowed *interactions*, the *adjusted- $R^2$*  values of the *optimal models* tended to improve.

**Table 5** The performance of *optimal models* for *dietary protein* for different *maximum interactions* settings

<i>Maximum interactions</i>	<i>Maximum number of basis functions</i>	$R^2$	<i>Adjusted-<math>R^2</math></i>	<i>GCV</i>	<i>Variables appeared in the final model</i>
no <i>interactions</i>	20	0.15	0.13	1.84	$X_5, X_6$
2-ways	37	0.53	0.51	1.18	$X_5, X_6$
3-ways	54	0.78	0.76	0.86	$X_2, X_5, X_6$
4-ways	75	0.81	0.79	1.22	$X_1, X_2, X_4, X_5, X_6$
5-ways	65	0.84	0.82	0.80*	$X_1, X_2, X_4, X_5, X_6$

As we enhanced *maximum interactions*,  $R^2$  and *adjusted- $R^2$*  values of *optimal models* increased steadily. Similarly, *GCV* values for *optimal models* showed a propensity decrease, but, increased by *maximum interactions* of 4. We observed the model with the best performance among the *optimal models*, when we set the *maximum interactions* to 5 (cf. Table 5). It had a *GCV* value of 0.80,  $R^2$  value of 0.84, and *adjusted- $R^2$*  value of 0.82. The performance of the *final model*, had a higher  $R^2$  value than the one we observed, in Section 4.2. However, it has a lower *GCV* value. It is probably because of the presence of irrelevant data objects, which reduce model performance.

Our *final model* equation consists of 20 *basis functions*. The model equation of the best model we achieved is as follows:



$$\begin{aligned}
Y = & 0.00760097 + 0.737043 \cdot h_4(X) - 0.334955 \cdot h_7(X) \\
& + 0.277449 \cdot h_9(X) - 0.10171 \cdot h_{11}(X) \\
& - 1.3086 \cdot h_{17}(X) - 2.12107 \cdot h_{20}(X) \\
& + 0.741619 \cdot h_{22}(X) + 1.94626 \cdot h_{23}(X) \\
& + 4.47154 \cdot h_{37}(X) - 0.960445 \cdot h_{41}(X) \\
& - 2.83687 \cdot h_{43}(X) + 0.0827298 \cdot h_{47}(X) \\
& - 0.297437 \cdot h_{49}(X) - 0.306253 \cdot h_{51}(X) \\
& + 0.24663 \cdot h_{52}(X) + 0.269962 \cdot h_{56}(X) \\
& - 0.158291 \cdot h_{57}(X) - 0.981747 \cdot h_{58}(X) \\
& - 0.649299 \cdot h_{60}(X) + 0.198785 \cdot h_{62}(X).
\end{aligned}$$

The *basis functions* used by *MARS* model are:

$$\begin{aligned}
h_1(X) &= \max(0, X_5 + 29.5), \\
h_3(X) &= \max(0, -11 - X_5), \\
h_4(X) &= \max(0, X_6 - 0.565889 \cdot h_3(X)), \\
h_5(X) &= \max(0, X_5 - 0), \\
h_6(X) &= \max(0, 0 - X_5), \\
h_7(X) &= \max(0, X_6 - 1.74775 \cdot h_6(X)), \\
h_9(X) &= X_2 \text{ in "0"} \cdot h_1(X), \\
h_{11}(X) &= \max(0, X_6 - 1.20256 \cdot h_9(X)), \\
h_{17}(X) &= X_4 \text{ in "1"} \cdot h_5(X), \\
h_{18}(X) &= X_4 \text{ in "0"} \cdot h_5(X), \\
h_{20}(X) &= \max(0, X_5 - 9), \\
h_{21}(X) &= \max(0, 9 - X_5), \\
h_{22}(X) &= \max(0, X_6 - 0.565889 \cdot h_{20}(X)), \\
h_{23}(X) &= \max(0, X_5 - 7.4), \\
h_{27}(X) &= X_4 \text{ in "1"} \cdot h_{21}(X), \\
h_{30}(X) &= \max(0, 4.28321 - X_6 \cdot h_{27}(X)), \\
h_{32}(X) &= \max(0, 3.16821 - X_6 \cdot h_{27}(X)), \\
h_{34}(X) &= \max(0, 3.75686 - X_6 \cdot h_{27}(X)), \\
h_{37}(X) &= X_2 \text{ in "0"} \cdot h_{34}(X),
\end{aligned}$$

$$\begin{aligned}
h_{40}(X) &= \max 0, 2.49981 - X_6 \cdot h_{27}(X), \\
h_{41}(X) &= X_2 \text{ in "0"} \cdot h_{40}(X), \\
h_{43}(X) &= X_2 \text{ in "0"} \cdot h_{30}(X), \\
h_{46}(X) &= X_1 \text{ in "1"} \cdot h_{34}(X), \\
h_{47}(X) &= X_2 \text{ in "0"} \cdot h_{46}(X), \\
h_{49}(X) &= \max 0, X_6 - 3.71982 \cdot h_9(X), \\
h_{51}(X) &= \max 0, X_6 - 0.565889 \cdot h_{18}(X), \\
h_{52}(X) &= \max 0, X_6 - 3.12628 \cdot h_9(X), \\
h_{54}(X) &= X_4 \text{ in "1"} \cdot h_9(X), \\
h_{55}(X) &= X_4 \text{ in "0"} \cdot h_9(X), \\
h_{56}(X) &= \max 0, X_6 - 2.75485 \cdot h_{55}(X), \\
h_{57}(X) &= \max 0, 2.75485 - X_6 \cdot h_{55}(X), \\
h_{58}(X) &= X_2 \text{ in "0"} \cdot h_{32}(X), \\
h_{60}(X) &= \max 0, X_6 - 2.2777 \cdot h_5(X), \\
h_{62}(X) &= \max 0, X_6 - 1.74775 \cdot h_{54}(X).
\end{aligned}$$

*Basis function* equations can also be written as follows to see the interactions between the variables more clearly:

$$\begin{aligned}
h_4(X) &= \max 0, X_6 - 0.565889 \cdot \max 0, -11 - X_5, \\
h_7(X) &= \max 0, X_6 - 1.74775 \cdot \max 0, 0 - X_5, \\
h_9(X) &= X_2 \text{ in "0"} \cdot \max 0, X_5 + 29.5, \\
h_{11}(X) &= \max 0, X_6 - 1.20256 \cdot X_2 \text{ in "0"} \cdot \max 0, X_5 + 29.5,
\end{aligned}$$

$$\begin{aligned}
h_{17}(X) &= X_4 \text{ in "1"} \cdot \max 0, X_5 - 0 , \\
h_{20}(X) &= \max 0, X_5 - 9 , \\
h_{22}(X) &= \max 0, X_6 - 0.565889 \cdot \max 0, X_5 - 9 , \\
h_{23}(X) &= \max 0, X_5 - 7.4 , \\
h_{37}(X) &= X_2 \text{ in "0"} \cdot \max 0, 3.75686 - X_6 \cdot X_4 \text{ in "1"} \cdot \max 0, 9 - X_5 , \\
h_{41}(X) &= X_2 \text{ in "0"} \cdot \max 0, 2.49981 - X_6 \cdot X_4 \text{ in "1"} \cdot \max 0, 9 - X_5 , \\
h_{43}(X) &= \left( X_2 \text{ in "0"} \right) \max \left\{ 3.16821 - X_6 \right\} \left( X_4 \text{ in "1"} \right) \max \left\{ 9 - X_5 \right\} \\
h_{47}(X) &= \left( X_2 \text{ in "0"} \right) \left( X_1 \text{ in "1"} \right) \max \left\{ 3.75686 - X_6 \right\} \left( X_4 \text{ in "1"} \right) \\
&\quad \cdot \max \left\{ 9 - X_5 \right\} \\
h_{49}(X) &= \max 0, X_6 - 3.71982 \cdot X_2 \text{ in "0"} \cdot \max 0, X_5 + 29.5 , \\
h_{51}(X) &= \max 0, X_6 - 0.565889 \cdot X_4 \text{ in "0"} \cdot \max 0, X_5 - 0 , \\
h_{52}(X) &= \max 0, X_6 - 3.12628 \cdot X_2 \text{ in "0"} \cdot \max 0, X_5 + 29.5 , \\
h_{56}(X) &= \max 0, X_6 - 2.75485 \cdot X_4 \text{ in "0"} \cdot X_2 \text{ in "0"} \cdot \max 0, X_5 + 29.5 , \\
h_{57}(X) &= \max 0, 2.75485 - X_6 \cdot X_4 \text{ in "0"} \cdot X_2 \text{ in "0"} \cdot \max 0, X_5 + 29.5 , \\
h_{58}(X) &= X_2 \text{ in "0"} \cdot \max 0, 3.16821 - X_6 \cdot X_4 \text{ in "1"} \cdot \max 0, 9 - X_5 , \\
h_{60}(X) &= \max 0, X_6 - 2.2777 \cdot \max 0, X_5 - 0 , \\
h_{62}(X) &= \max 0, X_6 - 1.74775 \cdot X_4 \text{ in "1"} \cdot X_2 \text{ in "0"} \cdot \max 0, X_5 + 29.5 .
\end{aligned}$$

*Basis functions* 20 and 23 are related to  $X_5$ , directly. *Basis functions* 4, 7, 22 and 60 are related to  $X_6$  directly and  $X_5$  indirectly. *Basis function* 9 is directly related to subset 1 of  $X_2$ , indirectly to  $X_5$ . *Basis function* 17 is directly related to subset1 of  $X_4$  and indirectly to  $X_5$ . *Basis functions* 11, 49, 52 and are related to the variables  $X_2$ ,  $X_5$  and  $X_6$ . *Basis function* 51 is related to the variables  $X_4$ ,  $X_5$ ,  $X_6$ . *Basis function* 47 is related to  $X_1$ ,  $X_3$ ,  $X_4$ ,  $X_5$ , and  $X_6$ . Remaining 7 *basis functions* are related to subset 0 in  $X_2$ ,  $X_6$ , Subset 1 of  $X_4$  and  $X_5$ .

Table 6 represents the coefficients of the *basis functions* which are extracted from the model equation.

**Table 6** The coefficients of the *basis functions* appeared in the *optimal model*

<b><i>Basis function</i></b>	<b>Coefficients</b>
0	0.0076
4	0.7370
7	-0.3350
9	0.2774
11	-0.1017
17	-1.3086
20	-2.1211
22	0.7416
23	1.9463
37	4.4715
41	-0.9604
43	-2.8369
47	0.0827
49	-0.2974
51	-0.3063
52	0.2466
56	0.2700
57	-0.1583
58	-0.9817
60	-0.6493
62	0.1988

Table 7 illustrates the variables or groups of interacting variables which affect the model performance. Here,  $X_5$  can be considered as the most important variable, because it appears in every *basis function* included in the model equation. The interacting affects are between:  $X_5$  and  $X_6$ ;  $X_2$  and  $X_5$ ;  $X_4$  and  $X_5$ ;  $X_2$ ,  $X_5$ , and  $X_6$ ;  $X_4$ ,  $X_5$ , and  $X_6$ ;  $X_2$ ,  $X_4$ ,  $X_5$ , and  $X_6$ ;  $X_1$ ,  $X_2$ ,  $X_4$ ,  $X_5$ , and  $X_6$ . According to the cost of emission values, the interaction effects from most important to less important are between the variables  $X_2$ ,  $X_4$ ,  $X_5$ , and  $X_6$ ;  $X_4$  and  $X_5$ ;  $X_2$  and  $X_5$ ;  $X_5$  and  $X_6$ ;  $X_1$ ,  $X_2$ ,  $X_4$ ,  $X_5$ ,  $X_6$ ;  $X_4$ ,  $X_5$ , and  $X_6$ ;  $X_2$ ,  $X_5$ , and  $X_6$ , respectively.

**Table 7** Cost of omission, the number of *basis functions* and variables related to each function of the model

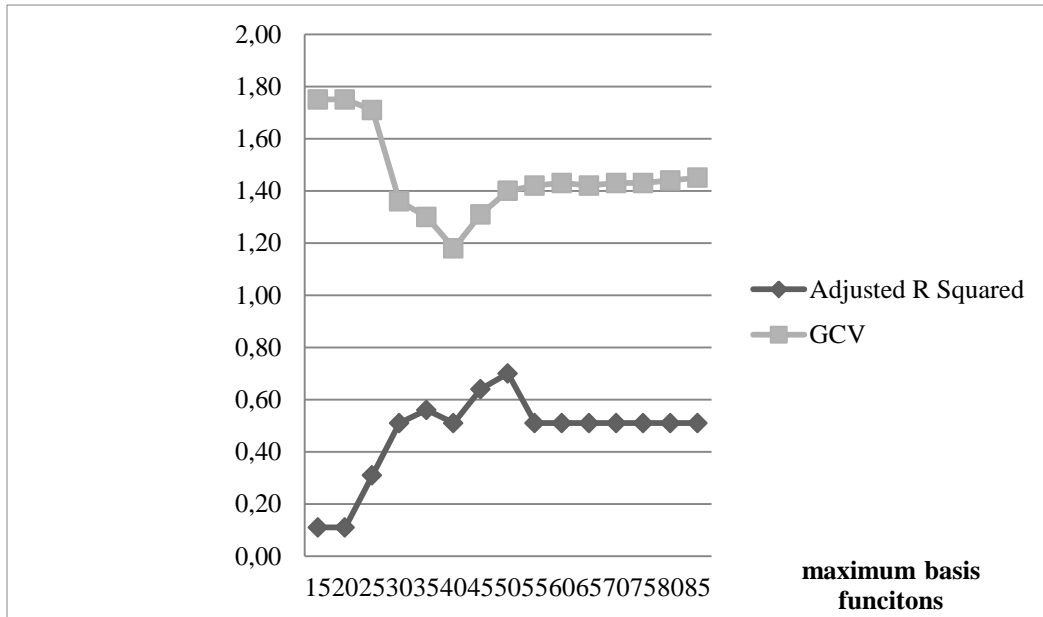
Function	Cost of omission	No of <i>basis functions</i>	Variables
1	0.88084	2	$X_5$
2	1.10663	4	$X_5, X_6$
3	1.13789	1	$X_2, X_5$
4	1.18222	1	$X_4, X_5$
5	0.95453	3	$X_2, X_5, X_6$
6	1.01270	1	$X_4, X_5, X_6$
7	2.69535	7	$X_2, X_4, X_5, X_6$
8	1.02422	1	$X_1, X_2, X_4, X_5, X_6$

We conducted the model again by randomly selecting 20% of the data for testing. The model performance (*adjusted-R<sup>2</sup>* and *R<sup>2</sup>* values) decreased dramatically.

#### 4.4. The Effect of Maximum Basis Functions and Minimum Observations between Knots on Model Performance

Until now, we observed the performance of the *optimal model* for each possible *maximum interaction* setting, by adjusting *maximum basis functions*. To illustrate the individual effect of *maximum basis functions*, we used a fixed value of 2 for *maximum interactions* and left the other parameters as default. Figure 4 illustrates how the *adjusted-R<sup>2</sup>* and *GCV* values change, as we set the *maximum basis functions* to greater values. As the *maximum basis functions* increase from 15 to 40, we observed an important improvement in the model performance. At 40, we observed the *optimal model* for these settings, with the lowest *GCV* value (1.18).

Between the *maximum basis functions* settings 40 and 50, the *GCV* value decreased slightly and remained constant for larger values. The *adjusted-R<sup>2</sup>* values tended to rise, by the increase of *maximum basis functions*. After reaching a peak at *maximum basis functions* settings of 50, it showed a slight decline and remained constant for larger settings.



**Figure 4** The effect of *maximum basis functions* change on the *adjusted-R<sup>2</sup>* and *GCV* values

So far, we performed *MARS* changing only the *maximum interactions* and *maximum basis functions* settings. We found the *optimal model* when we allowed 5-way *maximum interactions*.

To achieve a clearer interpretation, we limited the *interactions* by 2. Adjusting the *minimum observations between knots*, we observed how the performance of the model alters.

Table 8 represents the *optimal models* we observed when we changed the settings of *minimum observations between knots*. We achieved the *optimal model* with the lowest *GCV* value, when we set *minimum observations between knots* to 1. It had an *R<sup>2</sup>* value of 0.96, *adjusted-R<sup>2</sup>* value of 0.96 and *GCV* value of 0.30.

**Table 8** *Optimal models for dietary protein when maximum interactions are limited by 2*

<i>Min. obs. between knots</i>	<i>Max. basis functions</i>	$R^2$	<i>Adjusted-<math>R^2</math></i>	<i>GCV</i>
0 (default)	40	0.53	0.51	1.18
1	60	0.96*	0.95	0.30*
2	85	0.92	0.91	0.56
3	70	0.75	0.73	0.89
4	60	0.68	0.66	1.10
5	65	0.50	0.45	1.50
6	40	0.63	0.61	0.93
7	95	0.61	0.59	1.03
8	45	0.63	0.61	1.02
9	80	0.73	0.71	1.10
10	30	0.50	0.48	1.43
15	65	0.61	0.59	1.30
20	55	0.36	0.33	1.83

#### 4.5. The Optimal Model with Testing

So far, we used the whole data set as training set. To avoid *overfitting*, we used 0.20 of the data for random testing. We set the maximum *interactions* to 2 again to achieve a clearer interpretation. Changing the other *MARS* parameters (minimum observations between *knots*, maximum number of *basis functions* and speed) we observed various models. We observed the *final model* when we set the maximum number of *basis functions* to 45, speed parameter to 5, and minimum observations between *knots* to 1.

The backward stage ended up with a model containing *piecewise 5 basis functions*. These *basis functions* are combined and related to only 3 of the variables:  $X_4$ ,  $X_5$ , and  $X_6$  (*protein content*, *weight change* and baseline *HOMA-IR value*). In other words, only those three predictors had a contribution to the performance of the model.

The *basis functions*, remained at the end of backward pruning procedure, are illustrated below:

$$\begin{aligned}
 h_2(X) &= \max\{0, -11 - X_5\}, \\
 h_5(X) &= \max\{0, X_6 - 3.95351\} \cdot h_2(X), \\
 h_9(X) &= \max\{0, X_6 - 4.09755\} \cdot h_2(X), \\
 h_{10}(X) &= \max\{0, X_6 - 3.12628\} \cdot h_2(X), \\
 h_{24}(X) &= \max\{0, -9.4 - X_5\}, \\
 h_{27}(X) &= X_4 \text{ in } "1" \cdot h_{24}(X).
 \end{aligned}$$

To see the *interactions* between the predictors, may also be written as:

$$\begin{aligned}
 h_2(X) &= \max \{0, -11 - X_5\} , \\
 h_5(X) &= \max \{0, X_6 - 3.95351\} \cdot \max \{0, -11 - X_5\} , \\
 h_9(X) &= \max \{0, X_6 - 4.09755\} \cdot \max \{0, -11 - X_5\} , \\
 h_{19}(X) &= \max \{0, X_6 - 3.12628\} \cdot \max \{0, -11 - X_5\} , \\
 h_{24}(X) &= \max \{0, -9.4 - X_5\} , \\
 h_{27}(X) &= X_4 \text{ in "1"} \cdot h_{24}(X).
 \end{aligned}$$

The *final model* equation is as follows:

$$\begin{aligned}
 Y &= 0.090307 + 15.7047 \cdot h_5(X) - 13.47 \cdot h_9(X) - 2.30274 \cdot h_{19}(X) \\
 &\quad - 0.0168057 \cdot h_{27}(X) + \varepsilon.
 \end{aligned}$$

Can also be written as:

$$\begin{aligned}
 Y &= 0.090307 + 15.7047 \cdot \max \{0, X_6 - 3.95351\} \cdot \max \{0, -11 - X_5\} \\
 &\quad - 13.47 \cdot \max \{0, X_6 - 4.09755\} \cdot \max \{0, -11 - X_5\} \\
 &\quad - 2.30274 \cdot \max \{0, X_6 - 3.12628\} \cdot \max \{0, -11 - X_5\} \\
 &\quad - 0.0168057 \cdot X_4 \text{ in "1"} \cdot \max \{0, -9.4 - X_5\} + \varepsilon.
 \end{aligned}$$

Table 9 represents the coefficients of *basis functions* which are extracted from the model equation, and variables related to each *basis function* either directly or through another *basis function*. All the *basis functions* appeared in the *final model* equation are related to  $X_5$  directly or indirectly. Also  $X_6$  showed relatedness with most of the *basis functions*. Some *basis functions* are linked to  $X_6$  and  $X_5$  or  $X_4$  and  $X_5$ . However,  $X_4$  and  $X_6$  did not appear together in a *basis function*.

Some coefficients of *basis functions* related to  $X_5$  were remarkably high. Moreover,  $X_6$  and  $X_5$  were highly interacting with each other, and they had a strong combined effect on the model performance. We also observed an *interaction* between  $X_6$  and  $X_4$ . The variables  $X_1$ ,  $X_2$ , and  $X_3$  did not appear in the *final model*.



**Table 9** Coefficients of each basis function appeared in the model equation

<i>Basis Function</i>	<i>Coefficients</i>
0	0,0903
5	15,7047
9	-13,4700
19	-2,3027
27	-0,0168

#### 4.6. Comparing the Performance of MARS Models with the Performance of Multiple Linear Regression Model

We compared the performances of the *optimal MARS model* we achieved after doing the adjustments, and the *optimal MARS model* we achieved when we did testing with the *multiple linear model* which we conducted.

Since the variable *glycemic index* did not appear in any of the *MARS* models, we compared the performance of the models we conducted excluding *glycemic index*.

Table 10 illustrates the *adjusted-R<sup>2</sup>* values of each model. The *adjusted-R<sup>2</sup>* value of *multiple linear model*, 0.03, is absolutely lower than that of the *optimal MARS model* (0.82). When we conducted *MARS* models by separating 20 % of the data for random testing, the *adjusted-R<sup>2</sup>* values decreased remarkably. Doing the adjustments, we managed to find an *optimal model* with testing.

**Table 10** *Multiple linear regression* model versus *MARS* models

<b>Model</b>	<b><i>Adjusted-R<sup>2</sup></i></b>
<i>Multiple Linear Regression</i> model	0.031
<i>Optimal MARS</i> model	0.82
<i>Optimal MARS</i> model with testing	0.67



## CHAPTER 5

### CONCLUSION AND OUTLOOK

We used the clinical data from the DIOGenes research project. One of the objectives of this study was to use *MARS* to detect if *dietary protein* and *glycemic index patterns* and/or other predictors we selected were related to *insulin resistance* change. Moreover, we aimed to observe the performance of *MARS* model on the current data. We wanted to find out if *MARS* constitutes a good approximation for it. Adjusting the parameters, we observed how the performance of *MARS* changes, and thereby we tried to find a good prediction for our problem.

Formerly, in the concept of DIOGenes, Goyenechea et al. [13] performed a *multiple linear regression* analysis to observe the relationship between the different dietary patterns regarding the macronutrient content, i.e., *dietary protein* and *glycemic index patterns* and insulin resistance change. We aimed to find a model which constitutes a better approximation to the data.

After preparing the data set, we performed *multiple linear regression* to the same data. The model performance was different than that of Goyenechea et al., due to differences in the *pre-processing* procedure.

We observed that *multiple linear models* do not perform well on our data. We constructed a *MARS* model, first including all the variables. We observed the *optimal models* for different *maximum interactions* and *maximum basis functions*. We left all the other settings as default. We ended up with models having better performance on the data compared to *multiple linear regression*. We observed the *optimal model* with the best performance when we allowed the consideration of 5-way *interactions* between predictors. *Weight change*, *dietary protein*, baseline *insulin resistance*, center type and drop-out had an effect on the *final model*. However, *dietary glycemix index* did not appear in any of the results. Therefore, we could not observe the effect of it on the model performance.

We repeated the same procedure again but this time, we excluded *dietary glycemic index* from the data set. We achieved a better performance than our previous model.

According to our results, there was no link between *dietary glycemic index* and *insulin resistance* change. However, we managed to detect a relationship between *weight change*, *dietary protein*, baseline *insulin resistance* and *insulin resistance* change. Center type did not have a direct effect on the model performance. However, this variable was interacting with the other variables in the model.

Considering our *optimal model* without testing, drop-out, *dietary protein content*, and *weight change* was strongly related to *insulin resistance* change. Moreover, *protein content* and *weight change* were interacting with each other and they had a strong combined effect on the model performance. We also observed an interaction between drop-out and *weight loss* as well as between *weight change* and *baseline insulin resistance*. Centre type had an indirect effect on the *model performance*, occurred as a 5-way interaction with the other predictors.

So far, we used the whole data set as training set. To avoid *overfitting*, we used 0.20 of the data for random testing. However, the model performance was not as efficient as was expected.

To find a simpler model, we limited the *maximum interactions* by 2-ways, and to detect local relationships more accurately, we adjusted *MARS* parameters for a more intense search through the data points. Compared to our first models with testing, we ended up with an *optimal model* which fits the data better and provides a clearer interpretation.

Only, *protein content*, *weight change* and baseline *insulin resistance* appeared in the final model. In other words, only those three predictors had a contribution to the performance of the model.

There was an interaction between *weight change* and baseline *insulin resistance* and they had an important effect on the model performance. Similarly, *weight change* and protein content was interacting with each other. *Drop-out* did not appear in the *final model*. This may be because the individuals who completed dietary intervention had a variety of *insulin resistance* change values, although there was only one value for the withdraw group. This may have caused some noise and it may be the underlying reason why *drop-out* variable did not appear in the *final model*. Similarly, our *final model* with testing did not indicate any relationship between *center type* and *insulin resistance*. In other words, according to the model, applying the dietary intervention either by food supplement or by dietary instructions did not make an observable difference. Also, the absence of these two predictors in the *final model* means neither *center type* nor *drop-out* affected the performance of the model for the current settings.

Considering our observations, we conclude that scientific researches, investigating new prevention approaches to *type 2 diabetes* should take into account *weight change* and *dietary protein patterns*. They should also take baseline *insulin resistance* values into consideration.

*MARS* is a nonlinear, model based method, which can detect *interactions* between the variables [45]. It uses a trade off between stability and accuracy [39]. Alternative varieties of *MARS* exist (CMARS, RMARS, etc.) [41].

Future studies could focus on the use of further emerging optimization-supported data mining tools, such as *CMARS* and *RMARS* [41], and the comparison of their results with the results of this thesis.

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**APPENDIX A**

**DIOGENES PROJECT EXCLUSION CRITERIA FOR SUBJECTS**

Subject	Exclusion criteria
Generally healthy	psychiatric diseases eating disorders infectious or inflammatory diseases untreated hypo- or hyperthyroidism gastrointestinal, liver or kidney diseases cardiac diseases <i>type 1 or type 2 diabetes mellitus</i> cancer within the last 10 years food allergies blood pressure $\geq 160/100$ mmHg blood triglycerides $> 3$ mM blood total cholesterol $> 7$ mM fasting blood glucose $\geq 6.1$ mM urinary protein, glucose, pH, ketone and hemoglobin outside accepted reference ranges use of prescription medication alcohol consumption $> 21$ alcohol units/week (males), $> 14$ units/week (females) planned major changes in physical activity during the study period blood donation within the past 2 months <i>weight change</i> $> 3$ kg in the 3 months prior to the study participation in another scientific study up to 3 months before drug treatment, pregnancy or lactation, surgically or drug-treated <i>obesity</i> , drug abuse inability/unwillingness to engage in 8-week low-calorie diet (LCD) or 6-month randomized diet special diet and inability to give informed consent
At least one parent overweight /obese Body mass index (BMI) $> 27$	BMI $> 45$ kg/m <sup>2</sup>

Younger than age 65	-
At least one child between ages 8 and 15	-

## APPENDIX B

### DIOGENES ANTHROPOMETRIC MEASUREMENTS AND BLOOD SAMPLES

Anthropometric measurements (Body measurements)	Analyzed by
Weight	Calibrated digital balance
Height	Wall mounted stadiometer
BMI	Body weight/height <sup>2</sup> (kg/ m <sup>2</sup> )
Waist circumference	Standard procedure
Hip circumference	Standard procedure
Sagittal diameter	Standard procedure
Body composition	Dual energy X-ray absorption or by bioelectric impedance analysis

Blood Samples	Analyzed by
Fasting serum glucose	Colorimetric assay after an overnight fast of 12 h
Fasting serum insulin	Colorimetric assay after an overnight fast of 12 h
OGTT serum glucose	Colorimetric assay
OGTT serum and insulin	Colorimetric assay
Fasting insulin sensitivity index	Using the homeostasis model assessment for <i>insulin resistance</i> ( <i>HOMA-IR</i> )

Fasting: after an overnight fast of 12 h

OGTT: Subjects drank a 75 g glucose containing solution, before and 30, 60, 90 and 120 min plasma glucose and insulin

APPENDIX C

MULTIPLE LINEAR REGRESSION MODELS

*Multiple Linear Model for Dietary Patterns*

Model Summary

Model	<i>R</i>	<i>R</i> <sup>2</sup>	<i>Adjusted-R</i> <sup>2</sup>	Std. Error of the Estimate
1	.236 <sup>a</sup>	.056	.026	1.3592448

a. Predictors: (Constant), *X*<sub>6</sub>, *X*<sub>3</sub>, *X*<sub>4</sub>, *X*<sub>2</sub>, *X*<sub>1</sub>, *X*<sub>5</sub>

ANOVA<sup>b</sup>

Model	Sum of Squares	df	Mean Square	F	Significance	
1	<i>Regression</i>	20.634	6	3.439	1.861	.089 <sup>a</sup>
	Residual	351.034	190	1.848		
	Total	371.668	196			

a. Predictors: (Constant), *X*<sub>6</sub>, *X*<sub>3</sub>, *X*<sub>4</sub>, *X*<sub>2</sub>, *X*<sub>1</sub>, *X*<sub>5</sub>

b. Dependent Variable: *Y*

*Multiple Linear Model for Glycemix Index*

Model Summary

Model	<i>R</i>	<i>R</i> <sup>2</sup>	<i>Adjusted-R</i> <sup>2</sup>	Std. Error of the Estimate
1	.234 <sup>a</sup>	.055	.030	1.3561901

a. Predictors: (Constant), *X*<sub>6</sub>, *X*<sub>3</sub>, *X*<sub>2</sub>, *X*<sub>1</sub>, *X*<sub>5</sub>

ANOVA<sup>b</sup>

Model	<i>R</i>	<i>R</i> <sup>2</sup>	<i>Adjusted-R</i> <sup>2</sup>	F	Significance	
1	<i>Regression</i>	20.371	5	4.074	2.215	.054 <sup>a</sup>
	Residual	351.297	191	1.839		
	Total	371.668	196			

a. Predictors: (Constant), *X*<sub>6</sub>, *X*<sub>3</sub>, *X*<sub>2</sub>, *X*<sub>1</sub>, *X*<sub>5</sub>

b. Dependent Variable: *Y*

**Multiple Linear Model for Protein Content**

**Model Summary**

<b>Model</b>	<b>R</b>	<b>R<sup>2</sup></b>	<b>Adjusted-R<sup>2</sup></b>	<b>Std. Error of the Estimate</b>
1	.236 <sup>a</sup>	.055	.031	1.3557192

a. Predictors: (Constant), X<sub>6</sub>, X<sub>1</sub>, X<sub>5</sub>, X<sub>2</sub>, X<sub>4</sub>

**ANOVA<sup>b</sup>**

<b>Model</b>	<b>R</b>	<b>R<sup>2</sup></b>	<b>Adjusted-R<sup>2</sup></b>	<b>F</b>	<b>Sig.</b>
1 <i>Regression</i>	20.615	5	4.123	2.243	.052 <sup>a</sup>
Residual	351.053	191	1.838		
Total	371.668	196			

a. Predictors: (Constant), X<sub>4</sub>, X<sub>6</sub>, X<sub>1</sub>, X<sub>5</sub>, X<sub>2</sub>,

b. Dependent Variable: Y