RELEVANT FACTORS OF MULTIPLE SCLEROSIS IN A GROUP OF A SELECTED PART OF PUERTO RICO

by

Carmen L. Collazo Pérez

Project submitted in fulfillment of the requirements for the degree of

MASTER OF ENGINEERING

in

Management Systems Engineering

UNIVERSITY OF PUERTO RICO
MAYAGÜEZ CAMPUS

May 2006

Approved by:

_____	_____
José R. Deliz, Ph.D. President, Graduate Committee	Date
_____	_____
David González, Ph.D. Member, Graduate Committee	Date
_____	_____
Noel Artiles, Ph.D. Member, Graduate Committee	Date
_____	_____
Gilberto Villafañe, Ph. D. Representative, Graduate School	Date
_____	_____
Agustín Rullán Toro, Ph.D. Chairperson of the Departament	Date

Abstract

This study's objective is to identify which characteristics of persons with the condition of Multiple Sclerosis (MS) and a first order relative can predict its occurrence. A questionnaire and logistics regression was used to develop a prediction model for the probability of having MS condition. Six models were developed using eight important predictors: age, mother, sister or daughter having MS condition, persons' fibromialgy, sister allergy, sons' sinus, and age person got chicken pox. Female relatives with MS reduce the odds of the person having MS condition to 1:6221 (daughter), to 1:50 (sister) for one model, and sisters' allergy to 1:4.3. Sons' sinus odds is 8:1 and persons' fibromialgy odds of MS is 1:53, even though these three had no medical explanation; gender having women get MS 2.4:1 vs. men. Plots were developed to compare false positives and false negatives in predicting the condition of MS, and borderline cases.

Resumen

El objetivo de este estudio es identificar qué características de las personas con la condición de esclerosis múltiple (MS) y un familiar cercano (primer orden) sirven para predecir la incidencia de MS. Se usó un cuestionario y regresión logística para desarrollar un modelo para predecir la probabilidad de tener la condición de MS. Se desarrollaron seis modelos usando ocho variables predictoras importantes, a saber: edad, presencia de MS en la madre, hermana o hija, presencia de fibromialgia, alergia de la hermana, sinusitis del hijo y edad a la cual tuvo varicelas. La presencia de MS en parientes féminas reducen las probabilidades de tener MS a 1:6221 (hija), a 1:50 (hermana) y alergia de la hermana da 1:4.3. La probabilidad al hijo tener sinusitis, de tener MS aumenta de 8:1 y si la persona tiene fibromialgia la oportunidad de tener MS es 1:53, aunque no existe explicación médica para estas tres relaciones; las féminas tienen 2.4:1 mas oportunidad de tener la condición de MS que los hombres. Se desarrollaron gráficas para comparar el número de falsos positivos y de falsos negativos al predecir la condición de MS, además de los casos fronterizos para diferentes modelos.

Gratitude

There are too many people that I want to thank to name them all by name. But is my duty to name some of them. First I thank all the patients with the condition of MS and their relatives for spending their time to fill out the questionnaire and agreeing to participate in this study. Without them it would have been impossible to perform the study.

To Carmen González, Dr. Vélez Arocho, Dr. Pérez Canabal, Sandra, Dr. Andres Collazo, Jesus Saad Nasser, Professor Idalis, Arleen and her sister, Ana María, Segundo, Carmen, Cuca, Ruth and Dr. Freytes for helping me with the questionnaires in one way or another, THANKS!

To my friends for always telling me, don't give up! To my graduate committee for having the endurance to deal with me, especially Deliz, I think that with my case he can go to heaven, because he purified all his sins.:)

To my family, especially Cuca, Ludy, and Gerar for always being there for me.

And most important, to the Divine Jesus Christ Child to whom I dedicate this work and all the works in my life, for giving me the best persons at my side, you know who you are, and for giving me strength to always look up and never give up no matter what…

Table of contents

Table of figures vi

Table of tables viii

Chapter 1 INTRODUCTION 9

The immune system 11

Chapter 2 Revision of Literature 16

Genetics 18

Cognitive Impairment and MS 19

Psychosocial Factors in MS and the Role of Stress 20

Neuropsychological Findings 22

Chapter 3 Materials, methods, results and discussion 28

- Introduction for the Chapter 3 28
- Materials, methods, results and discussion 30

I. First group of data (patients with the condition of MS) 30

II. Second group of data (patients of MS and their relatives) 38

Chapter 4 Conclusions 67

Bibliography 69

APPENDICES: 71

Table of figures

Page

Figure 3.1 Histogram of age when symptoms first appeared 31

Figure 3.2 Histogram of year when symptoms first appeared 31

Figure 3.3 Histogram of age when diagnosed with MS Condition 32

Figure 3.4 Histogram of year when MS Condition Diagnosed 32

Figure 3.5 Histogram of time between exacerbations 33

Figure 3.6 Histogram of success or even in life before diagnosis 34

Figure 3.7 Symptoms of first attack of MS 35

Figure 3.8 Common Symptoms of MS 36

Figure 3.9 Symptoms of MS that persist 36

Figure 3.10 Histogram of the course of MS 37

Figure 3.11 Histogram of method used for diagnosing MS 38

Figure 3.12 Scatter plot of equation 1 Delta Betas Versus leverage 44

Figure 3.13 Scatter plot of equation 1 Expected Probability Versus leverage 44

Figure 3.14 Scatter plot of equation 2 Delta Betas Versus leverage 45

Figure 3.15 Scatter plot of equation 2 Expected Probability Versus leverage 46

Figure 3.16 Scatter plot of equation 3 Delta Betas Versus leverage 47

Figure 3.17 Scatter plot of equation 3 Expected Probability Versus leverage 47

Figure 3.18 Scatter plot of equation 4 Delta Betas Versus leverage 49

Figure 3.19 Scatter plot of equation 4 Expected Probability Versus leverage 49

Figure 3.20 Scatter plot of equation 5 Delta Betas Versus leverage 50

Figure 3.21 Scatter plot of equation 5 Expected Probability Versus leverage 51

Figure 3.22 Scatter plot of equation 6 Delta Betas Versus leverage 52

Page

Figure 3.23 Scatter plot of equation 6 Expected Probability Versus leverage 52

Figure 3.24 Scatter plot of equation 7 Std. Residuals Versus leverage 55

Figure 3.25 Scatter plot of equation 7 Delta Betas Versus leverage 56

Figure 3.25 Scatter plot of equation 7 Expected Probability Versus leverage 56

Figure 3.26 Scatter plot of equation 7 Std Residuals Versus age X9 57

Figure 3.27 Scatter plot of equation 7 Std Residuals Versus age got chicken pox 58

Figure 3.28 Scatter plot of equation 8 Delta Betas Versus leverage 60

Figure 3.29 Scatter plot of equation 8 Expected Probability Versus leverage 60

Figure 3.30 Scree plot of equation 1 Expected Probability Versus new case 61

Figure 3.31 Scree plot of equation 2 Expected Probability Versus new case 62

Figure 3.32 Scree plot of equation 3 Expected Probability Versus new case 63

Figure 3.33 Scree plot of equation 4 Expected Probability Versus new case 64

Figure 3.34 Scree plot of equation 5 Expected Probability Versus new case 65

Figure 3.35 Scree plot of equation 6 Expected Probability Versus new case 66

Table of tables

Page

Table 3.1 First Minitab output, with 22 predictor variables 39

Table 3.2 Second Minitab output, with 14 predictor variables 40

Table 3.3 Third Minitab output, with 10 predictor variables 41

Table 3.4 Fourth Minitab output, with 9 predictor variables 41

Table 3.5 Fifth Minitab output, with 8 predictor variables 42

Table 3.6 Sixth Minitab output, with 7 predictor variables 43

Table 3.7 Seventh Minitab output, with 6 predictor variables 45

Table 3.8 Eighth Minitab output, with 7 predictor variables 46

Table 3.9 Ninth Minitab output, with 7 predictor variables 48

Table 3.10 Tenth Minitab output, with 6 predictor variables 50

Table 3.11 Eleventh Minitab output, with 5 predictor variables 51

Table 3.12 T-test for predictor variables and simple LR for individual predictors 53

Table 3.13 Twelfth Minitab output, forward selection process, with 8 pred. var. 55

Table 3.14 Thirteenth Minitab output, with 5 predictor variables 59

Table 3.15 Comparison of Predictor Averages for original and validation cases 66

Chapter 1 **Introduction**

Multiple Sclerosis (MS) is five times more common in tempered climates than in tropical regions, based on reported studies in the medical literature, given the geographical localization of Puerto Rico (PR) would be in an area of low prevalence[1]. It is of great importance to look for possible factors that are contributing for the higher than average incidence[2] of MS cases in PR. The biggest incidence is in the north of Europe, north of the United States, (15 cases per 100,000 persons in 1991) the south of Australia and New Zealand; that is, Nordic and tempered countries.

The purpose of this investigation is to study the relevant factors for the high incidence of MS in a select group of people with the condition of MS and a relative, when PR should not be an area of high incidence.

Studies using standardized measures of the possible factors can give some guidance in order to avoid things that could contribute for the activation or relapses of the condition of MS. The research will identify what relevant factors are common in the selected group of people.

By applying the concepts of advanced statistics the behavior of a complex system, the incidence of MS in Puerto Rico is modeled using several factors as predictors. The factors considered were environmental conditions, genetic, previous health conditions in the family and neuropsychological conditions among other factors that gave an equation that established the probability for a person to have the condition of MS.

[1] The number of all new and old cases of a disease in a defined population at a particular point in time.
[2] The number of new cases of a disease in a specified population over a defined period of time.

With the purpose for the understanding of the project I will give a brief explanation about the condition of MS. According to an article published by Dr. Arbona (1991) MS is a chronic disease of the central nervous system[3] (CNS), which predominantly affects young adults during their most productive years (between 20 and 40 years). The earliest known description of a person with possible MS dates from the fourteenth century. MS is an unpredictable disease of the (CNS), it can range from relatively benign to somewhat disabling to devastating when communication between the brain and other parts of the body are disrupted.

Generally the MS is characterized by episodes of neurological deficit (exacerbation; synonymous with attack, relapse, and flare-up, or worsening) alternating with periods of normality and inactivity of the illness (remission; remitting). The central thing that happens in MS is that myelin breaks down. The damage to the brain and spinal cord occurs in many widely scattered areas. The disease is called **multiple** because there are many patches of damage (demyelinated areas in the CNS) and the damaged area becomes filled with hard material (scars), **sclerosis**. MS means **many scars**.

During an MS attack, inflammation occurs in areas of the white matter of the CNS in random patches called plaques. This process is followed by destruction of myelin[4]. Myelin facilitates the smooth, high-speed transmission of electrochemical messages between the brain, the spinal cord, and the rest of the body. When this transmission channel is damaged, neurological transmission of messages may be slowed or blocked completely, leading to diminished or lost function. How MS affects depends on the location in the brain and spinal cord of the scarring, or plaques.

[3] The central nervous system consists of the brain and the spinal cord.
[4] The fatty sheath that surrounds and insulates nerve fibers in the central nervous system.

No one knows exactly how many people have MS. It is believed that in 2001 there were approximately 250,000 to 350,000 people in the USA with MS diagnosed by physicians. This estimate suggests some 200 new cases are diagnosed each week. Most people experience their first symptoms of MS between the ages of 20 and 40, but a diagnosis is often delayed. This is due to both the transitory nature of the disease and the lack of a specific diagnostic test - specific symptoms and changes in the brain must develop before the diagnosis is confirmed. Scientists have documented cases of MS in young children and elderly adults but symptoms rarely begin before age 15 or after age 60. Whites are more than twice as likely as other races to develop MS. In general, women are affected at almost twice the rate of men; however, among patients who develop the symptoms of MS at a later age, the gender ratio is more balanced.

Alonso and Larrea (1994) divide the symptoms of MS in three categories; Primary symptoms are a direct result of demyelization, the destruction of myelin. This impairs transmission of nerve impulses to muscles and other organs. Secondary symptoms are complications that arise as a result of the primary symptoms. For example, bladder dysfunction can cause repeated urinary tract infections, inactivity can result in weakness (not related to demyelization). Tertiary symptoms are the social, vocational and psychological complications of the primary and secondary symptoms. In order to understand what happens when a person has MS, it is first necessary to know about how the healthy immune system works.

The immune system

The immune system - a complex network of specialized cells and organs - defends the body against attacks by foreign invaders such as bacteria, viruses, fungi, and

parasites. It does this by seeking out and destroying the interlopers as they enter the body. Substances capable of triggering an immune response are called antigens[5].

The immune system can recognize millions of distinctive foreign molecules and produce its own molecules and cells to match up with and counteract each of them. In order to have room for enough cells to match the millions of possible foreign invaders, the immune system stores just a few cells for each specific antigen. When an antigen appears, those few specifically matched cells are stimulated to multiply into a full-scale army. Later, to prevent this army from over expanding, powerful mechanisms to suppress the immune response come into play.

T cells, so named because they are processed in the thymus, appear to play a particularly important role in MS. They travel widely and continuously throughout the body patrolling for foreign invaders. In order to recognize and respond to each specific antigen, each T cell's surface carries special receptor molecules for particular antigens.

T cells contribute to the body's defenses in two major ways. Regulatory T cells help orchestrate the elaborate immune system. For instance, they assist other cells to make antibodies[6]. Antibodies typically interact with circulating antigens, such as bacteria, but are unable to penetrate living cells. Chief among the regulatory T cells are those known as helper (or inducer's) cells. Helper T cells are essential for activating the body's defenses against foreign substances. Yet another subset of regulatory T cells acts to turn off, or suppress, various immune system cells when their job is done.

[5] A structure foreign to the body such as a virus.
[6] Proteins made by the immune system that bind to structures they recognize as foreign to the body (antigens).

Killer T cells, on the other hand, directly attack diseased or damaged body cells by binding to them and bombarding them with lethal chemicals called cytokines[7]. Since T cells can attack cells directly, they must be able to discriminate between **self**-cells (those of the body) and **non-self** cell (foreign invaders; antigen). To enable the immune system to distinguish the **self**, each body cell carries identifying molecules on its surface. T cells likely to react against the **self** are usually eliminated before leaving the thymus; the remaining T cells recognize the molecular markers and coexist peaceably with body tissues in a state of self-tolerance.

In autoimmune diseases such as MS, the harmony between the immune system and the body is disrupted when the immune system seems to wrongly identify **self** as **non-self** and declares war on the part of the body (myelin) it no longer recognizes.

In an Internet article by the National Multiple Sclerosis's Society (NMSS) they said that each case of MS displays one of several patterns of presentation and subsequent course. MS isn't always easy to diagnose because early signs can be vague, such as fatigue or muscle weakness this leads to differential diagnosis. A diagnosis of MS is generally based on a complete medical history and neurological examination. There are five main courses of MS:

Benign - Mild infrequent sensory exacerbations with full recovery symptoms are mild to moderate, don't worsen and don't lead to permanent disability.

Relapsing-remitting - It is characterized by one or two flare-ups every 1 to 3 years, followed by periods of remission (symptoms last a few weeks or months, not all resolve completely).

[7] Is an important factor in the production of inflammation (a tissue's immunologic response to injury).

Primary progressive — from the first appearance of symptoms, neurological function deteriorates without periods of remission. Problems appear and gradually worsen over time.

Secondary progressive — usually after years of having relapsing-remitting MS, at least half will enter a stage of continuous deterioration. Relapses become more severe while remissions are less complete, shorter in duration, and eventually non-existent.

Progressive relapsing — this is primary progressive MS with the addition of sudden episodes of new symptoms or worsened existing ones.

Scheinberg, Labe, Raime and Cedric (1984) said that when faced with a patient whose symptoms, neurological examination, and medical history suggest MS, physicians use a variety of tools to rule out other possible disorders and perform a series of laboratory tests that, if positive, confirm the diagnosis. Because there is no single test that unequivocally detects MS, it is often difficult for the physician to differentiate between an MS attack and symptoms that can follow a viral infection or even an immunization.

There are different diagnostic categories that doctor's use for patients with MS:

- Definite MS - Consistent course (relapsing-remitting course with at least 2 bouts separated by at least 1 month, or slow or stepwise progressive course for at least 6 months). Documented neurological signs of lesions in more than one site of brain or spinal cord white matter. Onset of symptoms between 10 and 50 years of age. Absence of other more likely neurological explanation
- Probable MS - History of relapsing-remitting symptoms. Signs not documented and only one current sign commonly associated with MS. Documented single bout of

symptoms with signs of more than one white matter lesion; good recovery, then variable symptoms and signs. Absence of other more likely neurological explanation

- Possible MS - History of relapsing-remitting symptoms. No documentation of signs establishing more than one white matter lesion. Absence of other more likely neurological explanation.

Dr. Arbona (1991) concludes that the vast majority of patients are mildly affected, but in the worst cases MS can render a person unable to write, speak, or walk. A physician can diagnose MS in some patients soon after the onset of the illness. In others, however, physicians may not be able to readily identify the cause of the symptoms, leading to years of uncertainty and multiple diagnoses. Differential diagnosis for MS includes other demyelization diseases of the nervous system, often of a viral or post infectious origin.

Chapter 2 **Revision of Literature**

In a Mayo Clinic's article for the Internet site of the National Multiple Sclerosis Society (NMSS) there are different etiologies postulated including viral and autoimmune etiologies. Genetic and environmental factors are known to contribute to MS, but a specific cause for this disease is not identified. These are the major scientific theories about the causes of MS:

1. Immunologic: It is now generally accepted that MS involves an autoimmune process. An abnormal immune response directed against the (CNS). The exact antigen, the target the immune cells are sensitized to attack, remains unknown. The destruction of myelin causes the nerve impulses to be slowed or halted and produces the symptoms of MS.
2. Environmental: Migration patterns and epidemiological studies - those that take into account variations in geography, socioeconomic, genetics, and other factors - have shown that people, who are born in an area of the world with a high risk of MS and move to an area with a lower risk, acquire the risk of their new home, if the move occurs prior to adolescence. Such data suggest that exposure to some environmental agent encountered before puberty may predispose a person to develop MS later on.
3. Viral: Since initial exposure to numerous viruses occurs during childhood, and since some viruses are known causes of demyelization and inflammation; it is possible that a virus is the triggering factor in MS. This study considers the age that person gets varicella (chicken-pox) as a possible cause.

4. Genetic: While MS is not hereditary, having a first-degree relative such as a parent, children or sibling with MS increases an individual's risk of developing the disease several-fold above the risk for the general population. Studies have demonstrated a higher prevalence of certain genes in populations with high rates of MS. Common genetic factors have also been found in some families where there is more than one person with MS. Some neurologists theorize that MS develops because a person is born with a genetic predisposition to react to some environmental agent, which, upon exposure, triggers an autoimmune response.

The age of 15 seems to be significant in terms of risk for developing the disease. Studies suggest that people moving after age 15 maintain the risk of the area where they grew up and vice versa. These findings indicate a strong role for an environmental factor in the cause of MS. It is possible that, at the time of or immediately following puberty patients acquire an infection with a long latency period. Or, people in some areas may come in contact with an unknown protective agent during the time before puberty. Other studies suggest that the unknown geographic or climatic element may actually be simply a matter of genetic predilection and reflect racial and ethnic susceptibility factors.

Investigators are also looking for abnormalities or malfunctions in the blood/brain barrier, a protective membrane that controls the passage of substances from the blood into the CNS. It is possible that, in MS, components of the immune system get through the barrier and cause nervous system damage.

Scientists have studied a number of infectious agents (such as viruses) that have been suspected of causing MS, but have been unable to implicate any one particular agent. Inflammation and the production of gamma interferon, a naturally occurring body

chemical that has been shown to worsen the clinical course of MS usually accompany viral infections. It is possible that the immune response to viral infections may themselves precipitate an MS attack.

Genetics

Increasing scientific evidence of O. G. Segurado, A. Corel and A. Arnaiz (1994) suggests that genetics may play a role in determining a person's susceptibility to MS but it is unclear whether this is due mostly to genetic or environmental factors. In the population at large, the chance of developing MS is less than a tenth of one percent. However, if one person in a family has MS, that person's first-degree relatives have a one to three percent chance of getting the disease. For identical twins, the likelihood that the second twin may develop MS if the first twin does is about 30 percent; for fraternal twins (who do not inherit identical gene pools), the likelihood is closer to that for non-twin siblings, or about 4 percent. The fact that the rate for identical twins both developing MS is significantly less than 100 percent suggests that the disease is not entirely genetically controlled. Some of this effect may be due to shared exposure to something in the environment, or to the fact that some people with MS lesions remain essentially asymptomatic throughout their lives.

Further indications that more than one gene is involved in MS susceptibility comes from studies of families in which more than one member has MS. Several research teams found that people with MS inherit certain regions on individual genes more frequently than people without MS. The studies strengthen the theory that MS is the result of a number of factors rather than a single gene or other agent. Development of MS

is likely to be influenced by the interactions of a number of genes, each of which (individually) has only a modest effect.

Cognitive Impairment and MS

Huang, J. C. (Internet paper) suggests that cognition[8] as another word for thinking. He also writes in an Internet article that impairment of cognitive functions can occur as a result of brain disease or damage. Conditions that frequently cause impairments of cognition include Alzheimer's disease, head trauma, and stroke. MS can also affect the way the mind works and, in particular, how the brain performs cognitive tasks. Approximately one-half of persons with MS experience some degree of cognitive impairment. Of the MS patients with cognitive dysfunction, most (80 percent) exhibit relatively mild symptoms such as difficulties remembering lists of food items to buy in the supermarket or performing tasks in distracting environments. The remaining 20 percent experience more serious cognitive problems that may interfere with their ability to work and engage in everyday activities such as cooking and driving.

Many factors can cause cognitive impairment. Stress, anxiety, and depression can decrease our ability to remember, pay attention, and solve problems. Similar impairments can occur as a side effect of some types of medications. We are also quite aware that our ability to pay attention and retrieve information declines as we get older. In MS, the cause of cognitive dysfunction is directly related to changes that occur in the brain, lesions, in the white matter of the brain. Research has shown that the degree and type of cognitive impairment observed in MS patients is related to the amount and location of the lesions in the brain. Thus patients with a small number of lesions may not experience any

[8] It includes many different functions, including our abilities to pay attention, learn and remember information, solve problems, and use language to express our ideas.

cognitive dysfunction, whereas persons with a large number of lesions are at high risk for experiencing cognitive problems.

Psychosocial Factors in MS and the Role of Stress

Nicholas G. La Rocca (1984) recognizes that Hans Selye was largely responsible for the development of the modern concept of stress. He conceived of stress as any phenomenon leading to what he termed the general adaptation syndrome (GAS). The GAS is the body's way of adapting to a stressor. Three phases occur in the GAS: alarm, resistance, and exhaustion. If the GAS proves ineffective, a generalized susceptibility to illness may ensue. This susceptibility operates in concert with other etiological factors such as genetic predispositions, diet, exposure to viral agents, etc. Selye's seminal notion of the importance of physical and chemical stressors has been expanded to include the role of psychosocial phenomena as precipitants of the GAS. The scientific literature on stress and MS uses the term stress in at least two ways.

First, the term stress sometime refers to any set of circumstances that entails change or readjustment in the individual's life pattern, stressful life events. The second type of stress might not be the result of discrete events and might not involve any change or readjustment in a person's routine. This type of stress, chronic stress, includes such things as commuting every day in heavy traffic or social isolation it bring Selye's general adaptation syndrome. In addition, life events (e.g., a serious illness) can lead to chronic stress (e.g., difficulty in getting around).

La Rocca said that Charcot, who gave MS its name, observed that grief or anger might precipitate the disease. Certain of the symptoms of hysteria (e.g., paresthesias[9],

[9] Numbness of the extremities.

visual loss, difficulty walking, and lassitude) resemble MS so closely that the two disorders were frequently confused.

During the first part of the twentieth century, two schools of thought arose concerning the role of psychosocial factors in MS. The one most prominent in the United States held that certain personality types were MS-prone in the face of emotional stress (stress-illness model; stress leads to illness). The contrasting school of thought, more prominent in Europe, held that the psychological abnormalities seen in MS were either direct effects of the disease or were reactions to the realities of the illness (illness-stress model; illness leads to stress).

Controlled studies using standardized measures of personality failed to identify a cluster of traits common to MS patients. As a result, the notion of the MS-prone personality fell into disfavor and stress came to be regarded as only one of many possible precipitants of the illness. The stress-illness model of MS has thus evolved from the identification of MS with hysteria to the modern concept of stress as a possible precipitant of disease activity in those individuals predisposed, not by personality, but by exposure to a biological agent.

In modern times, stress-illness research in MS has pursued three main hypotheses:

(1) stress precipitates the onset of MS.

(2) stress triggers exacerbations and or hastens progression.

(3) stress transiently (for a few hours) worsens symptoms.

La Rocca also said that Brickner and Simons concluded that although emotional stress might sometimes provoke attacks, it could not be regarded as causing the disease. Pratt compared the case histories of 100 MS patients and 100 patients with other

neurological problems. The relationship between stress and onset or relapses of MS did not prove to be significant.

He found in work underway at Albert Einstein Hospital, medical anthropologist Dr.Louise Duval has been finding that the most significant sources of stress for people with MS are not the well-studied life events, but rather the everyday problems and uncertainties that are a part of any chronic disabling illness. The role of stress in inmunoregulatory deficit of cell-mediated immune response remains unexplored territory in MS.

The most accurate model may be one that views stress as both an antecedent and a consequence of illness. Although the etiology of MS remains unclear, the immune response is clearly involved in pathogenesis. Stress is known to have significant effects on the immune system, including powerful immunosuppressant effects. Three conclusions are evident:

(1) multiple sclerosis is a continuing source of stress,

(2) stress affects the immune system,

(3) the immune system is clearly involved in MS.

Neuropsychological Findings

Lindsay Vowels and G. R. Gates (1984) found that changes in intellectual performance and personality function have been reported in MS patients for at least 100 years: psychomotor impairment, memory deterioration, depression and euphoria have been among the most frequent problems noted. Many of these changes have been regarded as psychological reactions to the effects of physical disability or to alteration in

social circumstances as a result of the disease, or as an affective response to having an incurable illness.

Little attention has been paid to the possible role that actual deterioration in the (CNS) might play in psychological changes accompanying the disease. Although many of the cognitive and behavioral abnormalities, which have been reported as "common" in MS, resemble the changes that occur with lesions in the frontal lobes, no study has examined the possible association of psychological changes in MS patients and organic impairment of the front regions.

An investigation carried out by Lindsay Vowels and G. R. Gates of frontal lobe function in a group of 100 MS patients using neuropsychological tests sensitive to frontal-lobe impairment revealed deficits in the performance of MS patients when compared to that of a matched control group. Deficits observed in MS patients were only poorly correlated with duration of illness, age of patient, and severity of physical disability. The study suggested that the alteration of cognitive abilities and affective function in the MS group is due to organic deterioration of the frontal lobes as a result of the disease process, rather than to affective reaction to the disease. Frontal-lobe impairment may be a more frequent problem in MS than has been recognized previously, and may contribute significantly to the substantial problems of adjustment, new learning and rehabilitation experienced by many MS patients.

The earliest descriptions of the psychological characteristics of MS reveal that changes in mental function were a common feature of the disease. While many of the changes in behavior and intellect in MS, such as poor motivation, irritability, poor concentration, lack of insight, preservative behavior, euphoria, and poor planning, seem

to have no common causal explanation, such changes are frequently associated with frontal-lobe impairment.

The cerebral demyelization and plaque formation of MS, especially in the frontal lobes of MS patients, may be at least partially responsible for any of the intellectual, affective, and behavioral disturbances found in MS patients. It may help to explain, for example, behavioral difficulties as diverse as inability to track a moving target properly, or euphoria.

"Frontal-lobe syndrome" describes a variety of intellectual deficits, personality changes and behavioral abnormalities found in patients with lesions of the frontal lobes and have been described by many neurophysiologists. Intellectual changes are characterized by impairment in memory and ability for new learning, decline of the capacity to plan and organize reduction in flexibility of thinking and attitude, and deterioration in the ability to analyze and solve problems. Personality changes and behavioral abnormalities may include impairment of self control, concentration and arousal; emotional liability; lack of insight and self-evaluation; increase in perseveration; rigidity of attitude and insensitivity to the needs and viewpoints of others; failure to benefit by experience; and inability to adapt to new situations.

The severity of each deficit varies considerably, depending on the site and extent of the underlying pathology, the age and pre-morbid status of the individual, and the conditions under which the behaviors are observed.

The periventricular regions surrounding the anterior horn of the lateral ventricles and the anterior aspects of the third ventricle are among the sites of demyelization lesions in many MS cases. Lesions in these areas may have interruptive effects on a number of

important associative tracts connecting the frontal cortex with the basal ganglia and other cortical sub-cortical areas. Neuropsychological evidence suggests that disruption to these tracts results in significant impairment of cognitive functions in the manner of other "disconnection" lesions. In the case of MS patients, the frontal lobes could be functionally disconnected, leaving the rest of the brain without the superodinate, master control of the frontal lobes.

Three main cognitive deficits are apparent in the score of the MS patients investigated here. Of these deficits, memory impairment is the most common. It was the experience of one of the authors, in the testing of over 300 MS patients, that some degree of memory impairment is common, and may be an early diagnostic feature of the disease, rather than a late or end-stage characteristic of the disorder.

The second most common cognitive problem seen in the MS patients relate to frontal-lobe impairment. Almost one-third of the MS patients displayed a marked deficit in all tests requiring planning, organization, utilization of feedback, and problem solving. These patients also showed significant memory impairment and flattening of affect. In addition to this group, almost one-half of the patients showed signs of moderate impairment in the same test, although only half of these patients had memory problems and/or flattening of affective reaction.

The third problem observed in the MS group was that of psychomotor impairment on all tests of performance requiring speed and fine motor coordination. The relative contribution of poor motor capacity to poor test performance is difficult to judge; however, because other non-neurological disabled control groups have performed on similar tests, very much like the normal control group, poor motor capacity itself may not

be a major contributor to many of the deficits observed in MS patients. The fact that MS patients do poorly on test of frontal-lobe function not requiring skilful manipulation would suggest that motor deficit is not as important a determinant of poor test performance as the literature implies, although its influence cannot be completely ruled out.

One shortcoming of the authors' study was that there was no anatomical evidence of lesions or plaques in the frontal lobes of the patients to substantiate the claim that poor performance on tests known to be sensitive to frontal function actually is correlated with frontal lesions.

The MS population would appear to contain a significant number of individuals who are unable to or have difficulty in learning new skills, and in benefiting from training. They tend to make the same errors over and over again, and to forget material previously learned. This deterioration occurs at a time when they are also experiencing changes in their physical status, such as loss of muscle power and bladder function, as well as a change in body image and life-style. Many of these changes require some new learning: a new splint, a new pattern of compensatory walking, a new day program to attend, a new household to adapt to. Although these changes are usually carefully tailored to the physical "needs" of the person, frequently no account is taken of the new learning requirements of the change. If an MS patient has frontal-lobe impairment, he may have great difficulty adapting to the new situation.

The erroneous assumption that MS affects only physical functions, but spares personality and cognitive abilities, is a view publicized by the popular press and some of the scientific literature. Therefore, family members and hospital staff may blame the MS

sufferer himself for uncooperative or selfish behavior, rather than attributing such behaviors to the underlying organic cause.

Another important aspect of the study described here was the finding that MS patients do not comprise a uniform group of individuals with the same problems. Intellectual deterioration was not seen in all patients and examination of the relationship between age, severity of physical disability and duration of illness showed that these factors were not good predictors of cognitive impairment. In view of the wide range of disabilities shown by patients and differences in mode of expression of the disease, some consideration should be given to the view that MS neuron-anatomic evidence suggest that there are different forms of the disease. Moreover, multiviral causes have been proposed and may explain these differences.

The study also showed that a very substantial percentage of MS patients show signs of intellectual and behavioral deterioration consistent with damage to the frontal lobes. On the other hand, some MS patients may remain mentally intact, and although showing signs of depression or anxiety, are at least cognitively more amenable to effective individual rehabilitation programs.

Chapter 3 **Materials, methods, results and discussion**

Introduction for the Chapter 3

To investigate the possible factors that contribute to the incidence of MS in PR a representative sample of a group of people in PR were selected, consisting of patients with the condition of MS and first-degree family members preferably that don't suffer the condition of MS. A questionnaire was developed to determine the relevant factors that are responsible for the cases in PR based on literature review.

The number of questionnaires received were tabulated and Logistic Regression (LR) was used to analyze the results to find the best fitting and most reasonable model that describe the relationship between the outcome (dependent or response variable; if the person has MS or not, variable X1) and set of independent (predictor or explanatory; variables represented by the responses to questions in the questionnaires) variables. The outcome variable in LR is binary or dichotomous so the binomial distribution describes the distribution of the errors and will be the statistical distribution upon which the analysis is based.

According to Hosmer, Jr. and Lemeshow (1989) in the LR the key quantity is the mean value of the outcome variable (X1), given the value of the independent variable. This quantity is called the conditional mean and is expressed as E (Y|x) where Y denoted the outcome variable and x denoted a value of the independent variable. With the study of binary dichotomous data the conditional mean must be greater than or equal to zero and less than or equal to one [0≤ E (Y|x) ≤1], the conditional mean of the regression equation must be formulated to be bounded between 0 and 1. They recommend that any variable whose univariate test has a p-value less than 0.25 should be considered as a candidate for

the multivariate model along with all variables known to be biologically important. Use of the 0.25 level as screening criterion for selection of candidate variables is based on the work by Bendel and Afifi (1977) on Linear Regression. These authors show that use of more traditional level such as 0.05 often fails to identify predictors known to be important.

To satisfy this constraint the conditional mean for the LR model would be as follows:

$$\pi(x) = "E(Y|x)" = \frac{e^{\beta_0 + \beta_1 x}}{1 + e^{\beta_0 + \beta_1 x}} \qquad (1.1)$$

A transformation of $\pi(x)$ or logit transformation is defined as:

$$g(x) = \ln\left[\frac{(\pi(x))}{1 - \pi(x)}\right] = \beta_0 + \beta_1(x) \qquad (1.2)$$

This transformation of g(x) gives many of the desirable properties of a linear regression model. The logit, g(x) is linear in its parameters, may be continuous, and can range from $-\infty$ to $+\infty$, depending on the range of x.

The value of the outcome variable given x is $y = \pi(x) + \varepsilon$. The quantity ε may assume one of two possible values. If y =1 then $\varepsilon = 1 - \pi(x)$ with probability $\pi(x)$, and if y = 0 then $\varepsilon = -\pi(x)$ with probability $1 - \pi(x)$. Thus, ε has a distribution with mean zero and variance equal to $\pi(x)(1 - \pi(x))$. That is, the conditional distribution of the outcome variable follows a Bernoulli distribution with probability given by the conditional mean, $\pi(x)$.

Materials, methods, results and discussion

For the methodology to validate the questionnaires[10], they were handed three times to small groups of 10 to 15 people in which they had the opportunity to contribute to develop the final questionnaire for the study. They were able to request, to argue, dispute and discuss the questions asked in each questionnaire version and in what form these were formulated. Once the questionnaire was validated, it was distributed to a selected group and the data recollected was analyzed.

Using Minitab, Excel, and Splus the following procedure was followed. By the nature of the questionnaire it was divided in two groups. The first questions (2 to 8) were directed and examined for the individuals with MS (patients with the condition of MS) and the other questions included the whole group (patients with the condition of MS and their relative[11]).

I. First group of data (patients with the condition of MS)

A. Using Minitab and Excel different types of graphs for each question were made;

1. Question #2 was related to age when symptoms first appeared.

[10] Letters and questionnaires used appear in Appendices A and B respectively.
[11] Preferably without the condition of MS.

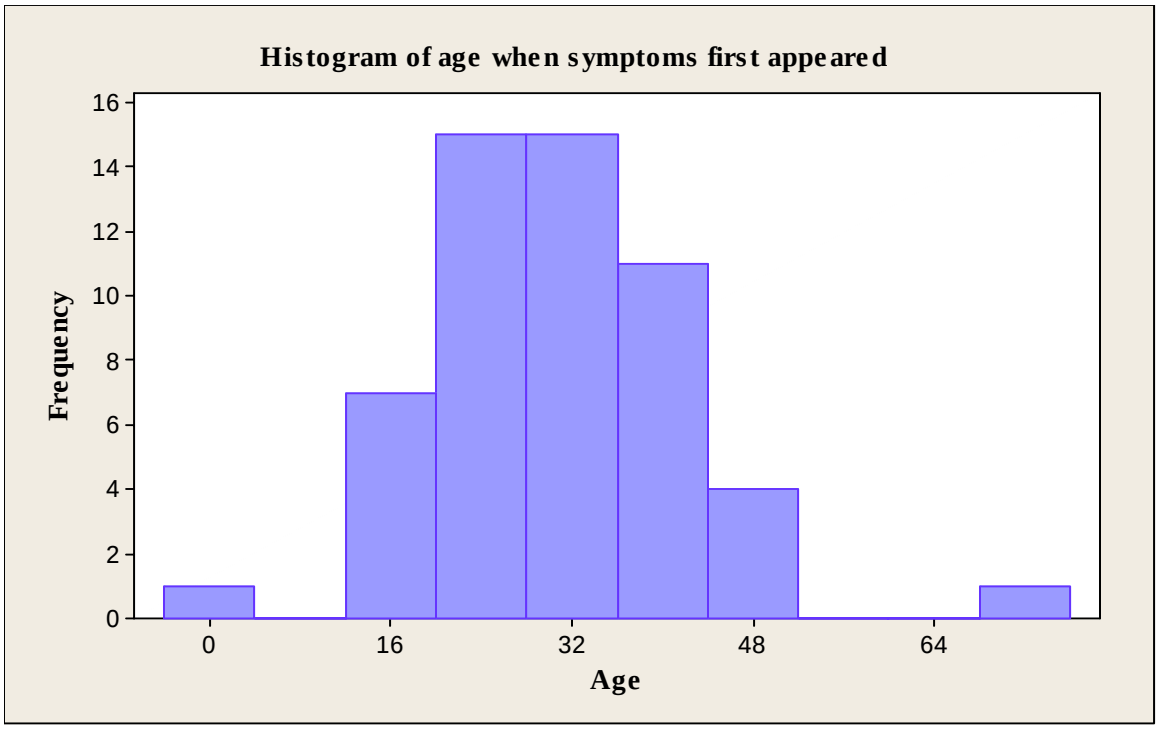

Figure 3.1: Histogram of age when symptoms first appeared.

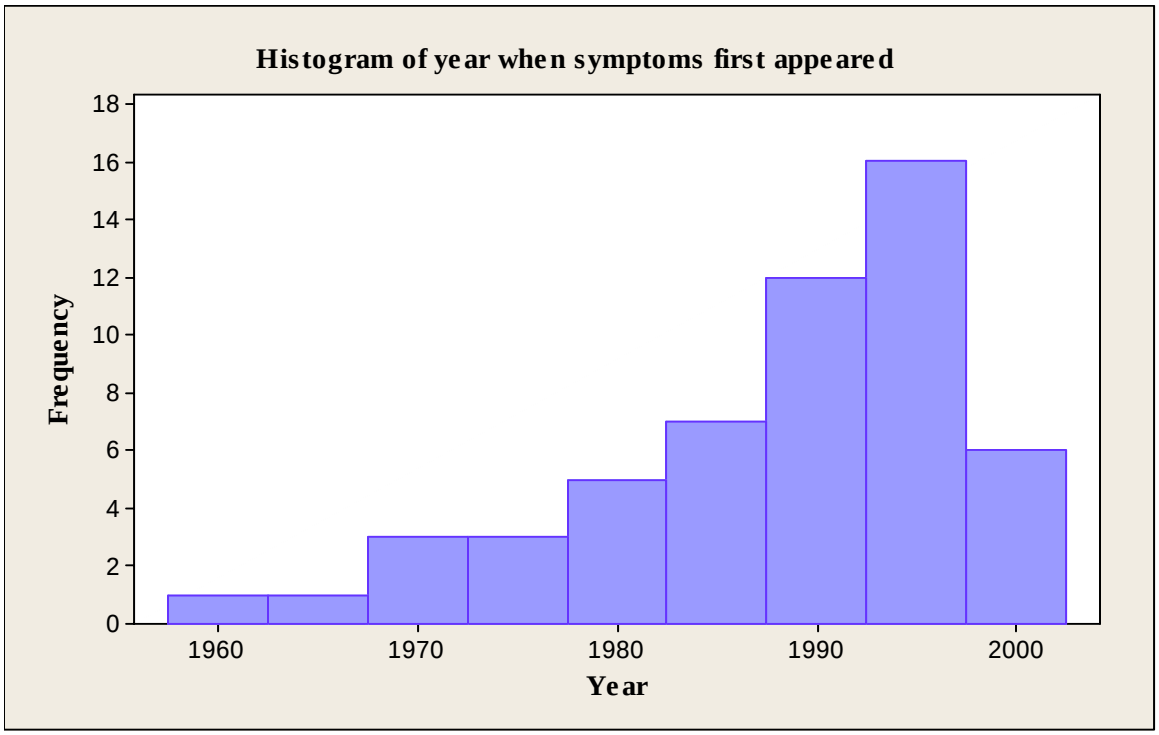

Figure 3.2: Histogram of year when symptoms first appeared.

2. Question #3 was related when symptoms were diagnosed.

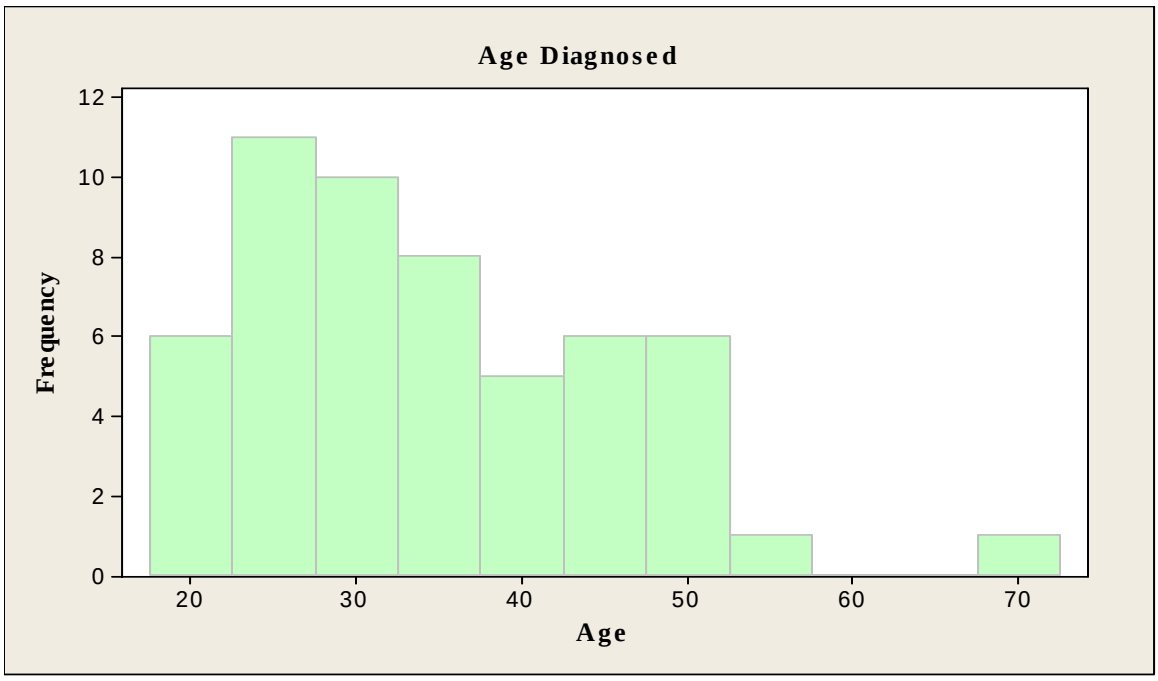

Figure 3.3: Histogram of the Age diagnosed.

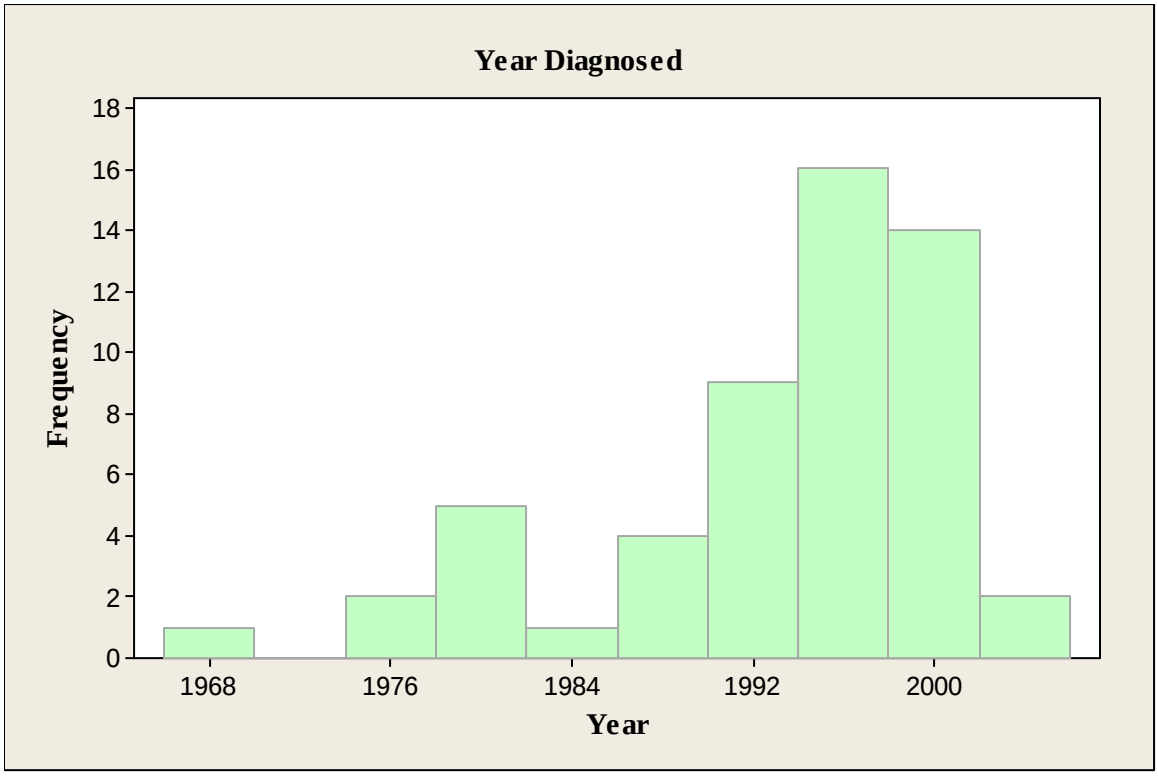

Figure 3.4: Histogram of the year diagnosed

This is congruent with what is said in the literature that most people experience their first symptoms of MS between the ages of 20 and 40, but a diagnosis is often delayed. This is due to both the transitory nature of the disease and the lack of a specific diagnostic test - specific symptoms and changes in the brain must develop before the diagnosis is confirmed, also you can see cases of MS in young and elderly adults beginning before age 20 and after age 40.

3. Question #4 was concern with how much time is between exacerbations.

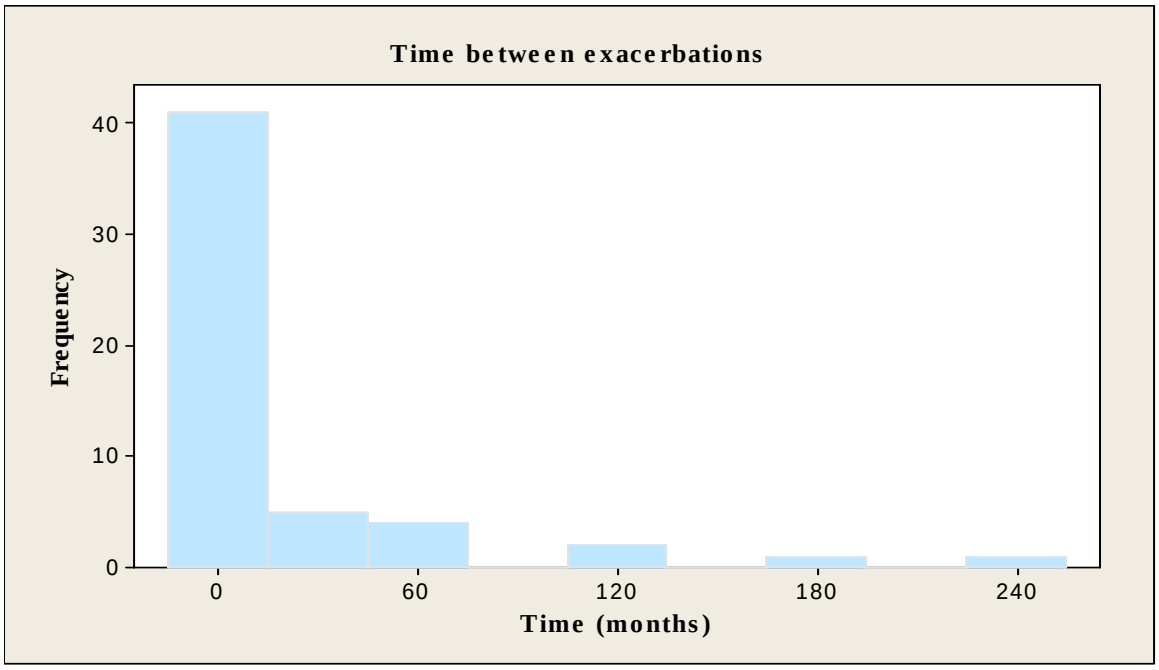

Figure 3.5: Histogram of the Time between exacerbations.

There is really no evidence on how much time has to lapse between exacerbations, only that it will dependent on how well the patients are taking care of themselves (treatments and common sense). Only the course relapsing-remitting is characterized by one or two flare-ups every one to three years followed by periods of remission.

4. Question #5 deals with if a stress event or change in life happened or not before the patient was diagnosed with the condition of MS.

As can be seen in the Figure 3.6 stress was has the largest percentage but if we see carefully all the variables are sources of stress in one way or another. It would be great to be able to determine how much stress can be caused by each variable (to have a scale of stress). This could be something to look in futures studies.

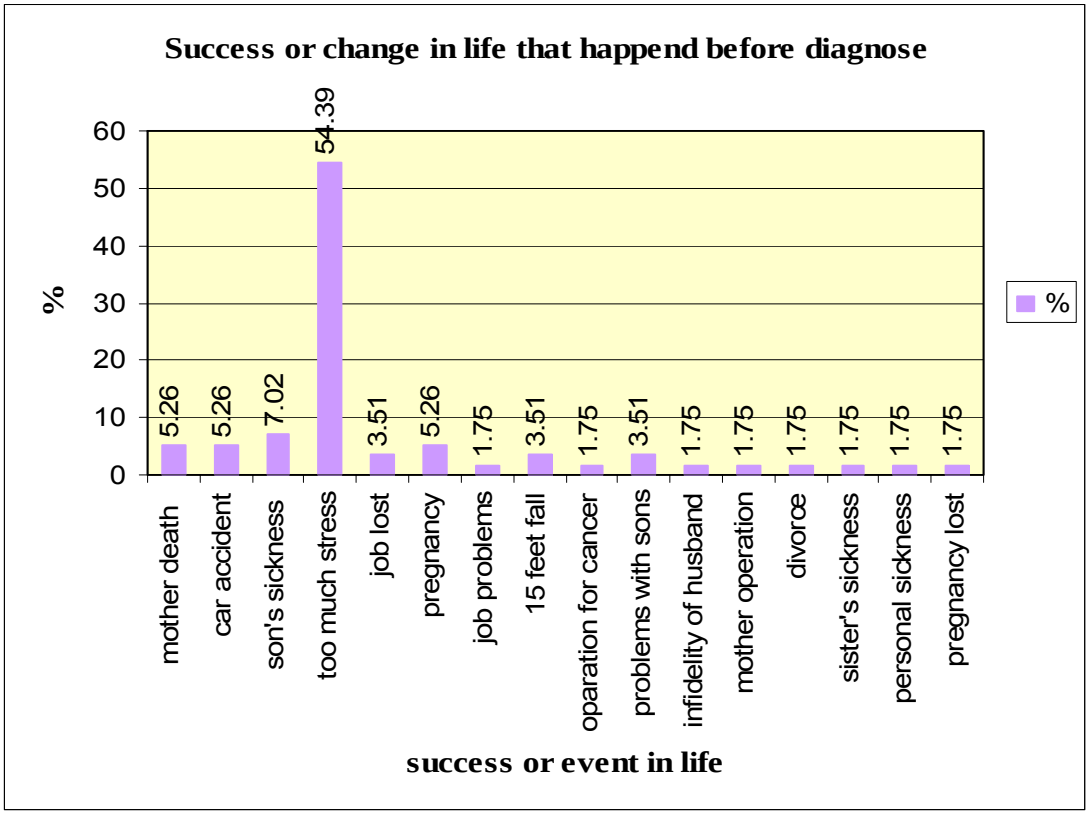

Figure 3.6: Success or change in life that happened before diagnose.

5. Question #6 was related with different kinds of symptoms that the patients with the condition of MS suffered.

As can be seen in Figure 3.7[12] symptoms found in the patients may be mild but have a duration that can affect daily life. The initial symptoms of MS were: numbness (16) sensations, imbalance (9), fatigue (7), sensation loss (11), double vision (22), and other symptoms that can cause difficulty in walking.

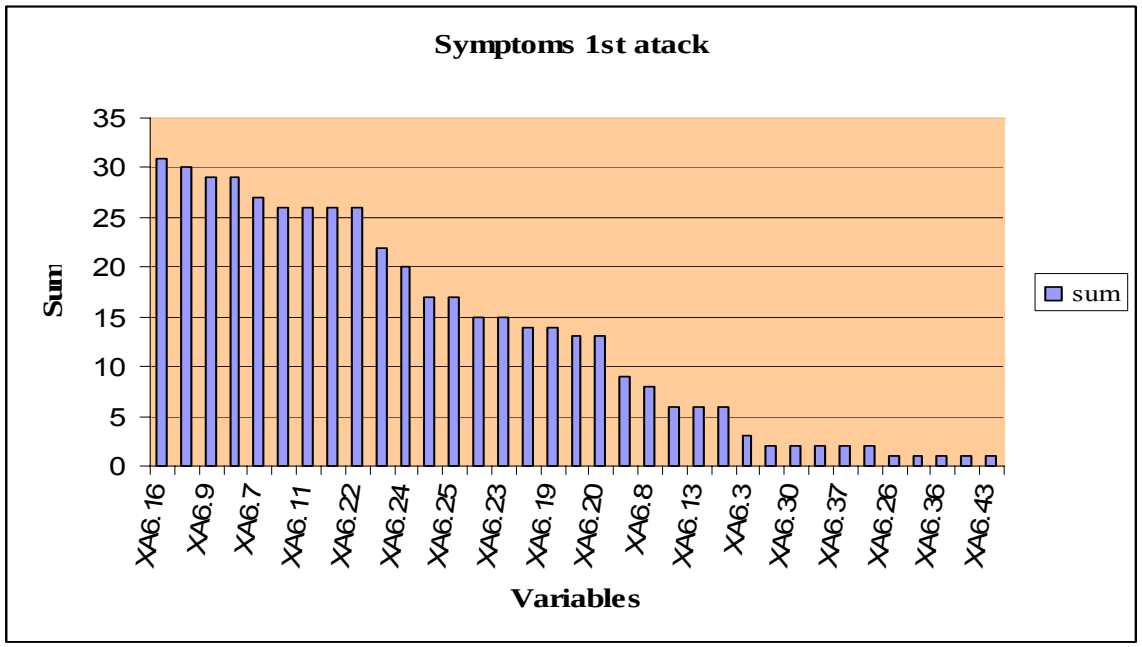

Figure 3.7: Symptoms 1st attack

[12] Kinds of symptoms that the patients with the condition of MS suffered will appear in Appendix C (table C.1) for the figures 3.7-3.9 and also will appear in descending order (table C.2).

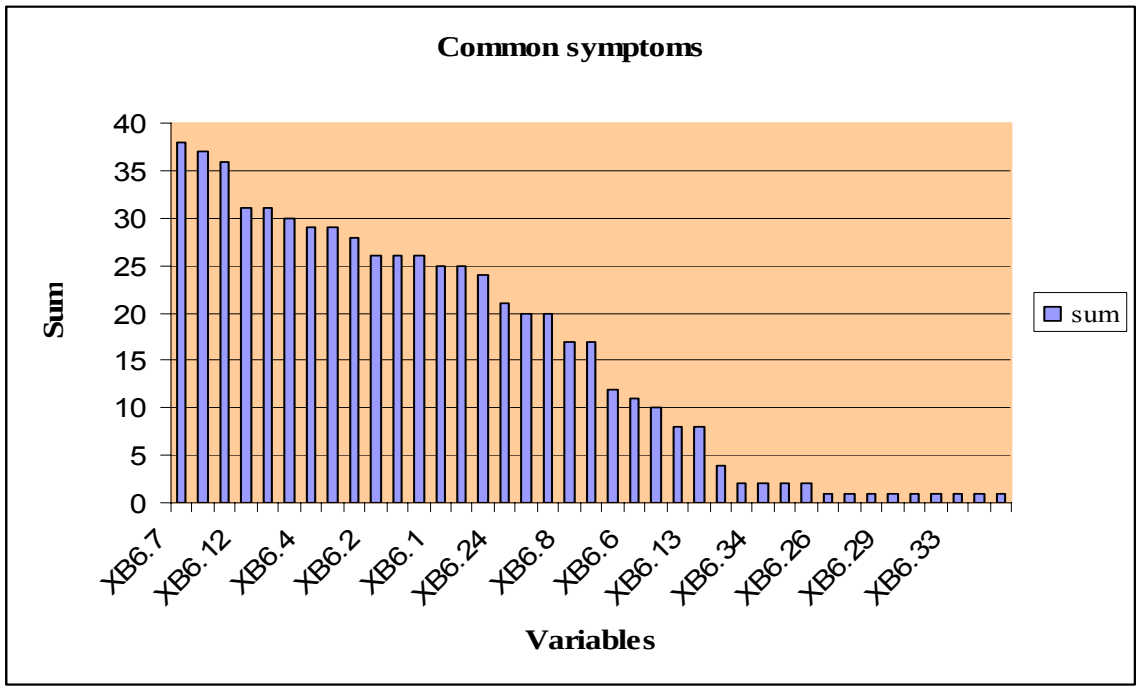

Figure 3.8: Common symptoms.

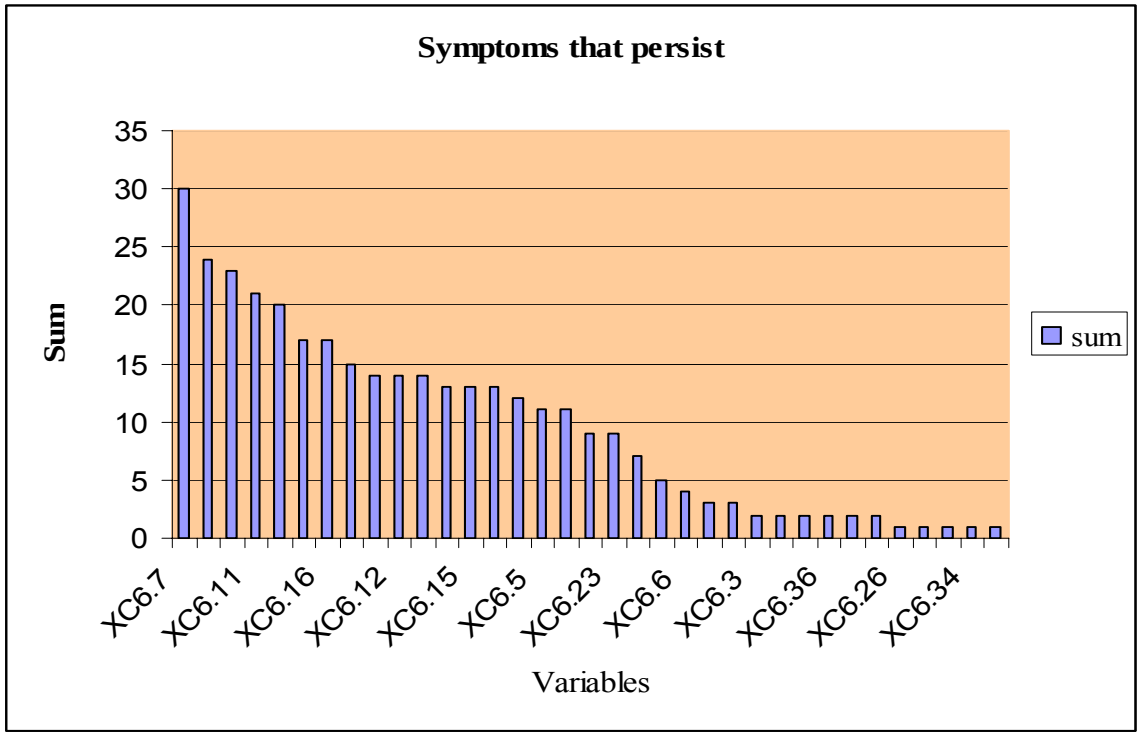

Figure 3.9: Symptoms that persist.

Complete or partial remission of the symptoms, especially in the early stages of the disease, will cause that a specific symptom will reappear again (common and persistent symptoms): fatigue or tiredness (7), imbalance (9), weakness in extremities (10).

6. Question #7 was concerned with the course of MS that the person has.

As can be seen from the Figure 3.10[13] below many people do not know the course of their condition, which can be of great importance in how well they can take care of themselves and which treatment is best for them. Relapsing-Remitting is the must common course of MS, but unfortunately, at least half of patients will enter a stage of continuous deterioration or the course of secondary progressive. What was found for the progressive relapsing was rare because it is not supposed to be that common (less than 5%).

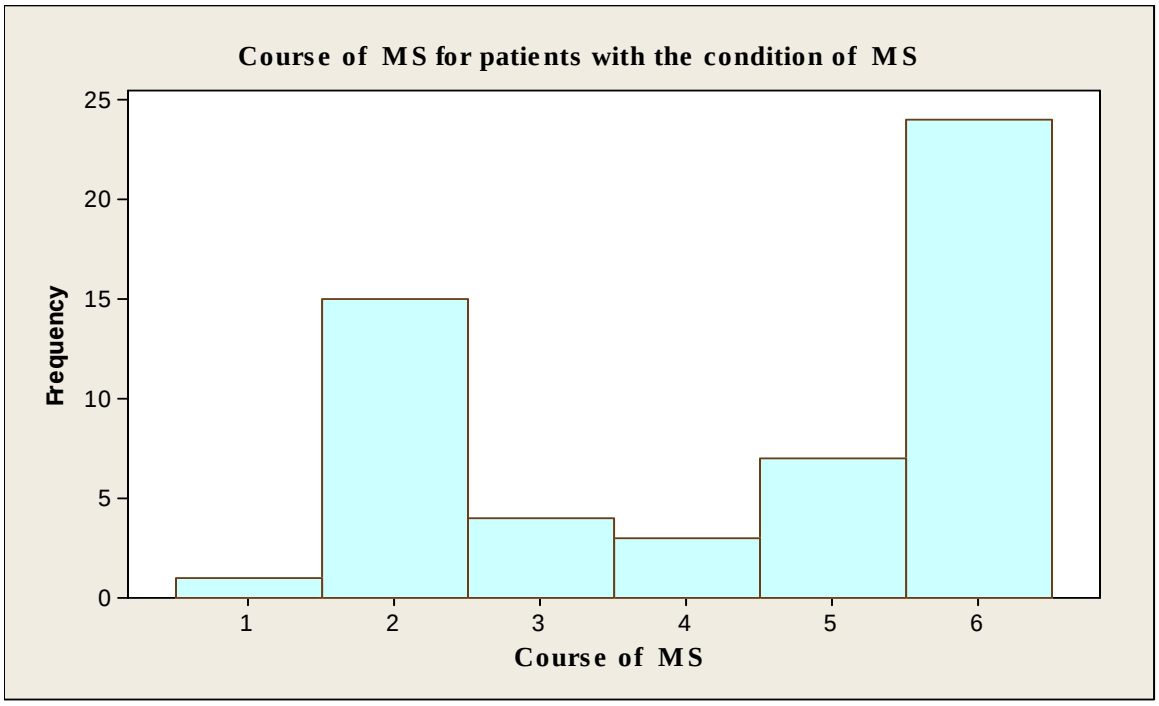

Figure 3.10: Histogram of the course of MS.

[13] Legend for the Figure 3.10; 1=benign, 2=relapsing-remitting, 3=primary progressive, 4=secondary progressive, 5= progressive relapsing, 6=don't know.

7. Question #8 deals with the methods used to diagnose a person with the condition of MS.

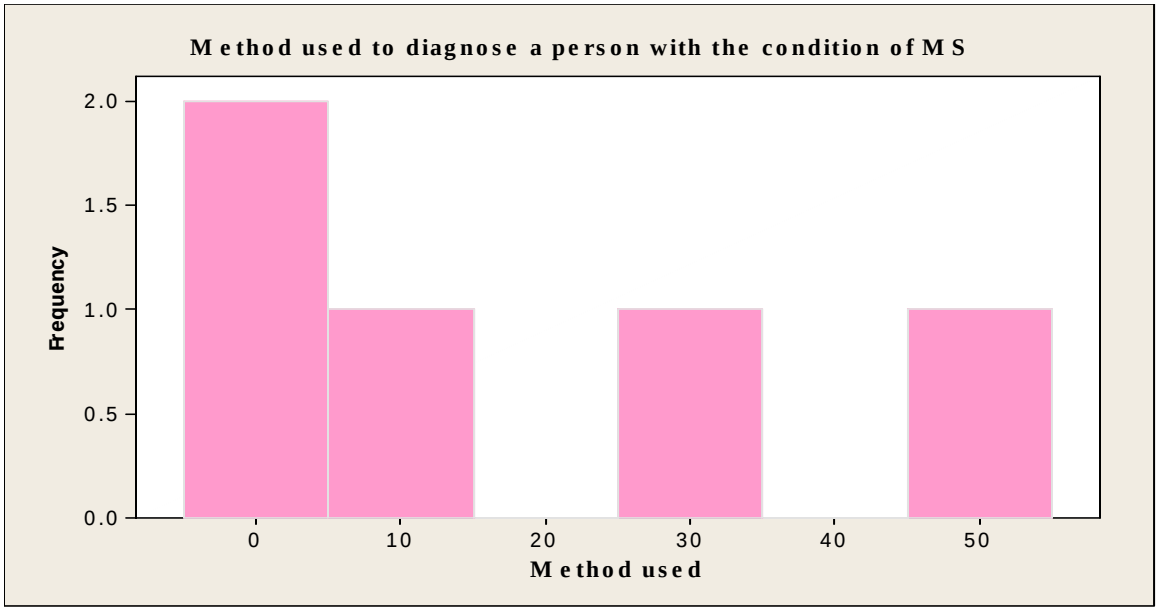

Figure 3.11: Histogram with Method used for diagnosing a person with MS.

The MRI was the must frequently used.

II. Second group of data (patients of MS and their relatives)

A. Using a $Z_{0.025} = 1.96$ a correlation (r) was calculated, then the initial list of candidate variables were selected by computing correlations with the dependent variables using Splus. Many variables in the questionnaire did not get responses with different values so they were excluded from the analysis.

$$n := 142 \qquad Z := \left[\left(\frac{\sqrt{n-3}}{2}\right)\cdot\left[\ln\left[\frac{(1+r)}{1-r}\right]\right]\right] \qquad Z := 1.96$$

$$r := \left|\frac{\left[\left[e^{\left[\frac{(2\cdot Z)}{\sqrt{(n-3)}}\right]}\right]-1\right]}{\left[\left[e^{\left[\frac{(2\cdot Z)}{\sqrt{(n-3)}}\right]}\right]+1\right]}\right| \qquad r = 0.165$$

Using this mathematical formula the number of predictor variables was reduced to 70 variables as shown in the table in Appendix D (table D.1).

B. Similarly when Binary Logistic Regression *(BLR)* was run with individual predictor variables and Minitab indicated too few variables differed (little variation in predictor cases), such variables were also eliminated from the analysis. Later on the predictors were reduced to 22 variables as shown in the Table E.1 in Appendix E. After discussing with Dr. Pérez[14] the importance of the variables, using Minitab in the BLR option the data was carefully analyzed, using the following procedure each time a *p*-value was used to eliminate several variables.

The following output was generated by Minitab:

Table 3.1: First Minitab® output, with 22 predictor variable

						95% CI	
Predictor	Coef	SE Coef	Z	P	Odds Ratio	Lower	Upper
Constant	-4.11545	2.14817	-1.92	0.055			
X9	0.143976	0.0612640	2.35	0.019	1.15	1.02	1.30
X10	0.0950703	1.19549	0.08	0.937	1.10	0.11	11.45
XB13.2	-0.0013573	0.0274722	-0.05	0.961	1.00	0.95	1.05
XC13.2	0.131504	0.0950153	1.38	0.166	1.14	0.95	1.37
XA16.2	-6.36312	2.97335	-2.14	0.032	0.00	0.00	0.59
XA16.21	-90.6956	707107	-0.00	1.000	0.00	0.00	*
XB16.1	-4.54319	1.74248	-2.61	0.009	0.01	0.00	0.32
XC16.17	-93.2341	577350	-0.00	1.000	0.00	0.00	*
XD16.19	1.67544	1.69757	0.99	0.324	5.34	0.19	148.81
XE16.1	-6.13107	1.75472	-3.49	0.000	0.00	0.00	0.07
XE16.11	-1.14370	1.56340	-0.73	0.464	0.32	0.01	6.82
XE16.20	-3.95626	1.76947	-2.24	0.025	0.02	0.00	0.61
XF16.12	-82.2436	632456	-0.00	1.000	0.00	0.00	*
XF16.41	-66.4882	774597	-0.00	1.000	0.00	0.00	*
XG16.16	99.2756	707107	0.00	1.000	1.30277E+43	0.00	*
XG16.19	-5.92044	12.0287	-0.49	0.623	0.00	0.00	46539634.81
XH16.1	-16.1775	6.06035	-2.67	0.008	0.00	0.00	0.01
XI16.1	-108.448	707107	-0.00	**1.000**	0.00	0.00	*
XI16.19	2.68117	2.19482	1.22	0.222	14.60	0.20	1078.18
XI16.20	-0.864163	2.37020	-0.36	**0.715**	0.42	0.00	43.88
X17.4	1.53749	1.80127	0.85	0.393	4.65	0.14	158.85
X18.1	0.216626	0.107548	2.01	0.044	1.24	1.01	1.53

Log-Likelihood = -20.008
Test that all slopes are zero: G = 105.307, DF = 22, P-Value = 0.000

[14] The predictors not medically related to MS according to Dr. Pérez are indicated in blue in Appendix E (table E.1) and underlined in Table 3.1.

```
Goodness-of-Fit Tests

Method           Chi-Square  DF      P
Pearson             68.9131  82  0.848
Deviance            40.0157  82  1.000
Hosmer-Lemeshow      9.4276   8  0.308

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs       Number  Percent  Summary Measures
Concordant    2691     97.9  Somers' D              0.96
Discordant      58      2.1  Goodman-Kruskal Gamma  0.96
Ties             1      0.0  Kendall's Tau-a        0.48
Total         2750    100.0
```

Choosing $p \geq 0.9999$, 8 predictors were eliminated as shown on Table 3.2.

Table 3.2: Second Minitab® output, with 14 predictor variable

```
                                                  Odds      95% CI
Predictor       Coef    SE Coef      Z      P  Ratio  Lower    Upper
Constant    -1.22053    1.55519  -0.78  0.433
X9         0.0574833  0.0383709   1.50  0.134   1.06   0.98     1.14
XC13.2     0.0482217  0.0629098   0.77  0.443   1.05   0.93     1.19
XA16.2      -4.18043    2.12151  -1.97  0.049   0.02   0.00     0.98
XB16.1      -4.07354    1.33718  -3.05  0.002   0.02   0.00     0.23
XD16.19     0.933116    1.62887   0.57  0.567   2.54   0.10    61.91
XE16.1      -4.04590    1.09361  -3.70  0.000   0.02   0.00     0.15
XE16.11    -0.669441    1.08849  -0.62  0.539   0.51   0.06     4.32
XE16.20     -2.23852    1.23454  -1.81  0.070   0.11   0.01     1.20
XG16.19     -3.15379    5.27447  -0.60  0.550   0.04   0.00  1318.41
XH16.1      -9.64765    3.73261  -2.58  0.010   0.00   0.00     0.10
XI16.19      2.03221    1.91509   1.06  0.289   7.63   0.18   325.64
XI16.20     0.235468    1.86148   0.13  0.899   1.27   0.03    48.62
X17.4        1.03759    1.13061   0.92  0.359   2.82   0.31    25.88
X18.1       0.134698  0.0675495   1.99  0.046   1.14   1.00     1.31

Log-Likelihood = -28.523
Test that all slopes are zero: G = 88.276, DF = 14, P-Value = 0.000

Goodness-of-Fit Tests

Method           Chi-Square  DF      P
Pearson             91.0616  89  0.419
Deviance            57.0463  89  0.997
Hosmer-Lemeshow      5.7806   8  0.672

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs       Number  Percent  Summary Measures
Concordant    2614     95.1  Somers' D              0.90
Discordant     131      4.8  Goodman-Kruskal Gamma  0.90
Ties             5      0.2  Kendall's Tau-a        0.45
Total         2750    100.0
```

Choosing $p \geq 0.50$, four predictor variables were eliminated as shown on table 3.3.

Table 3.3: Third Minitab® output, with 10 predictor variables

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	95% CI Upper
Constant	-0.906739	1.45935	-0.62	0.534			
X9	0.0486698	0.0350832	1.39	0.165	1.05	0.98	1.12
XC13.2	0.0505465	0.0613370	0.82	0.410	1.05	0.93	1.19
XA16.2	-3.98948	2.06177	-1.93	0.053	0.02	0.00	1.05
XB16.1	-4.09766	1.25555	-3.26	0.001	0.02	0.00	0.19
XE16.1	-4.08588	1.06653	-3.83	0.000	0.02	0.00	0.14
XE16.20	-2.19521	1.18643	-1.85	0.064	0.11	0.01	1.14
XH16.1	-9.06372	3.47366	-2.61	0.009	0.00	0.00	0.10
XI16.19	2.06066	1.43457	1.44	0.151	7.85	0.47	130.64
X17.4	0.937492	1.05055	0.89	0.372	2.55	0.33	20.02
X18.1	0.126445	0.0634572	1.99	0.046	1.13	1.00	1.29

Log-Likelihood = -29.095
Test that all slopes are zero: G = 87.132, DF = 10, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	87.6114	93	0.638
Deviance	58.1908	93	0.998
Hosmer-Lemeshow	3.2871	8	0.915

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	2609	94.9	Somers' D	0.90
Discordant	139	5.1	Goodman-Kruskal Gamma	0.90
Ties	2	0.1	Kendall's Tau-a	0.45
Total	2750	100.0		

Choosing $p \geq 0.40$, one predictor variable was eliminated as shown on table 3.4.

Table 3.4: Fourth Minitab® output, with 9 predictor variables

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	95% CI Upper
Constant	-0.733790	1.41411	-0.52	0.604			
X9	0.0489424	0.0341908	1.43	0.152	1.05	0.98	1.12
XA16.2	-3.97909	2.01122	-1.98	0.048	0.02	0.00	0.96
XB16.1	-4.17630	1.24632	-3.35	0.001	0.02	0.00	0.18
XE16.1	-4.05630	1.06106	-3.82	0.000	0.02	0.00	0.14
XE16.20	-1.89461	1.06924	-1.77	0.076	0.15	0.02	1.22
XH16.1	-8.90850	3.30941	-2.69	0.007	0.00	0.00	0.09
XI16.19	2.04552	1.41000	1.45	0.147	7.73	0.49	122.62
X17.4	0.863844	1.06572	0.81	0.418	2.37	0.29	19.16
X18.1	0.119011	0.0595784	2.00	0.046	1.13	1.00	1.27

Log-Likelihood = -29.454
Test that all slopes are zero: G = 86.414, DF = 9, P-Value = 0.000

```
Goodness-of-Fit Tests

Method           Chi-Square  DF      P
Pearson             75.2438  92  0.898
Deviance            58.9090  92  0.997
Hosmer-Lemeshow      5.0035   8  0.757

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs       Number  Percent  Summary Measures
Concordant    2603     94.7  Somers' D              0.89
Discordant     146      5.3  Goodman-Kruskal Gamma  0.89
Ties             1      0.0  Kendall's Tau-a        0.45
Total         2750    100.0
```

Choosing $p \geq 0.40$, one predictor variable was eliminated as shown on table 3.5

Table 3.5: Fifth Minitab® output, with 8 predictor variables

```
                                                  Odds      95% CI
Predictor          Coef    SE Coef      Z      P  Ratio  Lower   Upper
Constant       -0.514247    1.40307  -0.37  0.714
X9     age     0.0443396  0.0335378   1.32  0.186   1.05   0.98    1.12
XA16.2 Fibro  -3.96589    1.98409  -2.00  0.046   0.02   0.00    0.93
XB16.1 MS Mo  -4.20739    1.22945  -3.42  0.001   0.01   0.00    0.17
XE16.1 MS Ss  -4.05068    1.03881  -3.90  0.000   0.02   0.00    0.13
XE16.20 Alr S -1.47638   0.979708  -1.51  0.132   0.23   0.03    1.56
XH16.1 MS Dau -8.73572    3.21321  -2.72  0.007   0.00   0.00    0.09
XI16.19 Sin Sn 2.08080    1.39753   1.49  0.137   8.01   0.52  123.96
X18.1 Age vari 0.115865  0.0585625  1.98  0.048   1.12   1.00    1.26


Log-Likelihood = -30.361
Test that all slopes are zero: G = 84.602, DF = 8, P-Value = 0.000


Goodness-of-Fit Tests

Method           Chi-Square  DF      P
Pearson             76.2416  93  0.896
Deviance            60.7210  93  0.996
Hosmer-Lemeshow      3.2423   8  0.918

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs       Number  Percent  Summary Measures
Concordant    2589     94.1  Somers' D              0.88
Discordant     157      5.7  Goodman-Kruskal Gamma  0.89
Ties             4      0.1  Kendall's Tau-a        0.45
Total         2750    100.0
```

C. This last model was selected because of the Log-Likelihood and p- values were better than for the others to be manipulated more to find 6 different models.

Choosing $p \geq 0.180$, one predictor variable was eliminated as shown on table 3.6.

Table 3.6: Sixth Minitab® output, with 7 predictor variables

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	95% CI Upper
Constant	1.30766	0.492968	2.65	0.008			
XA16.2 fibromi	-3.94548	1.92754	-2.05	0.041	0.02	0.00	0.85
XB16.1 MS Moth	-4.75625	1.17149	-4.06	0.000	0.01	0.00	0.09
XE16.1 MS Sist	-3.77868	0.974007	-3.88	0.000	0.02	0.00	0.15
XE16.20 Alr Sis	-1.64780	0.987320	-1.67	0.095	0.19	0.03	1.33
XH16.1 MS Daugh	-7.46869	2.94230	-2.54	0.011	0.00	0.00	0.18
XI16.19 Sinu Son	2.54625	1.40955	1.81	0.071	12.76	0.81	202.14
X18.1 Age Varic	0.101246	0.0543522	1.86	0.062	1.11	0.99	1.23

Log-Likelihood = -31.279
Test that all slopes are zero: G = 82.764, DF = 7, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	33.7878	58	0.995
Deviance	32.0682	58	0.998
Hosmer-Lemeshow	0.9576	7	0.995

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	2557	93.0	Somers' D	0.88
Discordant	143	5.2	Goodman-Kruskal Gamma	0.89
Ties	50	1.8	Kendall's Tau-a	0.44
Total	2750	100.0		

The following figures 3.12 and 3.13 show the stratified scatter plots of Delta Betas versus leverage and predicted probability of having MS versus leverage stratified by actual MS case. The figure 3.13 shows two false negatives, four false positives, and three borderline cases (between 0.4 and 0.55) among the data.

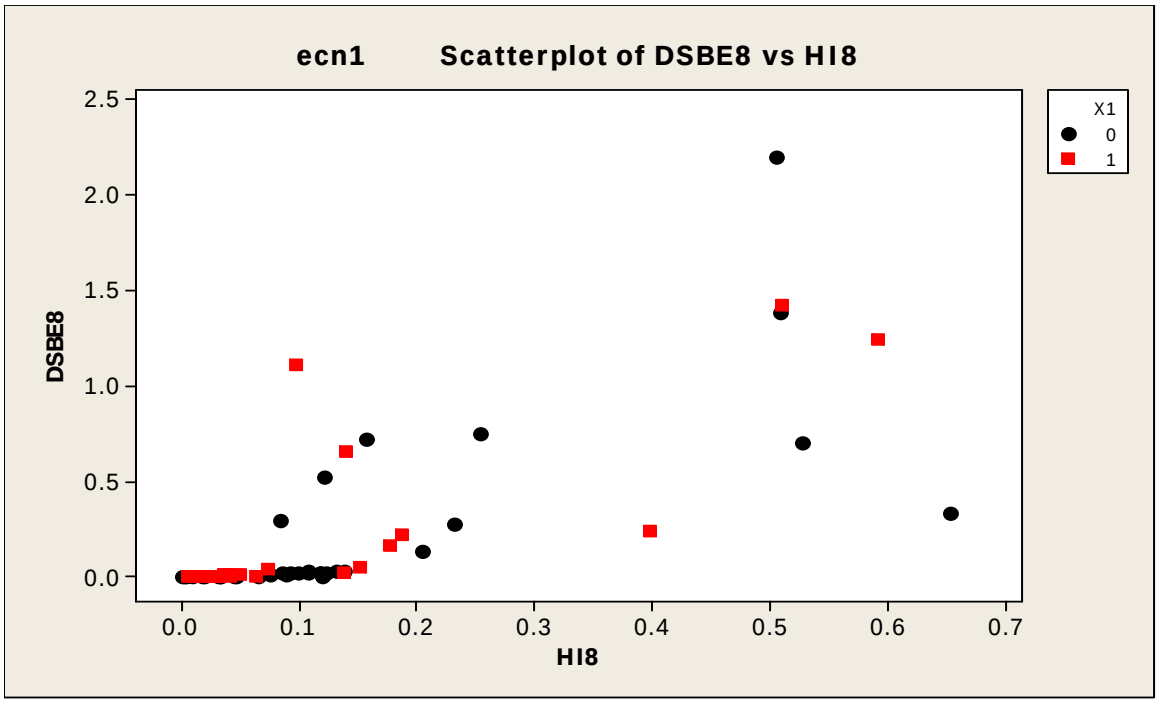

Figure 3.12: Scatterplot of equation 1 with Delta betas versus leverage.

.

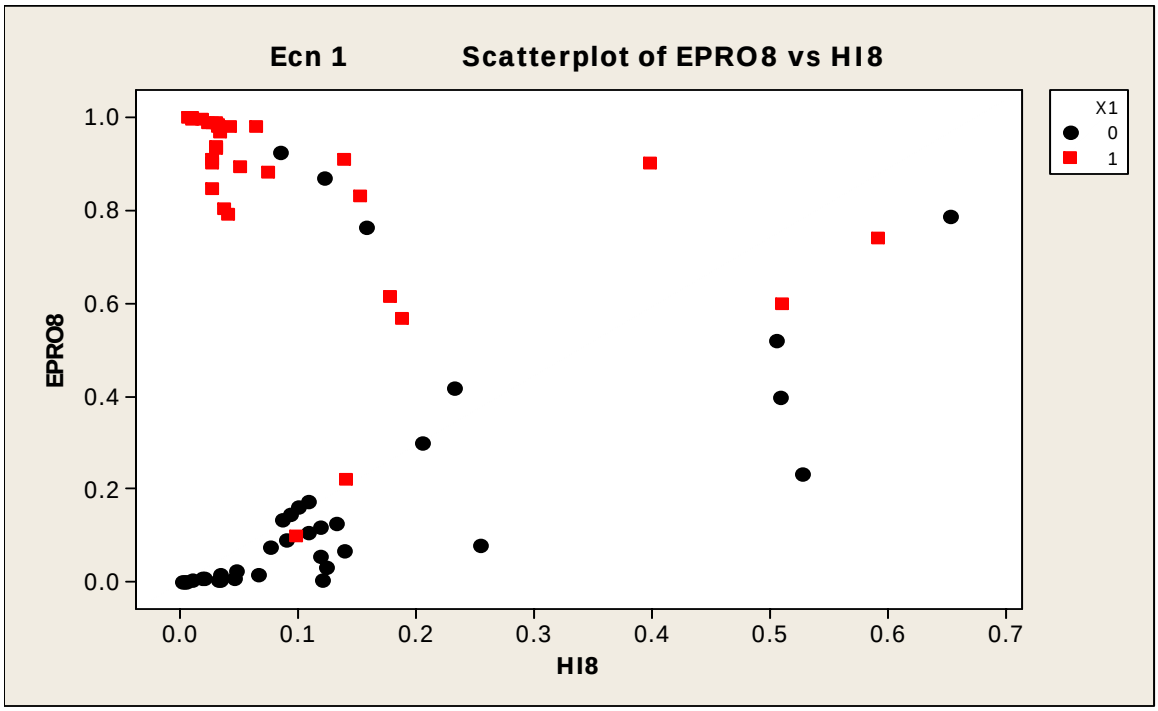

Figure 3.13: Scatterplot of equation 1 with Expected probability versus leverage.

Table 3.7: Seventh Minitab® output, with 6 predictor variables

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	95% CI Upper
Constant	1.49404	0.479346	3.12	0.002			
XA16.2	-3.79676	1.76473	-2.15	0.031	0.02	0.00	0.71
XB16.1	-4.84915	1.14318	-4.24	0.000	0.01	0.00	0.07
XE16.1	-3.58506	0.902445	-3.97	0.000	0.03	0.00	0.16
XE16.20	-1.19485	0.875555	-1.36	0.172	0.30	0.05	1.68
XH16.1	-5.98665	2.01128	-2.98	0.003	0.00	0.00	0.13
X18.1	0.0881455	0.0436904	2.02	0.044	1.09	1.00	1.19

Log-Likelihood = -33.457
Test that all slopes are zero: G = 78.408, DF = 6, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	33.5914	52	0.978
Deviance	30.7900	52	0.992
Hosmer-Lemeshow	2.5148	8	0.961

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	2513	91.4	Somers' D	0.85
Discordant	179	6.5	Goodman-Kruskal Gamma	0.87
Ties	58	2.1	Kendall's Tau-a	0.43
Total	2750	100.0		

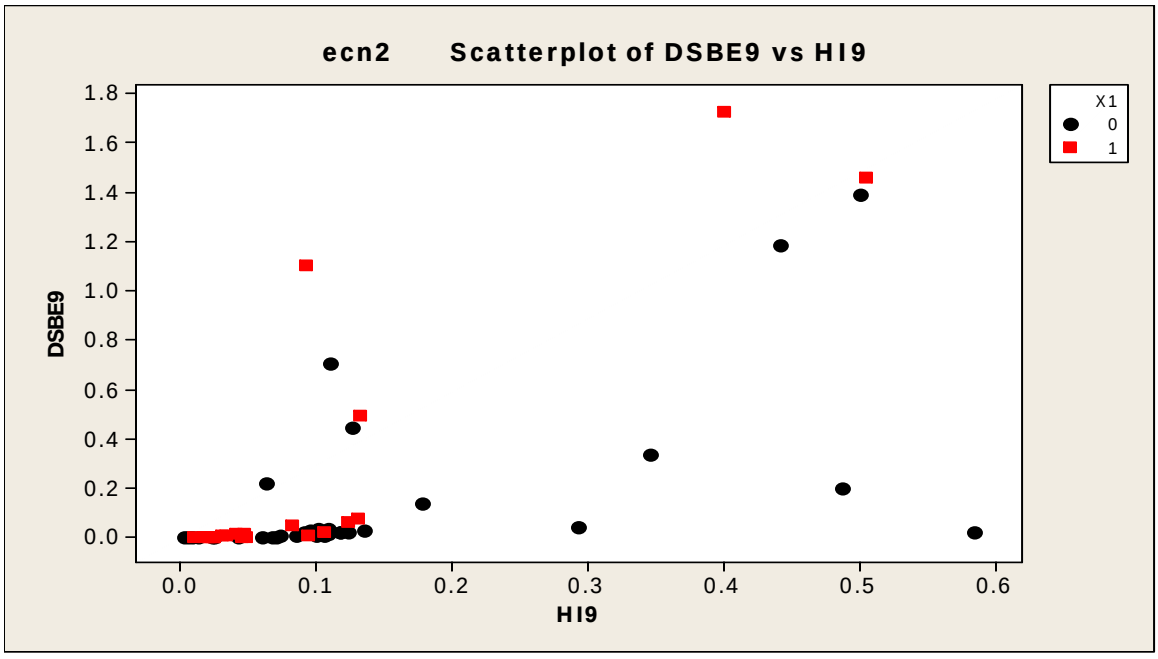

Figure 3.14: Scatterplot of equation 2 with Delta betas versus leverage.

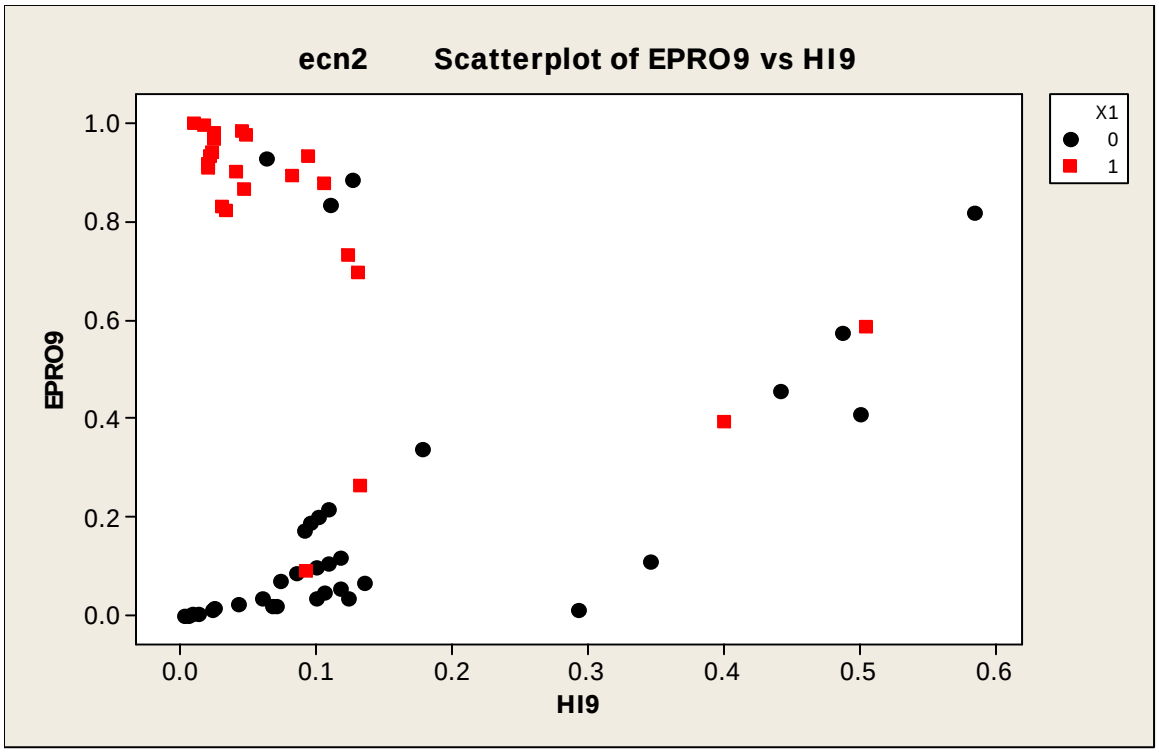

Figure 3.15: Scatterplot of equation 2 with Expected probability versus leverage.

The above figure 3.15 show three false negatives (the worst error), four false positives, and three borderline cases (one MS and two non-MS) among the original data.

Table 3.8: Eighth Minitab® output, with 7 predictor variables

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	95% CI Upper
Constant	-0.808409	1.32375	-0.61	0.541			
X9	0.0470023	0.0318424	1.48	0.140	1.05	0.98	1.12
XA16.2	-3.46673	1.85463	-1.87	0.062	0.03	0.00	1.18
XB16.1	-4.11025	1.19794	-3.43	0.001	0.02	0.00	0.17
XE16.1	-3.83162	0.978166	-3.92	0.000	0.02	0.00	0.15
XH16.1	-8.03818	2.76340	-2.91	0.004	0.00	0.00	0.07
XI16.19	1.81308	1.40050	1.29	0.195	6.13	0.39	95.40
X18.1	0.104000	0.0534001	1.95	0.051	1.11	1.00	1.23

Log-Likelihood = -31.509
Test that all slopes are zero: G = 82.304, DF = 7, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	80.6571	93	0.816
Deviance	63.0187	93	0.993
Hosmer-Lemeshow	1.7984	8	0.987

Measures of Association:

(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	2580	93.8	Somers' D	0.88
Discordant	165	6.0	Goodman-Kruskal Gamma	0.88
Ties	5	0.2	Kendall's Tau-a	0.44
Total	2750	100.0		

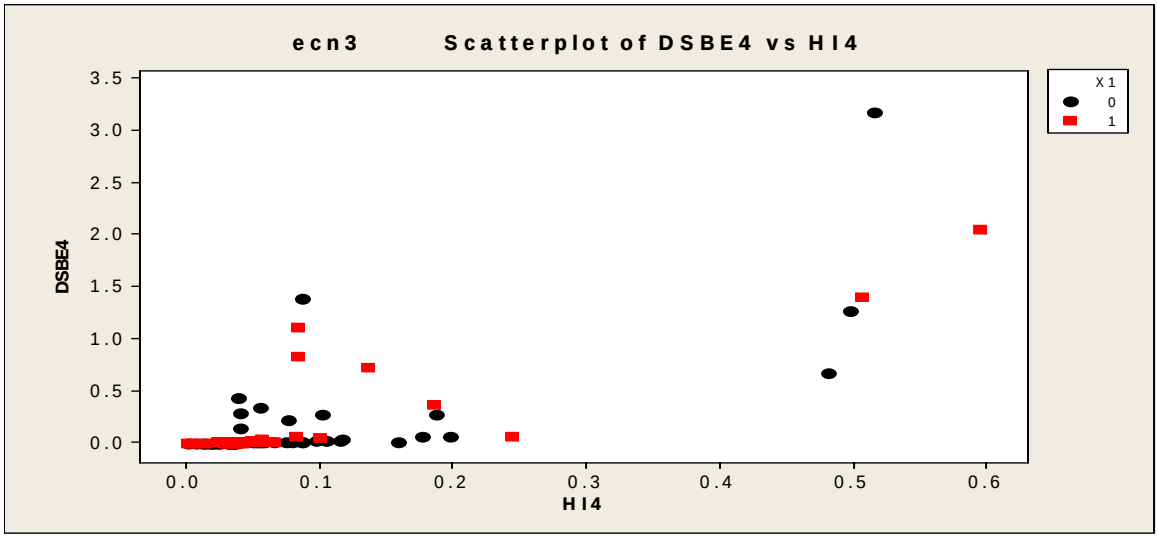

Figure 3.16: Scatterplot of equation 3 with Delta betas versus leverage.

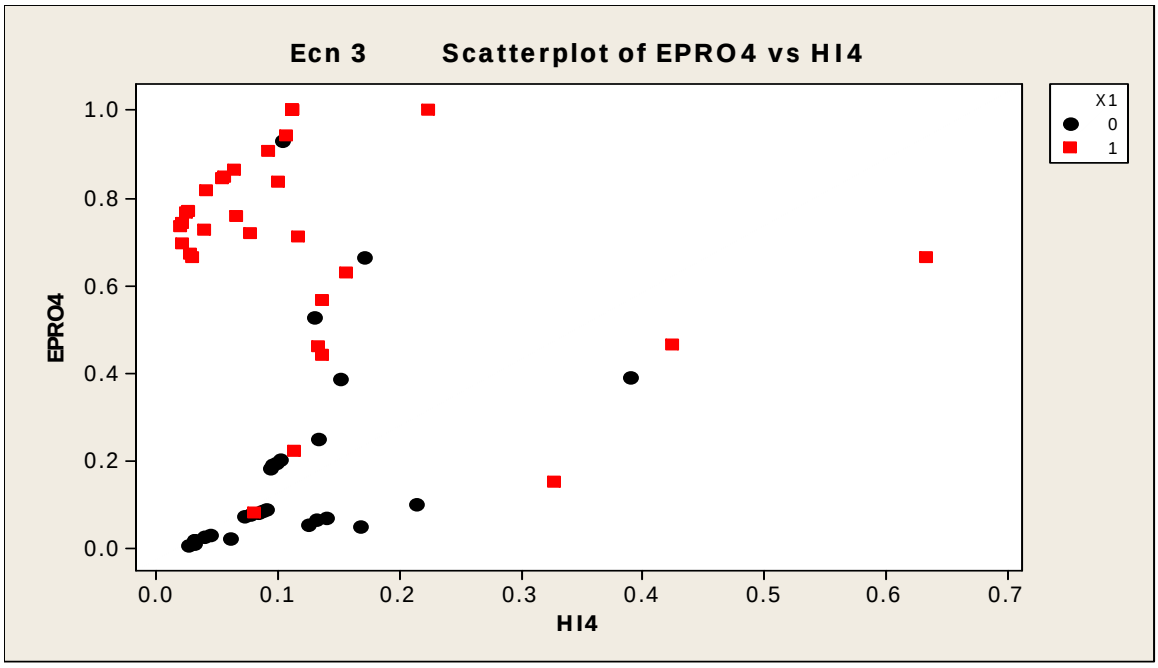

Figure 3.17: Scatterplot of equation 3 with Expected probability versus leverage.

The figure 3.17 above shows three false negatives and three false positives, with three positive MS that are predicted with borderline probabilities of MS. So this equation does not discriminate too well among cases with and without MS (no gap between MS and non-MS cases).

Table 3.9: Ninth Minitab® output, with 7 predictor variables

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	95% CI Upper
Constant	-0.896348	1.36240	-0.66	0.511			
X9	0.0588463	0.0333063	1.77	0.077	1.06	0.99	1.13
XA16.2	-3.77300	1.83846	-2.05	0.040	0.02	0.00	0.84
XB16.1	-4.12835	1.19748	-3.45	0.001	0.02	0.00	0.17
XE16.1	-3.96813	0.978681	-4.05	0.000	0.02	0.00	0.13
XE16.20	-1.12120	0.879354	-1.28	0.202	0.33	0.06	1.83
XH16.1	-7.81005	2.52570	-3.09	0.002	0.00	0.00	0.06
X18.1	0.104563	0.0492536	2.12	0.034	1.11	1.01	1.22

Log-Likelihood = -31.785
Test that all slopes are zero: G = 81.752, DF = 7, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	90.3398	94	0.588
Deviance	63.5702	94	0.993
Hosmer-Lemeshow	6.0548	8	0.641

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	2584	94.0	Somers' D	0.88
Discordant	166	6.0	Goodman-Kruskal Gamma	0.88
Ties	0	0.0	Kendall's Tau-a	0.44
Total	2750	100.0		

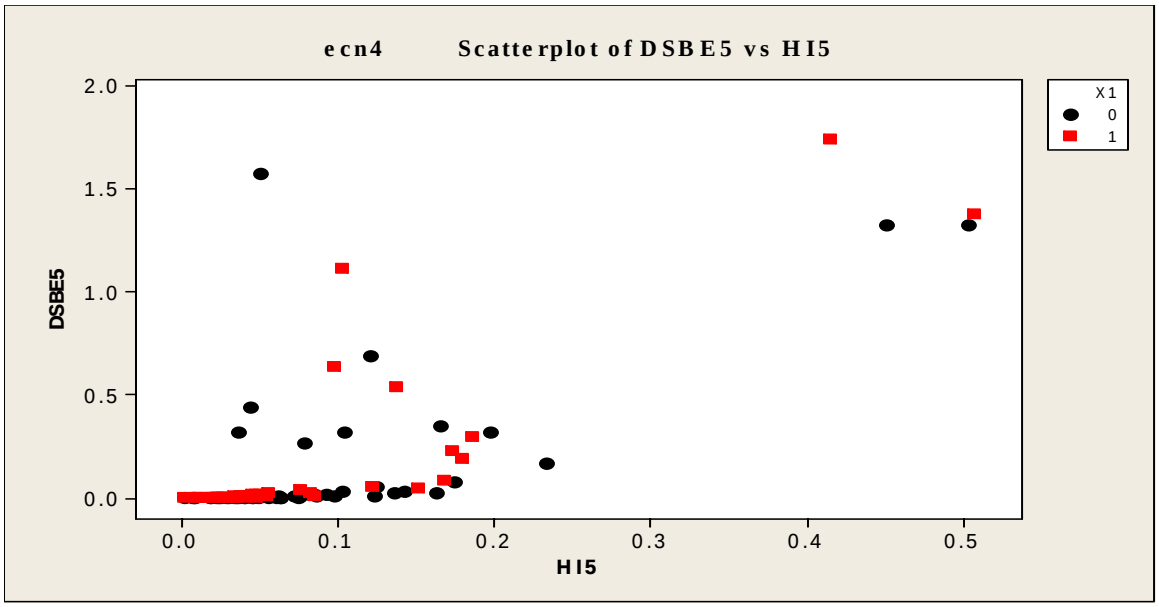

Figure 3.18: Scatterplot of equation 4 with Delta betas versus leverage.

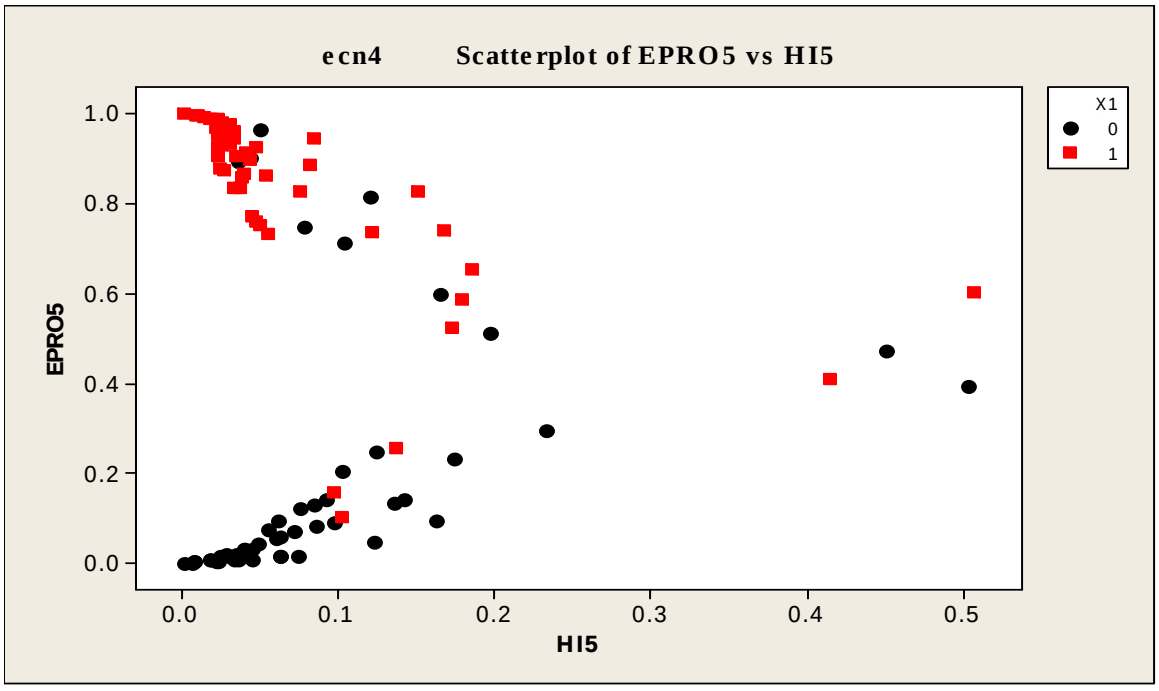

Figure 3.19: Scatterplot of equation 4 with Expected probability versus leverage.

This figure 3.19 shows that this equation has four false negatives and seven false positives with three borderline cases (around 0.5 predicted probabilities of MS).

Table 3.10: Tenth Minitab® output, with 6 predictor variables

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	95% CI Upper
Constant	-1.07988	1.30974	-0.82	0.410			
X9	0.0581307	0.0319670	1.82	0.069	1.06	1.00	1.13
XA16.2	-3.51788	1.79541	-1.96	0.050	0.03	0.00	1.00
XB16.1	-4.12420	1.19254	-3.46	0.001	0.02	0.00	0.17
XE16.1	-3.79657	0.933113	-4.07	0.000	0.02	0.00	0.14
XH16.1	-7.61471	2.39800	-3.18	0.001	0.00	0.00	0.05
X18.1	0.102107	0.0487842	2.09	0.036	1.11	1.01	1.22

Log-Likelihood = -32.586
Test that all slopes are zero: G = 80.150, DF = 6, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	90.8601	93	0.543
Deviance	65.1725	93	0.987
Hosmer-Lemeshow	2.4435	8	0.964

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	2562	93.2	Somers' D	0.86
Discordant	188	6.8	Goodman-Kruskal Gamma	0.86
Ties	0	0.0	Kendall's Tau-a	0.43
Total	2750	100.0		

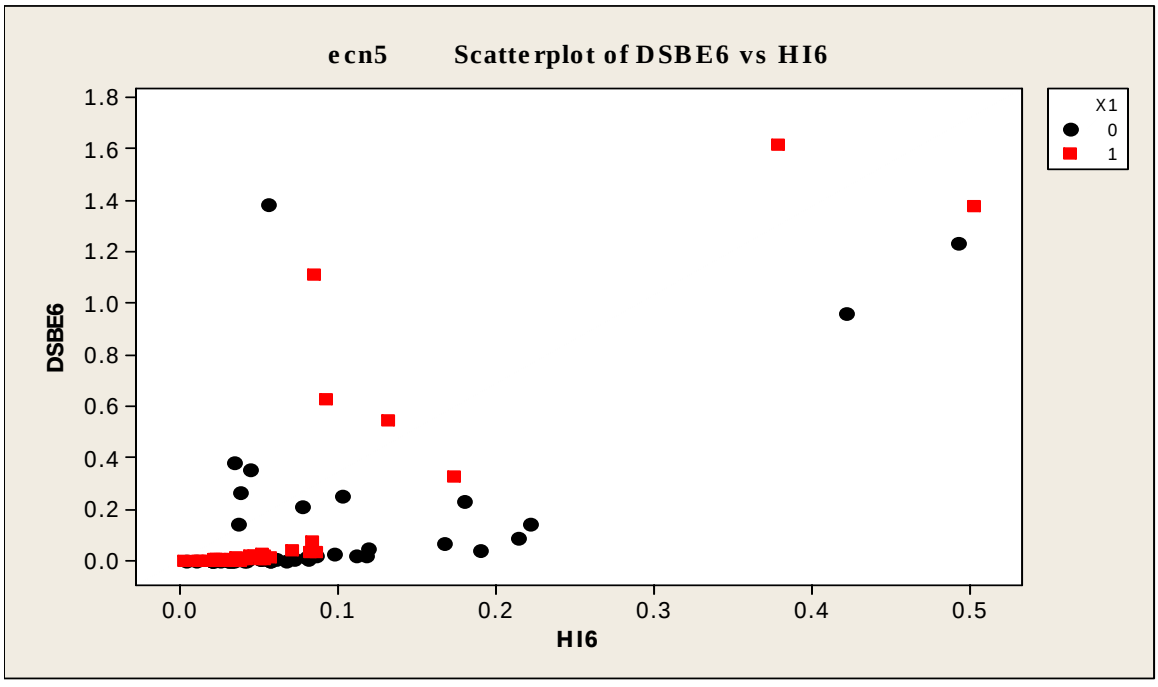

Figure 3.20: Scatterplot of equation 5 with Delta betas versus leverage.

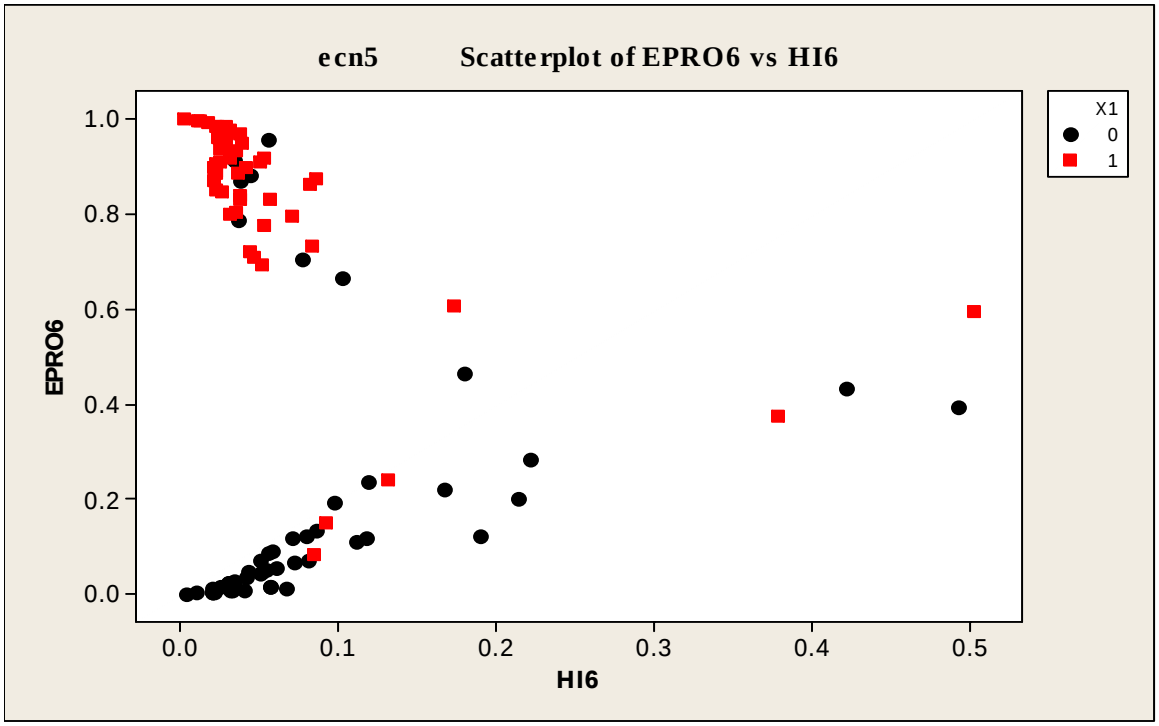

Figure 3.21: Scatterplot of equation 5 with Expected probability versus leverage.

This figure 3.21 shows that this equation has three false negatives and seven false positives four borderline (three non-MS and one MS) cases (0.4 to 0.55 probability).

Table 3.11: Eleventh Minitab® output, with 5 predictor variables

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	95% CI Upper
Constant	1.27608	0.431916	2.95	0.003			
XA16.2	-3.61443	1.74778	-2.07	0.039	0.03	0.00	0.83
XB16.1	-4.81995	1.13262	-4.26	0.000	0.01	0.00	0.07
XE16.1	-3.46434	0.876265	-3.95	0.000	0.03	0.01	0.17
XH16.1	-5.93247	2.00521	-2.96	0.003	0.00	0.00	0.14
X18.1	0.0889763	0.0445980	2.00	0.046	1.09	1.00	1.19

Log-Likelihood = -34.368
Test that all slopes are zero: G = 76.587, DF = 5, P-Value = 0.000

Goodness-of-Fit Tests

Method	Chi-Square	DF	P
Pearson	41.3672	46	0.666
Deviance	30.7834	46	0.959
Hosmer-Lemeshow	2.0558	7	0.957

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs	Number	Percent	Summary Measures	
Concordant	2484	90.3	Somers' D	0.84
Discordant	183	6.7	Goodman-Kruskal Gamma	0.86
Ties	83	3.0	Kendall's Tau-a	0.42
Total	2750	100.0		

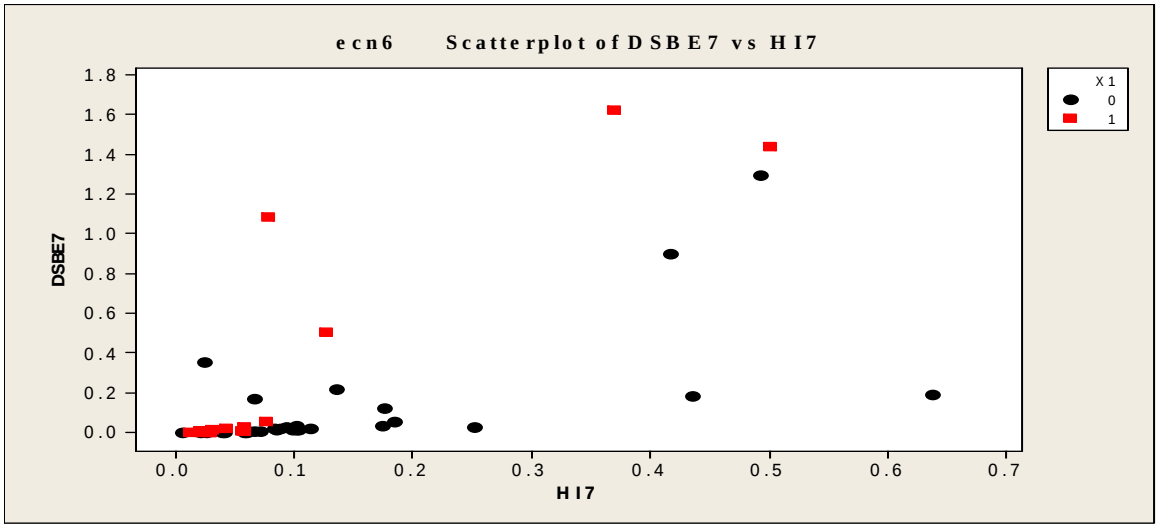

Figure 3.22: Scatterplot of equation 6 with Delta betas versus leverage..

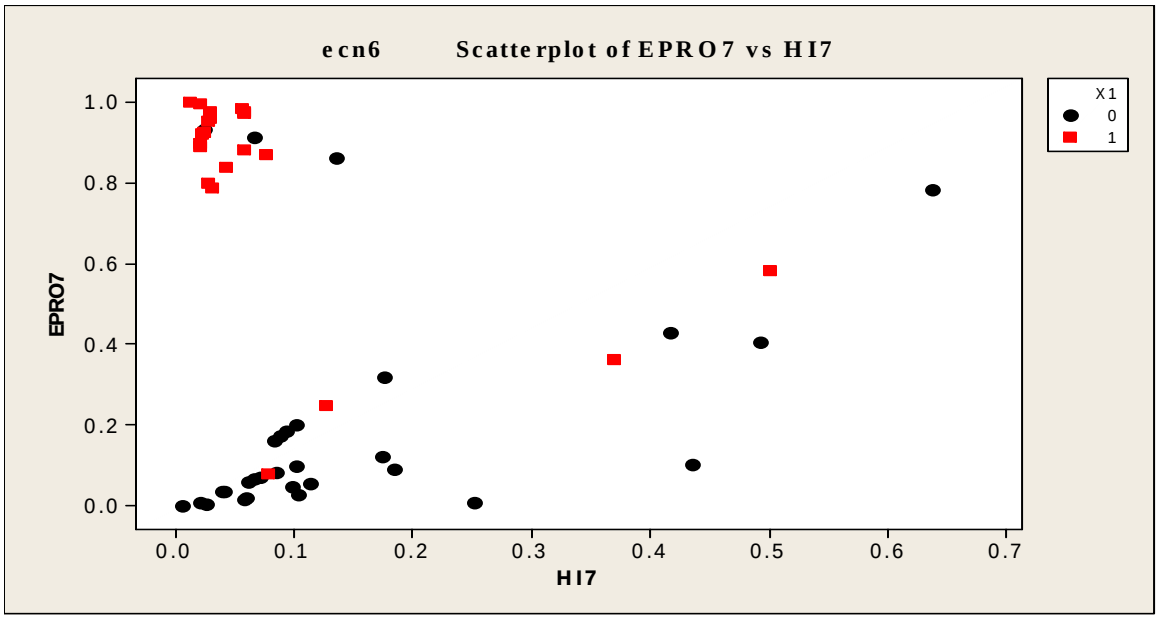

Figure 3.23: Scatterplot of equation 6 with Expected probability versus leverage.

This Figure 3.23 of equation 6 shows only four false positives and three false negatives with only one borderline case at around 0.6 predicted probabilities of MS.

D. Forward selection process was also used.

The first step is developing a t-test of the predictor variables versus the presence (absence) of MS. This is shown in the following table 3.12 along with the p-values for the one variable logistics regression, the log-likelihood value and estimated odds.

Table 3.12 T-tests for Predictor Variables and Simple Logistics Regression for Individual Predictors

Variable	t-value	T's p-value	RANK	Logistic p-value	Log-likelihood	Odds ratio
X9 Age years	-1.18	0.241	14	0.230	-71.929	1.02
XB13.2 Country child	-1.89	0.061	9	0.079	-70.817	1.03
XC13.2 Age in country	-1.91	0.060	10	0.067	-70.87	1.06
XA16.2 Fibriomialgy	1.76	0.083	11	0.108	-70.915	0.17
XB16.1 Mother MS	4.37	0.000	1	0.002	-62.507	0.04
XE16.1 Sister MS	3.53	0.001	2	0.003	-66.085	0.10
XE16.20 Sister allergy	1.76	0.082	12	0.082	-71.064	0.39
XG16.19 Ma's parent sinus	1.44	0.153	13	0.173	-71.496	0.21
XH16.1 Daughter MS	3.26	0.002	3	0.011	-66.690	0.07
XI16.20 Son allergy	-1.95	0.054	7	0.071	-70.770	3.48
XI16.19 Son sinus	-2.65	0,010	4	0.035	-69.052	9.59
X17.4 Herpes simplex	-1.86	0.068	8	0.142	-70.778	1.93
X18.1 Age got chicken pox	-2.04	0.044	6	0.056	-70.579	1.04
XD16.19 Brother sinus	2.04	0.045	5	0.069	-70.288	0.14

The forward stepwise method was used to develop the logistics regression model following the rank as order to enter the next predictor variable into the model. The first four predictors introduced were significant maximizing the log-likelihood value. When XD16.19 was introduced to the model it did not significantly increase the log-likelihood, so it was dropped and X18.1 was introduced. Then, XI16.20 was introduced but was not significant, so it was dropped. X17.4 was introduced and similarly dropped from the model. Next, XB13.2 was introduced and later dropped. XC13.2 was introduced next but the log-likelihood did not increase significantly, and then dropped. XA16.2 was

significant in the next variable added to the model. XE16.20 was introduced then dropped. XG16.19 was next introduced and dropped not being significant. X9 was the last variable introduced resulting significant in the model.

The resulting equation is as follows:

Table 3.13: Twelfth Minitab® output- Forward Selection Process, with 8 predictor variables

Predictor	Coefficient	SE Coef	Z	P-value	Odds Ratio	Lower	Upper
Constant	-0.514247	1.40307	-0.37	0.714			
XB16.1 Mother MS	-4.20739	1.22945	-3.42	0.001	0.01	0.00	0.17
XE16.1 Sister MS	-4.05068	1.03881	-3.90	0.000	0.02	0.00	0.13
XH16.1 Daughter MS	-8.73572	3.21321	-2.72	0.007	0.00	0.00	0.09
XI16.19 Son sinus	2.08080	1.39753	1.49	0.137	8.01	0.52	123.96
X18.1 Age got chicken pox	0.115865	0.0585625	1.98	0.048	1.12	1.00	1.26
XA16.2 Fibriomialgy	-3.96589	1.98409	-2.00	0.046	0.02	0.00	0.93
XE16.20 Sister allergy	-1.47638	0.979708	-1.51	0.132	0.23	0.03	1.56
X9 Age	0.0443396	0.0335378	1.32	0.186	1.05	0.98	1.12

Log-Likelihood = -30.361
Test that all slopes are zero: G = 84.602, DF = 8, P-Value = 0.000

This equation classifies correctly 91 out of the 105 cases used to develop the model, giving three false negatives and seven false positives; three with missing data could not be predicted as seen in Fig 3.26. All predictors have p-values less than 20% whereas Hosmer and Lemeshow recommend retaining predictors with p-values less than 25%.

A plot of standardized residuals versus leverages, figure 3.24, stratified by the response reveals no strange pattern.

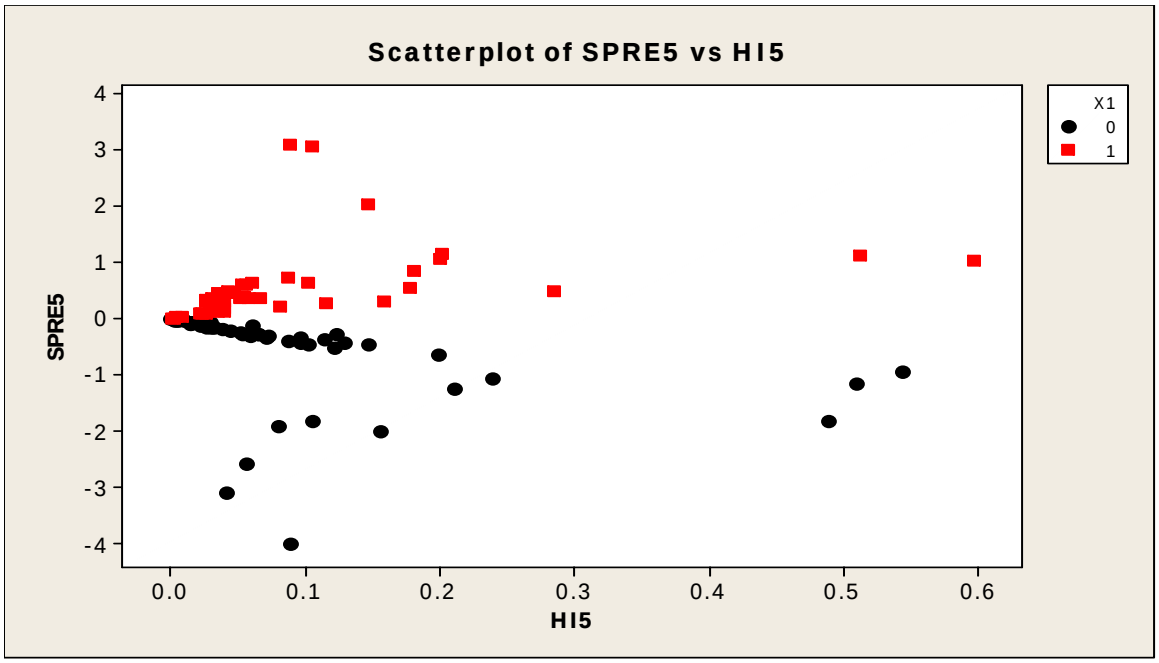

Figure 3.24: Scatterplot of equation generated by t-test with standardized residuals vs. leaverages.

Positive residuals correspond to MS cases. High leverage cases do not have large residuals and are evenly distributed among MS and non-MS cases.

The figure 3.25 shows the DFBETAS versus leverage. The case with largest DFBETAS corresponds to a 68 year old non-MS case.

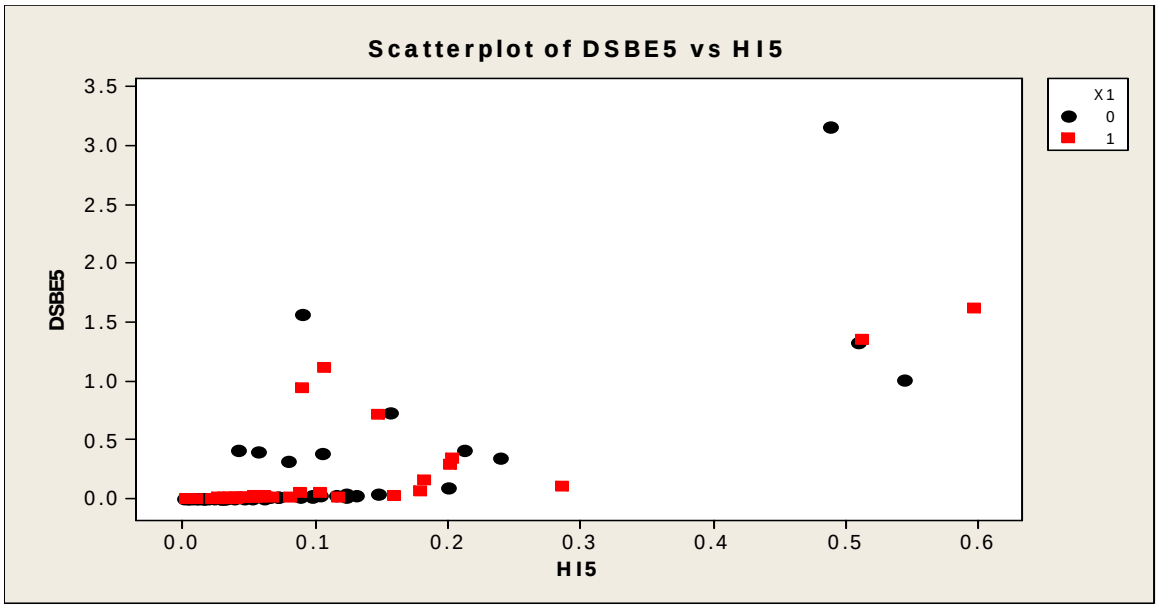

Figure 3.25: Scatterplot of equation generated by t-test with Delta betas versus leverage.

We conclude there is no bias introduced by this case.

The figure 3.26 compares the predicted probability of MS with the actual value of response.

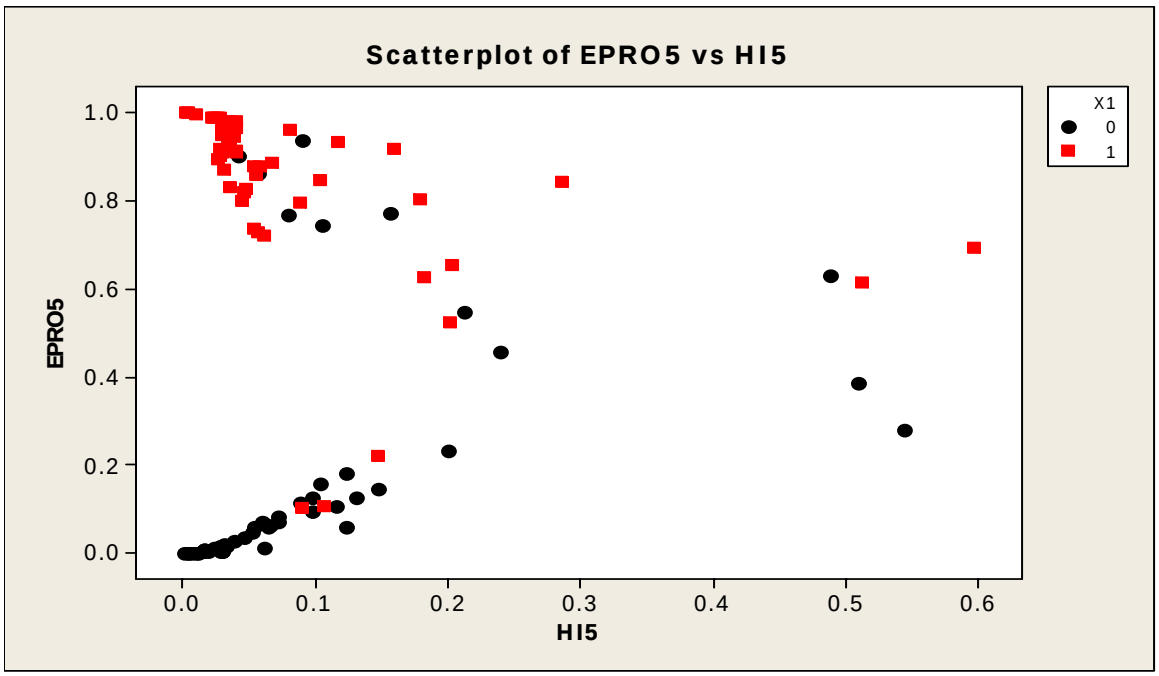

Figure 3.26: Scatterplot of equation generated by t-test with Expected probability versus leverage.

We see only three MS (red-squares) cases with low predicted probability (<0.4) or false negatives and seven non-MS cases (black-circles)) with predicted probability larger than 0.6 false positives and three borderline (one MS and two non-MS cases) with probabilities near 0.5.

The plot of residuals versus age, figure 3.27 is evenly distributed as shown below.

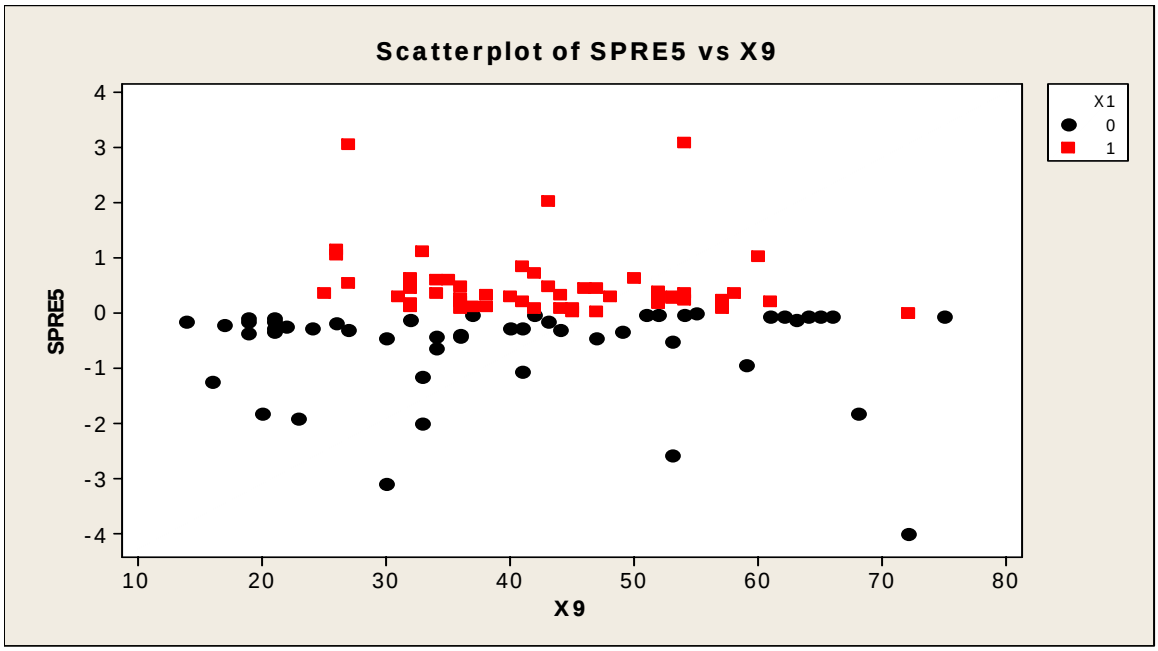

Figure 3.27: Scatterplot of equation generated by t-test with standardize residuals vs. age.

This plot shows most MS cases have positive residuals and non-MS cases have negative residuals. This means that the model does not contain all the information required to predict the occurrence of MS in Puerto Rico. But no statistical model can achieve this.

A similar behavior is observed in the plot of standardized residuals versus the age at which the case got "chicken pox" a virus caused disease. The older the person gets the disease the slightly larger the odds of getting MS (MS cases got varicella six years later).

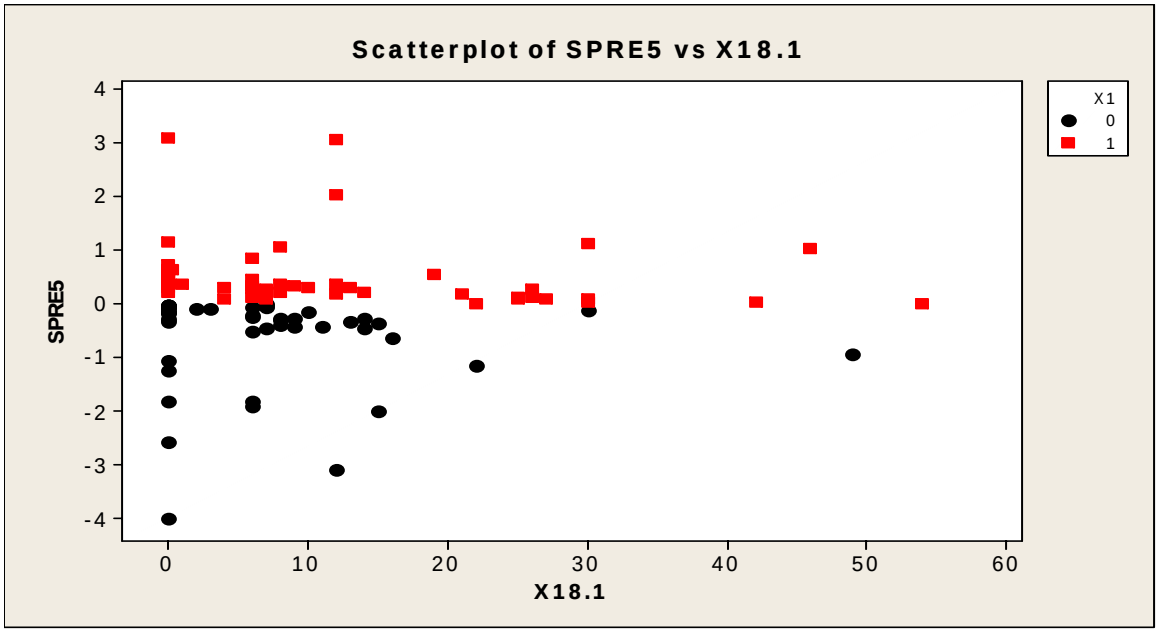

Figure 3.28: Scatterplot of equation generated by t-test with standardized residuals vs. age got chicken pox.

The goodness of fit tests shows non-significant results for this model.

```
Goodness-of-Fit Tests

Method           Chi-Square  DF      P
Pearson             76.2416  93  0.896
Deviance            60.7210  93  0.996
Hosmer-Lemeshow      3.2423   8  0.918
```

The measures of association are presented next.

```
Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs       Number   Percent  Summary Measures
Concordant    2589      94.1  Somers' D              0.88
Discordant     157       5.7  Goodman-Kruskal Gamma  0.89
Ties             4       0.1  Kendall's Tau-a        0.45
Total         2750     100.0
```

To summarize this first model one can conclude that there is a strong relationship between mother, daughter, or sister having MS that reduces the chances of the person

having MS. There seems to be a slightly lower chance of the person having MS when they have fibromialgy. The mechanism that explains this statistical relationship is yet to be discovered. The sister having allergy reduces slightly the chances of the person having MS. There seems to be a positive relationship between a son having sinus and the mother having MS, which is not medically explainable. There seems to be a higher chance of getting MS the older the person gets chicken pox.

Another model that was explored included gender that has been identified in literature to impact the chances of having MS, since females are four times more prone to have MS. In the sample of 55 persons with MS only eight males had MS. The following is a plausible model to predict MS, table 3.14.

Table 3.14: Thirteenth Minitab® output, with 5 predictor variables

Predictor	Coef	SE Coef	Z	P	Odds Ratio	95% CI Lower	Upper
Constant	-1.00831	1.50469	-0.67	0.503			
XA16.2 Fibromialgy	-4.40330	2.10701	-2.09	0.037	0.01	0.00	0.76
XB16.1 Mother MS	-4.23675	1.25121	-3.39	0.001	0.01	0.00	0.17
XE16.1 Sister MS	-4.05792	1.03303	-3.93	0.000	0.02	0.00	0.13
XE16.20 Sister aller	-1.62197	0.99770	-1.63	0.104	0.20	0.03	1.40
XH16.1 Daughter MS	-9.16291	3.42535	-2.68	0.007	0.00	0.00	0.09
XI16.19 Son sinus	2.01607	1.41272	1.43	0.154	7.51	0.47	119.70
X18.1 Age chick pox	0.123812	0.06282	1.97	0.049	1.13	1.00	1.28
X9 Age	0.0395137	0.0335642	1.18	0.239	1.04	0.97	1.11
X10 Sex	0.885252	0.836601	1.06	0.290	2.42	0.47	12.49

Log-Likelihood = -29.806
Test that all slopes are zero: G = 85.711, DF = 9, P-Value = 0.000

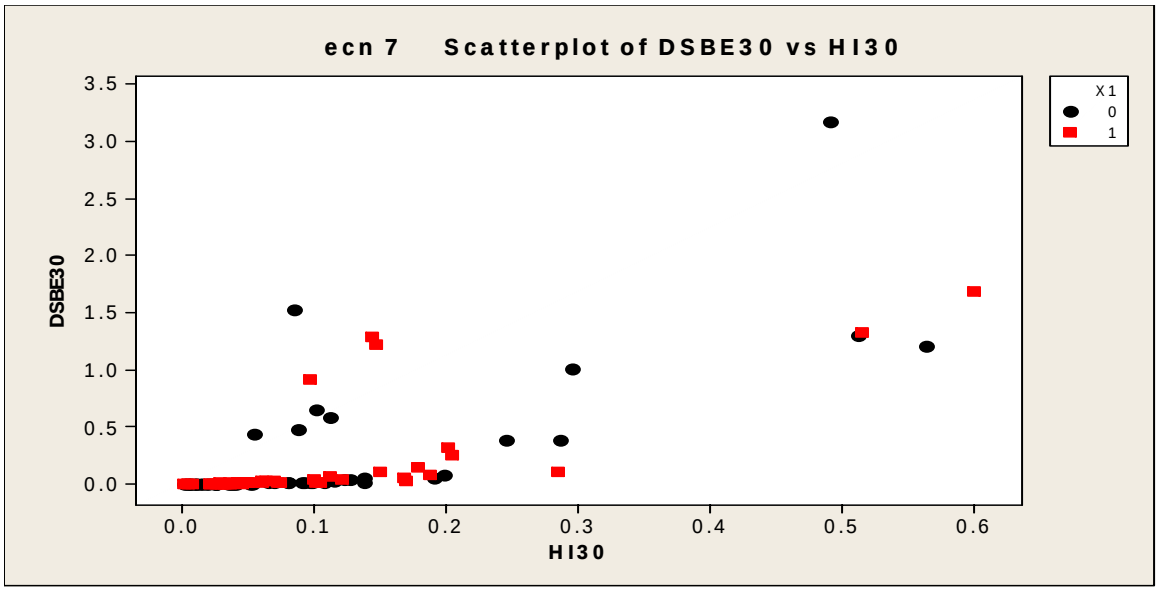

Figure 3.29: Scatterplot of equation generated by t-test with Delta betas versus leverage.

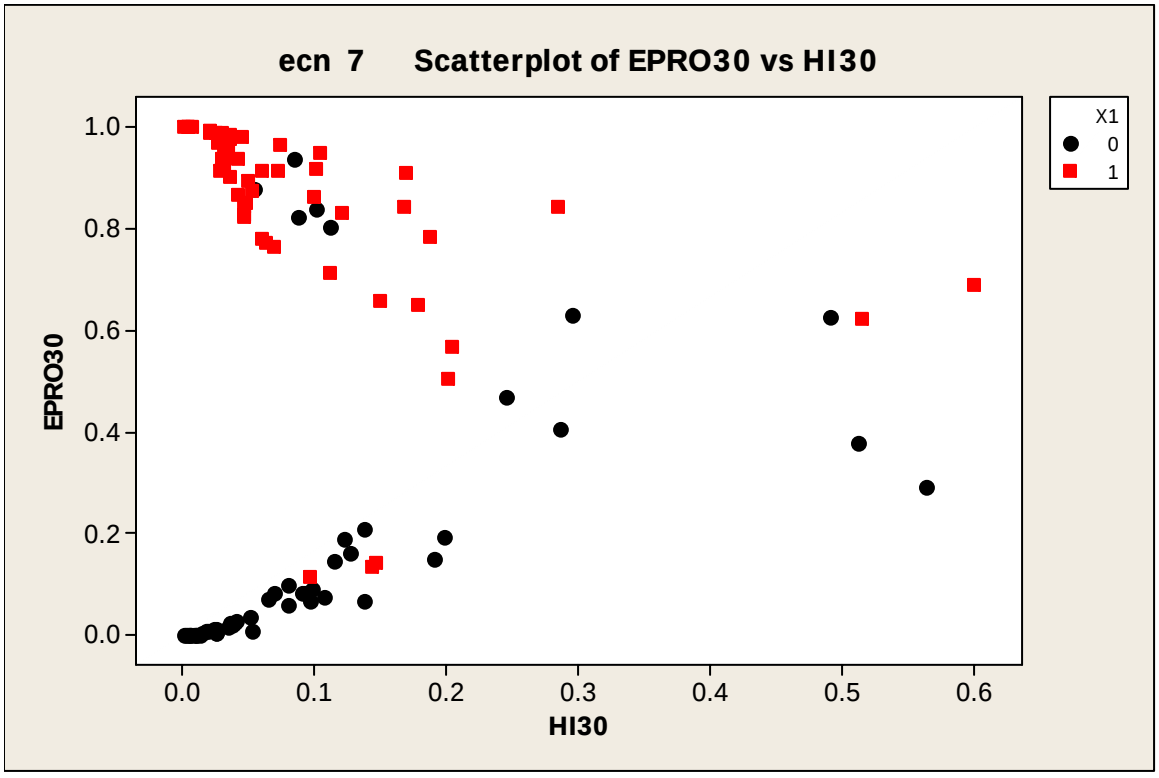

Figure 3.30: Scatterplot of equation generated by t-test with Expected probability versus leverage.

This equation has three false negatives, seven false positives, and two borderline cases one being an MS case and the other a non-MS case.

```
Goodness-of-Fit Tests

Method           Chi-Square  DF      P
Pearson             73.8594  94  0.938
Deviance            59.6121  94  0.998
Hosmer-Lemeshow      3.8936   8  0.867

Measures of Association:
(Between the Response Variable and Predicted Probabilities)

Pairs       Number  Percent  Summary Measures
Concordant    2600     94.5  Somers' D              0.89
Discordant     146      5.3  Goodman-Kruskal Gamma  0.89
Ties             4      0.1  Kendall's Tau-a        0.45
Total         2750    100.0
```

E. Using Excel with a new set of data of patients with the condition of MS (30 cases) the six equations (models developed in part C) were validated to predict the probability of having MS as seen in Appendix F (table F.1). It is of special interest the rate of false negatives that the equations predict.

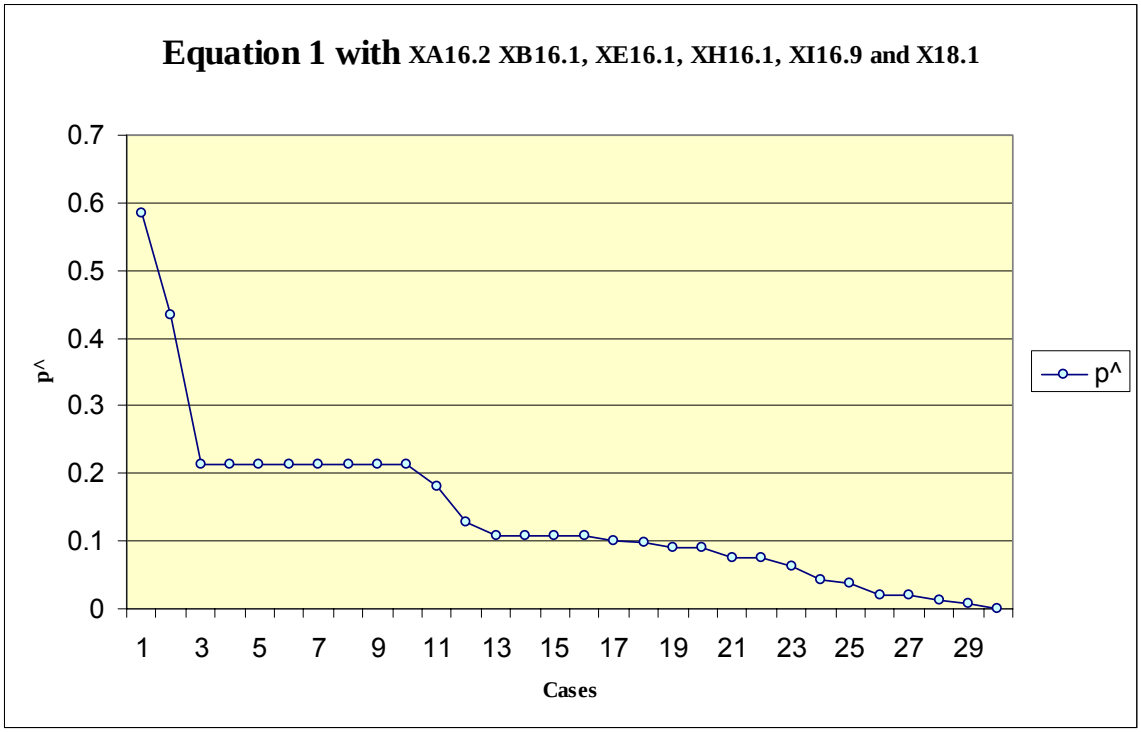

Figure 3.31: Predicted Probability of MS for New Cases

Examining Figure 3.31 for equation 1 there are seven cases with probability predicted less than 0.05, which could be considered false negatives. In general the probabilities predicted are much smaller than for the equation sample.

Examining Figure 3.32 for equation 2 there are five cases with probability predicted less than 0.05, which could be considered false negatives. In general the probabilities predicted are much smaller than for the equation sample. There is a larger discrimination in this equation.

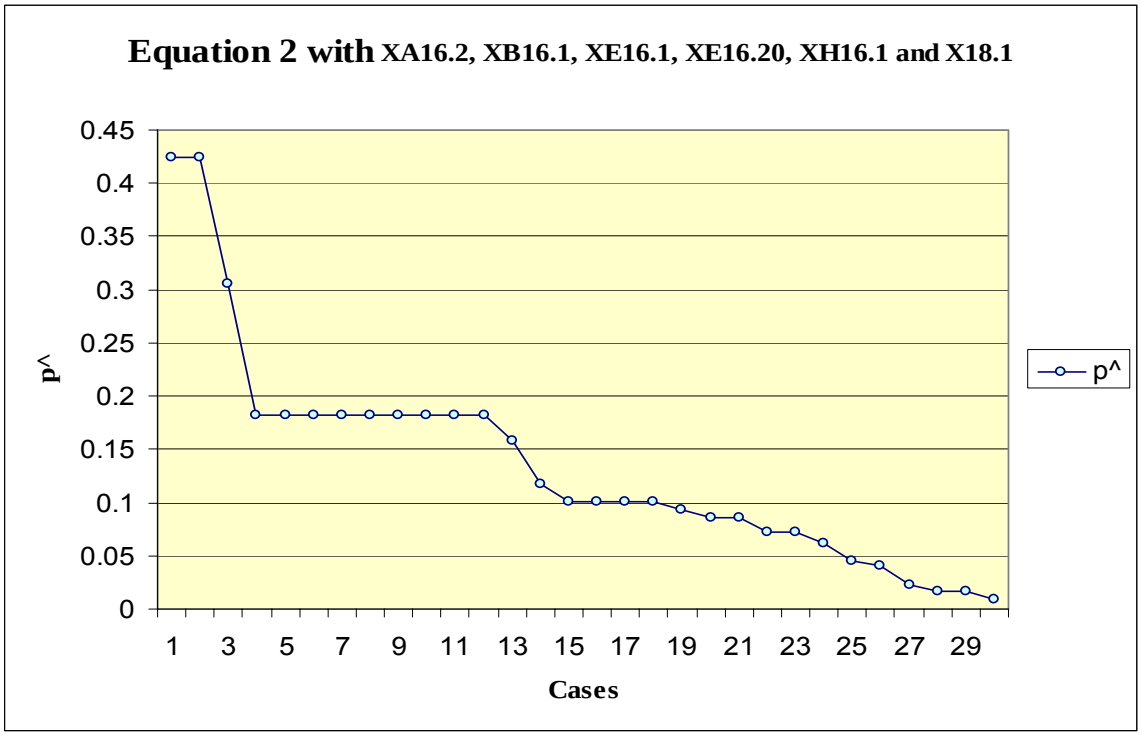

Figure 3.32: Predicted Probability of MS for New Cases

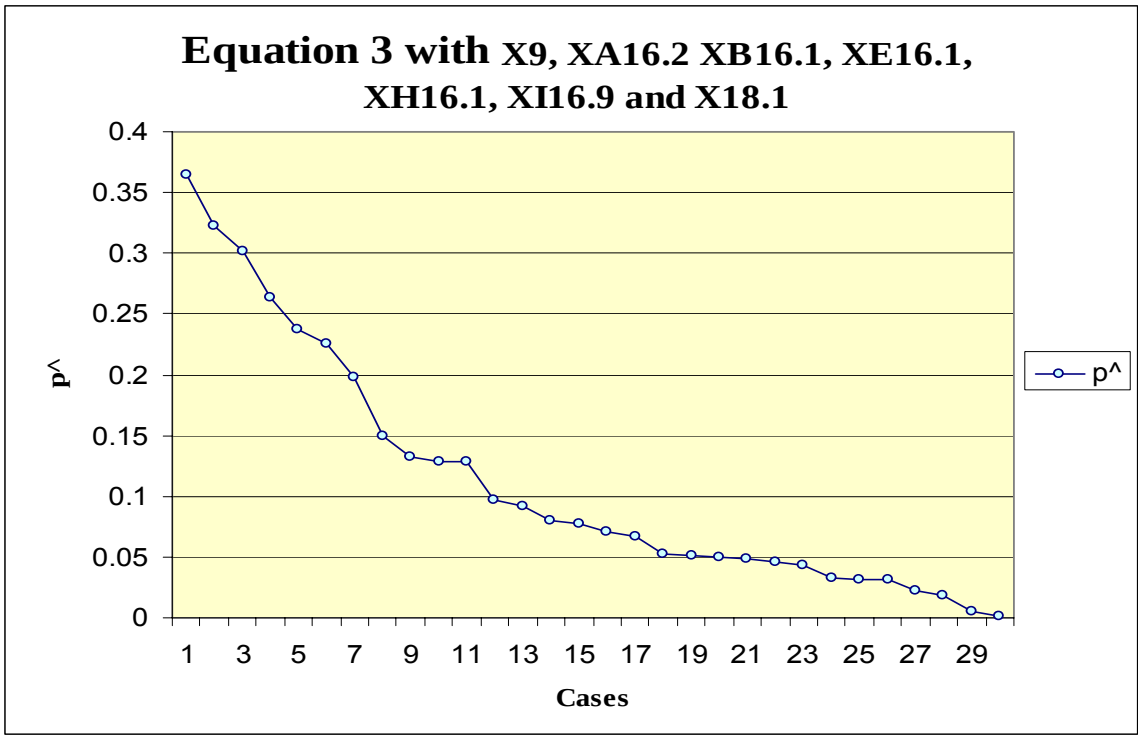

Figure 3.33: Predicted Probability of MS for New Cases

Figure 3.33 for equation 3 there are ten cases with probability predicted less than 0.05, which could be considered false negatives. If 0.04 is used as cutoff point then only seven false negatives would appear. In general the probabilities predicted are much smaller than for the equation sample.

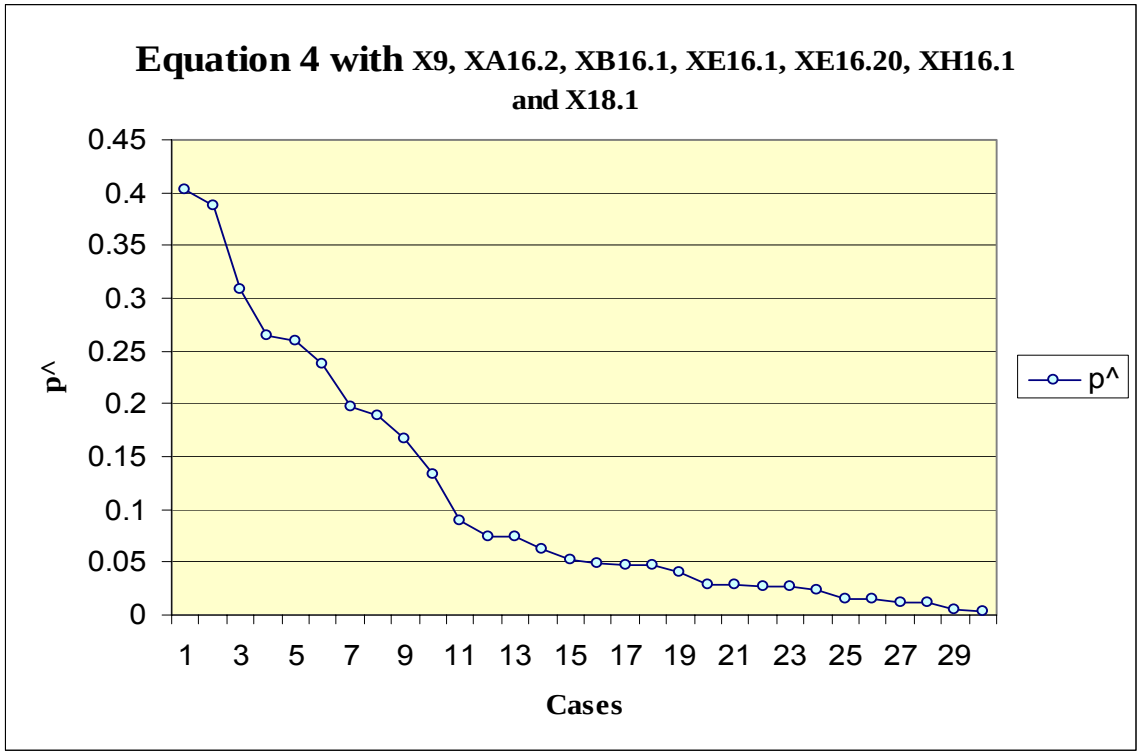

Figure 3.34: Predicted Probability of MS for New Cases

Figure 3.34 for equation 4 there are fifteen cases with probability predicted less than 0.05, which could be considered false negatives. Although the jump in probabilities occurs at a lower value something like 0.04, which has only eleven false negative cases. In general the probabilities predicted are much smaller than for the equation sample.

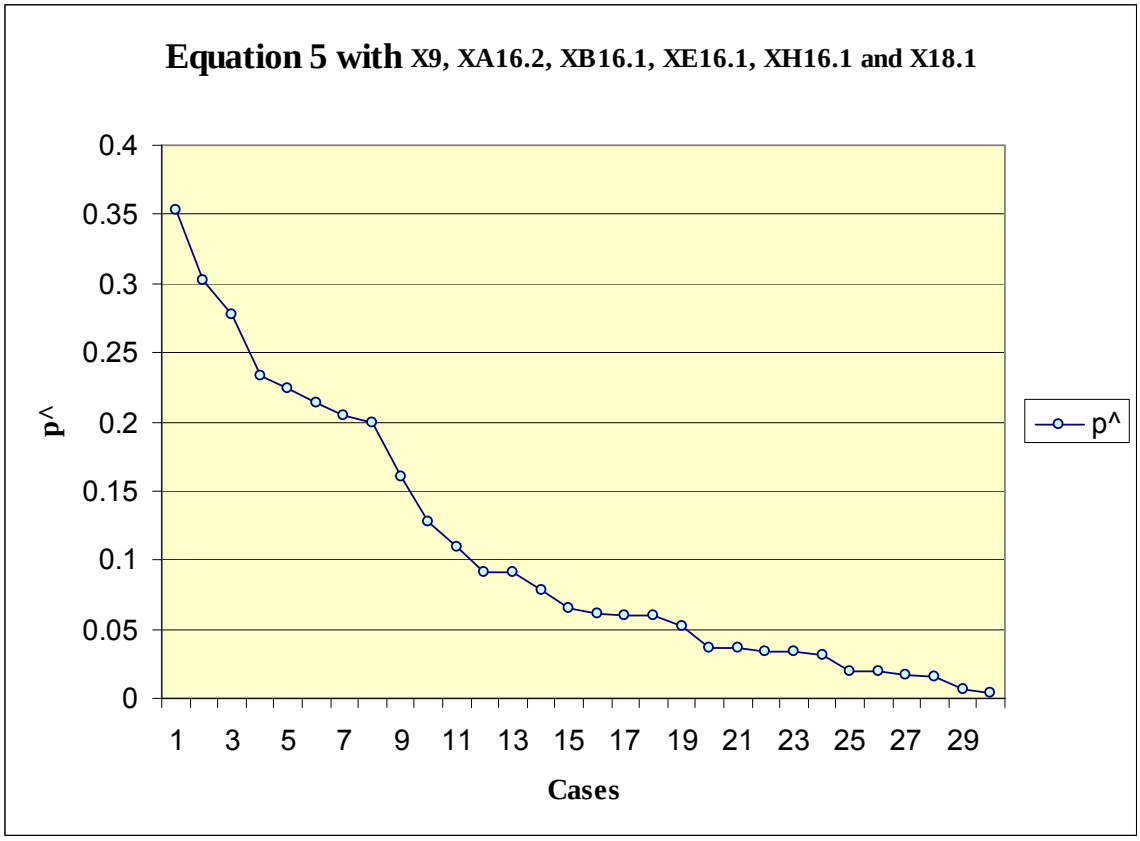

Figure 3.35: Predicted Probability of MS for New Cases

Figure 3.35 for equation 5 there are eleven cases with probability predicted less than 0.05, which could be considered false negatives. If the jump in probabilities occurs at a lower value something like 0.04, which has only six false negative cases. In general the probabilities predicted are much smaller than for the equation sample.

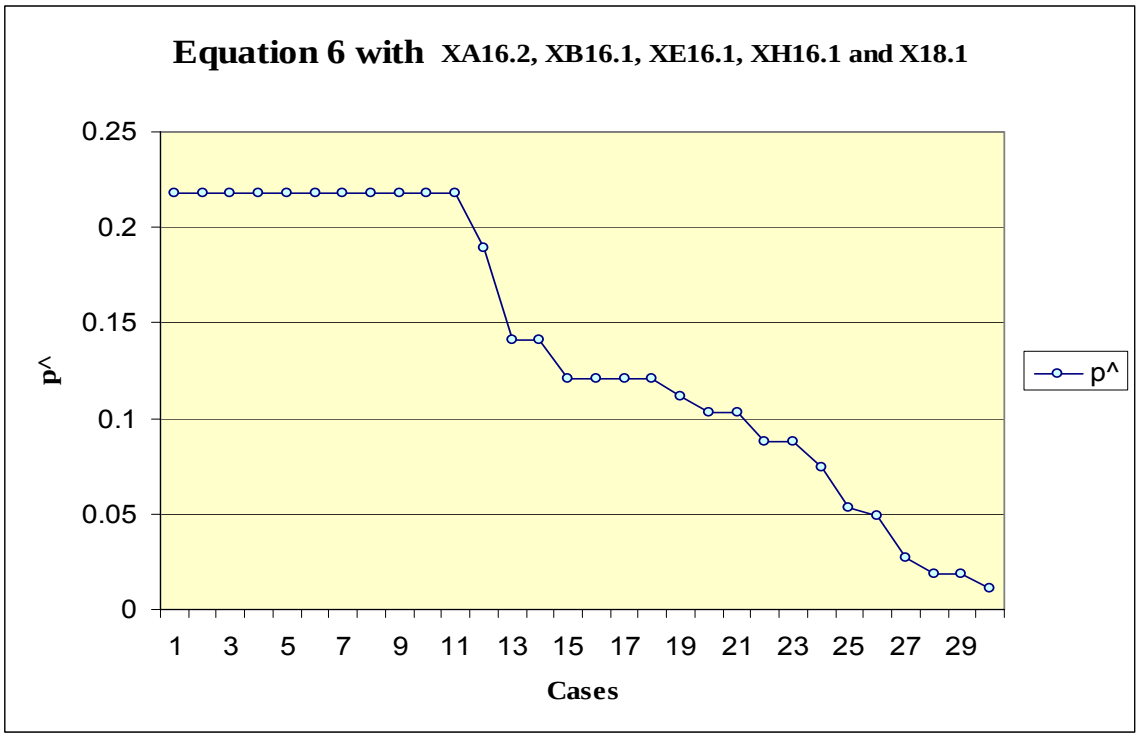

Figure 3.36 Predicted Probability of MS for New Cases

Figure 3.36 for equation 6 there are only four cases with probability predicted less than 0.05, which could be considered false negatives. In general the probabilities predicted are much smaller than for the equation sample but the larger probability case separate drastically from low probability cases. In general the probabilities predicted are much smaller than for the equation sample, which are explained by the difference in group averages for the most important predictors in the equations.

Table 3.15: Comparison of Predictor Averages for Original and Validation MS cases.

X9.1 Age got MS	XA16.2.1 Fibriomialgy	XB16.1.1 Mom MS	XE16.1.1 Sister MS	XE16.20.1 Sister Allergy	XH16.1.1 Daughter MS	XI16.19.1 Sinus Son	X18.1.1 Chicken pox
Cases	Used for	Regression					
43.09091	0.018182	0.018182	0.036364	0.1 09091	0.018182	0.163636	11.06
Cases	for	validation					
47.8	0	0	0	0.1	0	0.1	9.066667

The predicted probabilities are much smaller because of the absence of MS in women relatives in the validation samples.

Chapter 4 **Conclusions**

Logistic Regression with a binary outcome that indicates the occurrence or nonoccurrence of the condition of MS in a person gave us the models developed to enable a doctor to determine the factors that have the most influence in the condition of MS and to identify who will require further intervention studies to determine whether they really have MS, so we can conclude that the objective of the project was met.

Using scatterplots of the equations with their expected probabilities versus leverages one can see the false positives, the false negatives and the borderline cases of the probabilities of having MS. In most of the cases there were less false negatives than false positives, which are better to be false alarm than to be unaware of having the condition, so it is always better to perform the different types of studies and be aware of the clinical history to determine if the person has or not MS.

Also with these equations a person can asses the probability of having the condition of MS given a set of values for the predictor variables and how each predictor variable affects such probability. With the study there will be a better understanding of which factors affect MS in PR, supposedly being a low prevalence country, there are cases of MS and there is a need to identify at risk persons.

The most important factors among all studied were;

Variable	Name of variable
X9	Age of the person when they fill out the questionnaire
XA16.2	Fibriomialgy of the person
XB16.1	MS of the mother
XE16.1	MS of the sister
XE16.20	Allergy of sister
XH16.1	MS of daughter
XI16.19	Sinus of son
X18.1	Age when the person got chicken pox

Among the six equations developed (part C of chapter 3) the factors XB16.1 and XH16.1 (mother and daughter) are the most influential variables in the value of the response with a negative coefficient that means that XB16.1 and XH16.1 have an inverse relation between this factors and the value of the response X1 (If the person has MS or not). X9 (age) and X18.1 (age got chicken pox) are the least influential ones, have positives coefficients that gave a direct relation with the response so the probability of having the condition of MS will increase as the variables X9 and X18.1 increase.

For example if the mother or the daughter (X(BorH)16.1) have MS then the chance of the person of having MS is reduced to 1: 100, 1:50. The presence of sinus in a son increases the odds (probabilities) 2.5 to 1 that the person has the condition of MS. This is statistical evidence only. Similarly, the presence of allergy in a sister decreases the odds to 1 in 5 and when the person has fibriomialgy decreases the odds to 1 in 100 of having the condition of MS. These are statistically significant results for which there is no medical explanation. It is urged by the researcher to corroborate whether this findings are true or wrong.

Bibliography

1. Arbona, N. 1991. Esclerosis Múltiple: ¿Enfermedad Tropical? Information Bulletin About Multiple Sclerosis.
2. Alonso and Larrea. 1994. Quoted in Fernández, O. 1994.
3. Bogoch, S. 1968. The Biochemistry of Brain. Oxford University Press.
4. Breida, H. 1979. Communication Breakdown of Brain Injured Adults. College Hill Press.
5. Calvin, W. H. and G. Ojemann. 1980. Inside the Brain. New American Library, Ontario.
6. Corraze, J. 1988. Las Bases Neurológicas del Movimiento. Editorial Paidotribe, S. A.
7. De Fonseca, V. 1998. Manual de Observación Psicomotriz. Inde Publicaciones.
8. Fernández, O. 1994. Esclerosis Múltiple: Una Aproximación Multidisciplinaria. Asociación Española de Esclerosis Múltiple (AEDEM) Travesera, Barcelona.
9. Graham, J. 1989. MS: A Self-help Guide to its Management. Healing Press, Vermont.
10. Huang, J. C. Neuroanatomy and Physiology. Continuum Health Partners. http://www.bethisraelny.org/inn/anatomy/anatomy.html
11. Johnson, G. 1991. In the Palaces of Memory. Vintage Book, New York.
12. Label, L. and Mosby. 1997. Injuries and Disorders of the Head and Brain. Mathew Bender & Co.
13. Lambert, D., R. Swann, S. Besonko, R. Cohen and K. Seed. 1982. The Brain: A User's Manual. Berkely Books, N. Y.
14. La Rocca, N. G. 1984. Quoted in Scheinberg, Labes Raime and Edrie 1984.

15. www.nmss.org

16. Olson, W., R. Brumback and G. Gascon. 1989. Handbook of Symptom-oriented Neurology. Yearbook Medical Publishers.

17. Rose, A. and C. Pearson. 1963. Mechanisms of Demyelination. Mc. Graw-Hill Book

18. Scheinberg, Labe, Raime and Cedric. 1984. MS: Experimental and Clinical Aspects. Annals of the New York Academy of Sciences, vol.436.

19. Segurado, Corel, and Arnaiz. 1994. Quoted in Fernández, O. 1994.

20. Simons, A. 1984. MS: Psychological and socials Aspects. Heinemann Medical Books.

21. Trembly, B. and Slikker. 1999. Neuroprotective Agents Fourth International Conference. New York Academy of Sciences.

22. Vowels, L. and Gates, G. R, 1984. Quoted in Simons. 1984.

23. Causes of Multiple Sclerosis. http://www.mscenter.ucsf.edu/causes.html

24. Information About Multiple Sclerosis. http://www.nmss.org/

25. Multiple Sclerosis. http://www.msonly.com

26. Information About Multiple Sclerosis. http://www.medstat.utah.edu

27. Bendel R. B. and Affifi, A. A. 1977. Comparison of stopping rules in forward regression. Jour. of American Statistical Assoc. Vol.72

28. Samprit Chatterjee and Bertram Price. 1997. Regression Analysis by Example. John Wiley & Sons, Inc. (JW&SInc)

29. Norman Draper and Harry Smith. 1981. Applied Regression Analysis. (JW&SInc)

30. Homers, Jr. and Lemeshow, David. 1989. Applied Logistic Regression. (JW&SInc)

APPENDICES:

For the purpose of a better understanding of this investigation, included this additional documentation for the same relevant items:

A. The different letters used for the study.

B. The different questionnaires used for the study.

C. Kinds of symptoms that patients with the condition of MS suffered.

D. Variable correlation table after first elimination.

E. Variable correlation table after second elimination.

F. Health conditions table for the final equation validation.

APPENDIX A

The different letters used for the study.

Estimados pacientes de esclerosis múltiple y familiares:

Hola, mi nombre es Carmen L. Collazo Pérez y soy estudiante de maestría del Programa en Ingeniería de Sistemas de Control de Calidad del Departamento de Ingeniería Industrial en el Recinto Universitario de Mayagüez. Al igual que usted tengo la condición de Esclerosis Múltiple (**EM**). Como parte del requisito de graduación se me requiere hacer un trabajo de investigación o tesis, el mismo consiste en analizar estadisticamente que factores contribuyen a que en Puerto Rico (**PR**) haya tantos casos de **EM**, puesto que **PR** es un lugar donde se supone no existan casos de **EM**. He elaborado un cuestionario donde se le pide información al paciente y a un familiar. La información recolectada en el cuestionario servirá para saber qué factores son las posibles causas de **EM** en **PR**.

Usted está invitado a participar en este estudio, su **participación** en la misma **es libre y voluntaria**, esto significa que usted está en la libertad de participar o no en el mismo. La información obtenida del cuestionario será utilizada para mi trabajo de investigación de **manera anónima y confidencial** por lo que se le pide su autorización correspondiente. Su participación consistirá en llenar el cuestionario adjunto, firmar la autorización del mismo y por favor enviarmelos a la mayor brevedad posible en los sobres provistos. El sobre amarillo es para que mande los cuestionarios completados y el blanco pequeño es para que firme la parte inferior de esta hoja y nos la envíe por separado. De esta forma se mantendrá la información de manera confidencial y anónima.

Usted no sufrirá ningún daño por participar en este estudio ni recibirá incentivo económico porque el mismo se está haciendo sin ayuda económica externa. Sin embargo, su participación es muy valiosa para mí porque podré cumplir con mis requisitos de graduación y podría ayudar a que profesionales de la salud utilicen esta información para beneficio de los pacientes de **EM** y nosotros mismos conocer más de nuestra condición. Una vez se termine el estudio podrá ver un informe de los resultados generales en la oficina de la Asociación contra el Esclerosis Múltiple de Puerto Rico, teléfono 787-763-0303. Cualquier duda que surja sobre el cuestionario puede llamarme al teléfono 787-738-8449. En espera de su gentil colaboración y agradeciéndole anticipademente por la atención prestada me despido hasta una nueva oportunidad.

Cordialmente,

_____ fecha_____
Carmen L. Collazo Pérez

CORTAR AQUI

Nosotros _____(letra de molde) paciente con la condición de esclerosis múltiple y _____(letra de molde) familiar del paciente, hemos leído el contenido de esta hoja y autorizamos a la estudiante Carmen L. Collazo Pérez, a utilizar la información brindada en el cuestionario ofrecido para este fin.

_____fecha_____ _____fecha_____
(firma del paciente) (firma del familiar del paciente)

Dr. Perez Canabal

Mayo 16, 2006

Pacientes de Esclerosis Múltiple

Familiares de los Pacientes

Estimado Paciente y Familiar:

Saludos, les escribo estas líneas para solicitar su cooperación en una investigación sobre Esclerosis Múltiple que se va a realizar durante los próximos meses. En esta investigación se tratará de clarificar que factores influyen para que en Puerto Rico muchas personas tengan la condición de Esclerosis Múltiple siendo Puerto Rico un lugar de baja incidencia. Para este propósito se les requiere que tanto el paciente como un familiar (orden de preferencia; hermanos, padres o hijos) llenen los cuestionarios que se les envían y los devuelvan a vuelta de correo en el sobre provisto a la dirección indicada en el mismo. La información provista es de vital importancia en el estudio por lo cual se les pide que lean y contesten detenidamente cada pregunta en el cuestionario y aclaren cualquier duda que puedan tener sobre alguna pregunta. Su participación en el estudio es voluntaria y la información se utilizará de manera confidencial. Agradezco su cooperación y tiempo prestado, cuídense mucho.

Cordialmente,

Alfredo Pérez Canabal
Neurólogo

Dr. Luis Freytes
P. O. Box 1329
San Germán, P.R. 00683

Dr. Luis Freytes

Mayo 16, 2006

Pacientes de Esclerosis Múltiple

Familiares de los Pacientes

Estimado Paciente y Familiar:

Saludos, les escribo estas líneas para solicitar su cooperación en una investigación sobre Esclerosis Múltiple que se va a realizar durante los próximos meses. En esta investigación se tratará de clarificar que factores influyen para que en Puerto Rico muchas personas tengan la condición de Esclerosis Múltiple siendo Puerto Rico un lugar de baja incidencia. Para este propósito se les requiere que tanto el paciente como un familiar (orden de preferencia; hermanos, padres o hijos) llenen los cuestionarios que se les envían y los devuelvan a vuelta de correo en el sobre provisto a la dirección indicada en el mismo. La información provista es de vital importancia en el estudio por lo cual se les pide que lean y contesten detenidamente cada pregunta en el cuestionario y aclaren cualquier duda que puedan tener sobre alguna pregunta. Su participación en el estudio es voluntaria y la información se utilizará de manera confidencial. Agradezco su cooperación y tiempo prestado, cuídense mucho.

Cordialmente,

Luis Freytes
Neurólogo

Asociación contra la Esclerosis Múltiple de Puerto Rico

Mayo 16, 2006

Pacientes de Esclerosis Múltiple

Familiares de los Pacientes

Estimado Paciente y Familiar:

Les saluda cordialmente Jesús Saad Nazer, presidente de la Asociación contra la Esclerosis Múltiple de Puerto Rico (AEMPR), el objetivo de la presente es presentar a una joven estudiantes y miembro de nuestra asociación, quien esta haciendo un estudio estadístico sobre la codición por lo cual solicito su pronta cooperación en esta investigación sobre Esclerosis Múltiple que se va a realizar durante los próximos meses. En esta investigación se tratará de clarificar que factores influyen para que en Puerto Rico muchas personas tengan la condición de Esclerosis Múltiple siendo Puerto Rico un lugar de baja incidencia. Para este propósito se les requiere que tanto el paciente como un familiar (orden de preferencia; hermanos, padres o hijos) llenen los cuestionarios que se les envían y los devuelvan a vuelta de correo en el sobre provisto a la dirección indicada en el mismo. La información provista es de vital importancia en el estudio por lo cual se les pide que lean y contesten detenidamente cada pregunta en el cuestionario y aclaren cualquier duda que puedan tener sobre alguna pregunta. Su participación en el estudio es voluntaria y la información se utilizará de manera confidencial. Agradezco su cooperación y tiempo prestado, cuídense mucho.

Cordialmente,

Jesús Saad Nazer
Presidente de la AEMPR

APPENDIX B

The different questionnaires used for the study.

Questionnaire B1.1

CUESTIONARIO

1. Mencione el pueblo de su residencia actual: _____

   Urbana ☐ Rural ☐

2. Lugar de nacimiento: _____

3. País de procedencia de su familia (antepasados): _____

4. Sexo: Femenino ☐ Masculino ☐

5. Edad: Actual: _____ Al comienzo de los síntomas: _____

   En el momento del diagnóstico _____

6. Estatura: _____

7. Tipo de personalidad: Extrovertido ☐ Introvertido ☐

   Sensorial ☐ Intuitivo ☐

   Cognoscitivo ☐ Sensitivo ☐

   Judger(Estructurado) ☐ Perceiver (Flexible) ☐

8. Enfermedades que ha padecido en su vida:

   Alta Presión ☐ Baja Presión ☐ Artritis ☐ Cáncer ☐

   Corazón ☐ Diabetes ☐ Hepatitis ☐ Ulceras ☐

   Problemas de la Circulación ☐ Otros _____

9. Mantenimiento Personal: Dieta ☐ Ejercicio ☐ Terapia Física ☐

   Técnicas de Relajación ☐ Explique _____

   Otros ☐ Explique _____

10. Familiar cercano que padece o ha padecido de esclerosis múltiple:

    Señale el parentesco: Padre ☐ Madre ☐ Hermano(a) ☐

    Abuelo(a) ☐ Tío(a) ☐

11. Factor o causa que precipitó la enfermedad. _____

Cont. Questionnaire B1.1

12. Síntomas en el primer ataque: Neuritis ☐ Debilidad en las piernas ☐

    Pérdida de Balance ☐ Pérdida de coordinación ☐

    Otros _____

    Dónde o cómo ocurrieron: _____

13. Enfermedades previas en la familia. Indique la relación con la persona, sexo y edad en que ocurrió._____

    _____

14. Exposición a virus. Indique número de veces, fechas y edad.

    _____

    _____

15. Transfusiones de sangre. Indique número de veces, fechas y edad.

    _____

    _____

16. Tiempo entre cada episodio: _____

17. Tiempo que lleva con la condición: _____

18. Síntomas más comunes o frecuentes. Indique. _____

    _____

19. Síntomas que persisten. Indique. _____

    _____

Questionnaire B1.2

CUESTIONARIO

1. Mencione el pueblo de su residencia actual: _____

   Zona Urbana ☐

   Zona Rural ☐
2. Lugar de nacimiento: _____

3. País de procedencia de su familia (antepasados): _____

4. Sexo:

   Femenino ☐
   Masculino
5. Edad Actual: _____ ☐

   Al comienzo de los síntomas: _____
   En el momento del diagnóstico _____
6. Estatura en pies y pulgadas: _____

7. Tipo de personalidad (Marque una en cada par):

   a) Extrovertido (exterioza lo que siente) ☐

      Introvertido (no expresa lo que siente) ☐

   b) Sensorial (prefiere las cosas prácticas y no las ideas) ☐

      Intuitivo (prefiere posibilidades y significado, sigue su intuición) ☐

   c) Analitico (analiza antes de actuar) ☐

      Sensitivo (sigue su impulso y sentimiento) ☐

   g) Juicioso (planificador, ordenado, tiene control de sus actos) ☐

      Perceptivo (Observador, flexible, expontáneo, sensible) ☐

8. Enfermedades que ha padecido en su vida (marque todas las que apliquen):

   Alta Presión ☐ Baja Presión ☐ Artritis ☐

   Cáncer ☐ Corazón ☐ Diabetes ☐

   Hepatitis ☐ Ulceras ☐ Problemas de la Circulación ☐

   Otros _____

9. Mantenimiento Personal:

   Buena Alimentación ☐ Ejercicio ☐

Cont. Questionnaire B1.2

Terapia Física ☐ Técnicas de Relajación ☐
Explique _____

Otros ☐ Explique _____

10. Familiar cercano que padece o ha padecido de **esclerosis múltiple (EM)**

Señale el parentesco: Padre ☐ Madre ☐ Hermano(a) ☐
Abuelo(a) ☐ Tío(a) ☐

11. Marque o seleccione las enfermedades previas en la familia e indique el parentesco con la persona y edad.

Enfermedad	Parentesco	Edad
Alta Presión	_____	_____
Baja Presión	_____	_____
Artritis	_____	_____
Cáncer	_____	_____
Corazón	_____	_____
Diabetes	_____	_____
Hepatitis	_____	_____
Ulceras	_____	_____
Problemas de la Circulación	_____	_____

Otros _____

12. Factor o causa que le precipitó a usted la **EM** _____

_____

13. Síntomas en su primer ataque:

Neuritis (visión periferal) ☐ Debilidad en las piernas ☐
Pérdida de Balance ☐ Pérdida de coordinación ☐
Otros _____

Cont. Questionnaire B1.2

Dónde y cómo ocurrieron: _____

14. Indique el núnero de veces y la edad en que ha estado expuesto a virus:

Virus	Número de veces	Edad
a) dengue	_____	_____
b) Herpes	_____	_____
c) influenza pulmonía	_____	_____
d) sarampión	_____	_____
e) varicela	_____	_____
f) otros	_____	_____
	_____	_____

15. ¿Ha recibido transfusiones de sangre? Indique número de veces y fechas.

Sí ☐

Número de Veces	Fecha
_____	_____
_____	_____

No ☐

16. Apróximadamente cuánto tiempo transcurre entre un episodio de **EM** y otro:

_____

17. Indique el tiempo que lleva con la condición de **EM**

_____

_____

18. Indique los síntomas más comunes o frecuentes que padece _____

_____

_____

_____

Cont. Questionnaire B1.2

19. Indique los síntomas que persisten una vez termine el episodio de actividad de **EM,** con los cuales continúa siempre o nunca se recupera.

_____

_____

_____

Questionnaire B2

Se ha elaborado éste cuestionario donde se pide información al paciente de Esclerosis Múltiple y a un familiar cercano (orden de preferencia; hermanos, padres e hijos). El cuestionario servirá para colectar información para tratar de saber qué factores son relevantes o pueden ser posibles causas de que en Puerto Rico haya muchos casos de Esclerosis Múltilpe, siendo Puerto Rico un lugar donde se supone la condición no exista. La información colectada con el cuestionario será utilizada de manera confidencial y la participación en el mismo es de forma voluntaria. Se le agradece la colaboración brindada. Favor escriba con letra de molde o de forma legible.

1. ¿Tiene usted la condición de Esclerosis Múltiple?

   _____ Si _____ No

   Si padece la condición de Esclerosis Múltiple, conteste las preguntas de la 2 a la 11 antes de continuar con las otras, cuando aplique puede marcar más de una alternativa. Si no tiene la condición de Esclerosis Múltiple, favor pasar a la pregunta 12.

2. Indique la edad al **comienzo de los síntomas**. _____ años

   Fecha _____

3. Indique la edad que usted tenía **cuando se le diagnosticó la condición** de Esclerosis Múltiple. _____ años Fecha _____

4. Aproximadamente, ¿**cuánto tiempo**, mayormente, **transcurre entre un ataque** (exacerbación) de Esclerosis Múltiple y **otro**? _____

5. Indique el tiempo **que lleva con la condición** de Esclerosis Múltiple. _____

6. Seleccione el síntoma/as en su primer ataque.

   _____ Neuritis _____ Pérdida de coordinación

   _____ Debilidad en las piernas _____ Adormecimiento en las manos

   _____ Pérdida de balance _____ Otros, especifique _____

   _____

Cont. Questionnaire B2

7. Indique los **síntomas más comunes o frecuentes** de la condición.

_____ Debilidad en las piernas _____ Mareos

_____ Adormecimiento en las manos _____ Fatiga o cansancio extremo

_____ Incontinencia urinaria _____ Otro, especifique _____

_____

_____

8. Indique qué síntomas persisten una vez termine el episodio de actividad de Esclerosis Múltiple (ataque); síntomas con los cuales continúa o de los cuales nunca logra una recuperación total.

_____ Visión doble
_____ Espasticidad
_____Pérdida de coordinación
_____ Mareos
_____ Dificultad para tragar
_____ Otros, especifique _____
_____
_____
_____

Especifique si algún **suceso inesperado o cambio grande ocurrió antes** de que tuviera su primer ataque de Esclerosis Múltiple y se le diagnosticara con la condición.

_____ Muerte del cónyugue
_____ Accidente de carro
_____ Enfermedad propia
_____ Divorcio
_____ Pérdida de trabajo
_____ Otros, especifique _____
_____
_____

9. ¿Qué clase de Eclerosis Múltiple le han dicho que usted padece?

_____ Bening _____Relapsing-Remitting _____Primary Progresive

_____Secondary Progressive _____Progressive Relapsing _____No se

10. ¿Qué método fue utilizado, por su médico, para diagnosticarle la condición de Esclerosis Múltiple?

Cont. Questionnaire A2

_____ MRI _____CT Scan _____Función Espinal _____No se

_____ Otro; especifique _____

11. Indique su edad. _____ años

12. Sexo o Género _____ Femenino _____ Masculino

13. Mencione el pueblo e indique la zona de su residencia actual;

Pueblo _____ _____ zona urbana (pueblo)

_____ zona rural (campo)

14. Indique el pais y el pueblo donde nació.

Pais _____ Pueblo _____

15. Especique los lugares dónde vivió los primeros 16 años de su vida; indique el pais, pueblo y edad.

Pais	Pueblo	Edad

16. Especique el pais y pueblo de procedencia de su familia; indique el pais y pueblo según el parentesco familiar.

Parentesco Familiar	Pais	Pueblo
Padre		
Madre		
Abuelo Paterno		
Abuela Paterna		
Abuelo Materna		
Abuela Materna		

Cont. Questionnaire A2

17. Indique la raza o el color de piel según el parentesco familiar.

Color de piel	Blanco	Asiático	Negro	Trigueño
Usted				
Padre				
Madre				
Abuelo paterno				
Abuela paterna				
Abuelo materno				
Abuela materna				

18. Se le provee una lista de condicones de salud o enfermedades para que usted marque (√) en el espacio correspondiente todas las condiciones o enfermedades que apliquen e indique quien/es las padecen. Escriba cualquier otra condición existente en su familia o que usted tenga en los espacios vacios provistos y marque el espacio correspondiente a la persona o familiar, indique cualquier otro miembro que no este en la lista. Cuando sea necesario, en el espacio correspondiente, indique con paréntesis si más de un miembro familiar tiene alguna condición.

Condiciones de salud o Enfermedades	Usted	Madre	Padre	Hermanos	Hermanas	Abuelos Paternos	Abuelos Maternos	Hijas	Hijos	Otros: Indique
Esclerosis Múltiple										
Alta/Baja Presión										
Artritis										
Cancer										
Problemas del Corazón										
Diabetes										
Hepatitis										
Ulceras										
Problemas de Circulación										
Tuberculosis										
Migraña										
Osteoporosis										
Parkinson										
Problemas de la Próstata										
Epilepsia										
Sinusitis										
Alergias										
Glaucoma										
Reflujo o Acidez										
Cataratas										
Otros; especifique										

19. Indique, si aplica, el número de veces que le han dado las siguientes enfermedades virales por año.

Frecuencia	1 vez por mes	1 vez cada 2 a 6 meses	1 ves por año	Otra; indique
Catarro				
Dengue				
Pulmonía				
Herpes simple				
Herpes genital				
Otros; especifique				

20. Indique, si aplica, la edad a la que le han dado las siguientes enfermedades virales.

Enfermedad Viral	**Edad**
Varicela	
Sarampión Común	
Culebrilla	
Sarampión Aleman	
Paperas	
Otros; especifique	

21. Si aplica, indique cuándo y a qué edad fue vacunado contra la Influenza.

Cuando (fecha; año)	Edad	No he sido vacunado
		Contra la Influenza

22. Si aplica, indique cuándo y a qué edad fue vacunado contra la Hepatitis B.

Cuando (fecha; año)	Edad	No he sido vacunado
		Contra la Hepatitis B

Si aplica, indique si usted recibió alguna otra vacuna además de las que se ponen

Cuando (fecha; año)	Edad	Nombre Vacuna	No he recibido
			Otra vacuna

Cont. Questionnaire B2

23. Son sus padres primos hermanos. _____ SI _____ NO

24. ¿Es usted un gemelo? _____ Idéntico _____ Fraterno _____ No soy gemelo

    ¿Padece su gemelo de Esclerosis Múltiple? _____ Si _____ No

25. Indique el ingreso anual actual de su familia:

_____ menos de 15,000 _____ entre 41,000 @ 55,000

_____ entre 16,000 @ 25,000 _____ entre 56,000 @ 75,000

_____ entre 26,000 @ 40,000 _____ otro; indique _____

26. Indique el grado más alto obtenido por sus padres _____

27. Indique el grado más alto obtenido por usted _____

28. Mencione el nombre,grados que cursó, localización, edad y años de las escuelas o instituciones en las que usted ha estudiado durante su vida.

Institución o Escuela	Grados	Localización	Edad	Años

29. Si tiene alguna platificación en su dentadura, indique las edades en las que le fueron hechas la mayoria de las platificaiones y a qué se debieron las platificaciones.

Edades	Porqué o Razón	No Tengo Platificaciones

Cont. Questionnaire B2

Esta sección se le provee para que usted haga cualquier anotación, comentario o sugerencias que crea pertinente. En la misma le pedimos que nos indique su nombre y cualquier forma de contacto con usted, ya sea telefono, dirección o correo electrónico, para poder contactarlo, ya que su ayuda puede ser requerida a la hora de validar y analizar el cuestionario. Esta información será utilizada de manera confidencial.

ANOTACION, COMENTARIOS O SUGERENCIAS

_____

_____

_____

_____

_____

Una vez más se le agradece la colaboración brindada, la misma ha sido de vital importancia para el estudio. Cualquier duda sobre las preguntas aquí formuladas o sobre el progreso del estudio se pueden comunicar con Carmen Collazo, la persona encargada del estudio, a los teléfonos (738-8449 ó 964-1507).

Questionnaire B3

Se ha elaborado éste cuestionario donde se **pide información al paciente de Esclerosis Múltiple y a un familiar cercano** (orden de preferencia; hermanos, padres ohijos). El cuestionario servirá para colectar información para tratar de saber qué factores son relevantes o pueden ser posibles causas de que en Puerto Rico haya muchos casos de Esclerosis Múltilpe, siendo Puerto Rico un lugar donde se supone la condición no exista. La información colectada con el cuestionario será utilizada de manera confidencial y la participación en el mismo es de forma voluntaria. Se le agradece la colaboración brindada. Favor escriba con letra de molde o de forma legible.

1) ¿Tiene usted la condición de Esclerosis Múltiple?

_____ Si _____ No

Si **padece la condición** de Esclerosis Múltiple, conteste las preguntas de la 2 a la 8 antes de continuar con las otras, cuando aplique puede marcar más de una alternativa. Si **no tiene la condición** de Esclerosis Múltiple, favor pasar a la pregunta 9.

1. Indique la edad al **comienzo de los síntomas**. _____ años

   Fecha _____

2. Indique la edad que usted tenía **cuando se le diagnosticó la condición** de Esclerosis Múltiple. _____ años Fecha _____

3. Aproximadamente, ¿**cuánto tiempo**, mayormente, **transcurre entre un ataque** (exacerbación) de Esclerosis Múltiple y **otro**? _____

4. Especifique si algún **suceso inesperado o cambio grande ocurrió antes** de que tuviera su primer ataque de Esclerosis Múltiple y se le diagnosticara con la condición.

   _____ Muerte de la madre _____ Mucho Stress

   _____ Accidente de carro _____ Pérdida de trabajo

   _____ Enfermedad del hijo _____ Otros, especifique _____

5. Se le provee una lista de síntomas relacionados a la Esclerosis Múltiple para que usted marque (**X**), en el espacio correspondiente a la derecha, **todos los síntomas**

que usted haya padecido o padezca según la situación especificada a la derecha. Escriba cualquier otro síntoma que usted tenga en los espacios vacios provistos y marque el espacio correspondiente a la derecha.

Síntomas relacionados con la MS	Síntomas en su primer ataque de Esclerosis Múltiple	Síntomas más comunes o frecuentes	Síntomas de los cuales no recupera totalmente una vez el episodio de MS termina
Estreñimiento			
Incontinencia Urinaria			
Disfución Cognocitiva			
Depresión			
Mareos o Vértigos			
Dificultad al Tragar			
Fatiga o Cansancio			
Espasticidad			
Desbalance			
Debilidad en Extremidades			
Pérdida de Sensación			
Dolor de Cabeza			
Pérdida de Audición			
Hormigueo			
Dolor en el Cuerpo			
Adormecimiento Cuerpo			
Temblores			
Picor			
Movimientos Involuntarios			
Dificultad al Hablar			
Neuritis Optica			
Visión Doble			
Pérdida de Visión			
Pérdida de Coordinación			
Calor Extremo			
Otros; especifique			

6. ¿Qué clase de Eclerosis Múltiple le han dicho que usted padece?

   _____ Bening _____Relapsing-Remitting _____Primary Progresive

   _____Secondary Progressive _____Progressive Relapsing _____No se

7. ¿Qué método fue utilizado, por su médico, para diagnosticarle la condición de Esclerosis Múltiple?

_____ MRI _____CT Scan _____Función Espinal _____No se

_____ Otro; especifique _____

8. Indique su edad. _____ años
9. Sexo o Género _____ Femenino _____ Masculino
10. Mencione el pueblo e indique la zona de su residencia actual;

    Pueblo _____ _____ zona urbana (pueblo)

    _____ zona rural (campo)

11. Indique el pais y el pueblo donde nació.

    Pais _____ Pueblo _____

12. Especique los **lugares dónde vivió los primeros 16 años** de su vida; indique el pais, pueblo y edad.

Pais	Pueblo	Edad

13. En la tabla **especifique el pais y pueblo de procedencia** de su familia; indique el pais y pueblo según el parentesco familiar. En la tabla, tambien **indique la raza o el color de piel** según el parentesco familiar.

Parentesco Familiar	Pais	Pueblo	Raza o color de piel (blanco,asiático,negro ó trigueño)
Usted			
Padre			
Madre			
Abuelo Paterno			
Abuela Paterna			
Abuelo Materno			
Abuela Materna			

14. Indique **cuándo y a qué edad** fue vacunado contra la Influenza y contra la Hepattis B. Tambien indique **si usted recibio alguna otra** vacuna además de las que se ponen cuando niño o las antes mencionadas. **Si no ha recibido ninguna indíquelo.**

Nombre de la vacuna recibida	Fecha (año) cuando se vacunó	Edad a la que se vacuno	No he sido vacunado
Hepatits B			
Influenza			
Otra;indique			

15. Se le provee una lista de condicones de salud o enfermedades para que usted marque (**X**) en el espacio correspondiente todas las condiciones o enfermedades que apliquen e indique quien/es las padecen. Escriba cualquier otra condición existente en su familia o que usted tenga en los espacios vacios provistos y marque el espacio correspondiente a la persona o familiar, indique cualquier otro miembro que no este en la lista. Cuando sea necesario, en el espacio correspondiente, indique con paréntesis si más de un miembro familiar tiene alguna condición.

Cont. Questionnaire B3

Condiciones de salud o Enfermedades	Usted	Madera	Padre	Hermanos	Hermanas	Abuelos Paternos	Abuelos Maternos	Hijas	Hijos
Esclerosis Múltiple									
Fibromialgia									
Artritis Reumatoidea									
Cancer									
Aids									
Parkinson									
Síndrome CREST									
Síndrome Sjogren									
Epilepsia									
Diabetes									
Migraña									
Osteoporosis									
Hepatitis									
Escleroderma									
Problemas de Circulación									
Tuberculosis									
Hernia Esofago									
Problemas del Corazón									
Sinusitis									
Alergias									
Glaucoma									
Reflujo o Acidez									
Cataratas									
Otros; especifique									

16. Indique, si aplica, el **número de veces** que le han dado las siguientes enfermedades virales por año.

Frecuencia	1 vez por mes	1 vez cada 2 a 6 meses	1 ves por año	Otra; indique
Catarro				
Dengue				
Pulmonía				
Herpes labial				
Hepatitis A ó C				
Otros; especifique				

17. Indique, si aplica, la **edad** a la que le han dado las siguientes enfermedades virales.

Enfermedad Viral	Edad
Varicela	
Sarampión Común	
Mononucleosis	
Sarampión Aleman	
Paperas	
Otros; especifique	

18. Son sus padres primos hermanos. _____ SI _____ NO

19. ¿Es usted un gemelo? _____ Idéntico _____ Fraterno _____ No soy gemelo

¿Padece su gemelo de Esclerosis Múltiple? _____ Si _____ No

20. Indique el ingreso anual actual de su familia:

_____ menos de 15,000 _____ entre 41,000 @ 55,000

_____ entre 16,000 @ 25,000 _____ entre 56,000 @ 75,000

_____ entre 26,000 @ 40,000 _____ otro; indique _____

21. Indique el grado más alto obtenido por sus padres _____Madre _____Padre

22. Indique el grado más alto obtenido por usted _____

23. Si tiene alguna platificación en su dentadura, indique las **edades** en las que le fueron hechas la mayoria de las platificaiones y a **qué se debieron** las platificaciones.

Edades	Porqué o Razón	Numero de Platificaciones	No Tengo Platificaciones

Una vez más se le agradece la colaboración brindada, la misma ha sido de vital importancia para el estudio. Cualquier duda sobre las preguntas aquí formuladas o sobre el progreso del estudio se pueden comunicar al teléfono (738-8449).

APPENDIX C

Kinds of symptoms that patients with the condition of MS suffered.

Table C.1: Kinds of symptoms that patients with the condition of MS suffered in figures3.7, 3.8 and 3.9.

Variable	Variable name
XA,B or C6.1	Constipation
XA,B or C6.2	Urinary Incontinence
XA,B or C6.3	Cognitive Dysfunction
XA,B or C6.4	Depression
XA,B or C6.5	Dizziness and Vertigo
XA,B or C6.6	Difficulty swallowing
XA,B or C6.7	Fatigue or tiredness
XA,B or C6.8	Spasticity
XA,B or C6.9	Loss of balance
XA,B or C6.10	Weakness Extremities
XA,B or C6.11	Loss of Sensation
XA,B or C6.12	Headache
XA,B or C6.13	Hearing loss
XA,B or C6.14	Prickling
XA,B or C6.15	Body pain
XA,B or C6.16	Numbness
XA,B or C6.17	Tremors
XA,B or C6.18	Itching
XA,B or C6.19	Involuntary movements
XA,B or C6.20	Speech difficulty
XA,B or C6.21	Optic neuritis
XA,B or C6.22	Double vision
XA,B or C6.23	Visual loss
XA,B or C6.24	Coordination loss
XA,B or C6.25	Extreme heat
XA,B or C6.26	Urinary retention
XA,B or C6.27	Difficulty in walking
XA,B or C6.28	Muscle pain
XA,B or C6.29	Anxiety
XA,B or C6.30	Nausea
XA,B or C6.31	Burning sensation
XA,B or C6.32	Hallucinations
XA,B or C6.33	Insomnia
XA,B or C6.34	Hair loss
XA,B or C6.35	Extreme cold
XA,B or C6.36	Bowel incontinence
XA,B or C6.37	Stuttering
XA,B or C6.38	Bad temper
XA,B or C6.39	Muscle immobility
XA,B or C6.40	Mental lapses
XA,B or C6.41	Dysarthias
XA,B or C6.42	Dysphasia
XA,B or C6.43	Loss of smell sense

Table C.2: Kinds of symptoms that patients with the condition of MS suffered in descending order.

Symptoms 1st attack	sum	Common symptoms	sum	Symptoms that persist	sum
XA6.16	31	XB6.7	38	XC6.7	30
XA6.10	30	XB6.9	37	XC6.10	24
XA6.9	29	XB6.10	36	XC6.9	23
XA6.14	29	XB6.12	31	XC6.11	21
XA6.7	27	XB6.14	31	XC6.25	20
XA6.5	26	XB6.16	30	XC6.2	17
XA6.11	26	XB6.4	29	XC6.16	17
XA6.12	26	XB6.5	29	XC6.19	15
XA6.22	26	XB6.11	28	XC6.1	14
XA6.4	22	XB6.2	26	XC6.12	14
XA6.24	20	XB6.15	26	XC6.14	14
XA6.21	17	XB6.19	26	XC6.4	13
XA6.25	17	XB6.1	25	XC6.15	13
XA6.17	15	XB6.25	25	XC6.24	13
XA6.23	15	XB6.17	24	XC6.8	12
XA6.2	14	XB6.24	21	XC6.5	11
XA6.19	14	XB6.20	20	XC6.17	11
XA6.15	13	XB6.22	20	XC6.22	9
XA6.20	13	XB6.8	17	XC6.23	9
XA6.1	9	XB6.18	17	XC6.21	7
XA6.8	8	XB6.23	12	XC6.20	5
XA6.6	6	XB6.6	11	XC6.6	4
XA6.13	6	XB6.21	10	XC6.18	3
XA6.18	6	XB6.3	8	XC6.27	3
XA6.3	3	XB6.13	8	XC6.3	2
XA6.27	2	XB6.36	4	XC6.13	2
XA6.30	2	XB6.30	2	XC6.31	2
XA6.34	2	XB6.34	2	XC6.36	2
XA6.37	2	XB6.37	2	XC6.37	2
XA6.42	2	XB6.42	2	XC6.42	2
XA6.26	1	XB6.26	1	XC6.26	1
XA6.29	1	XB6.27	1	XC6.29	1
XA6.36	1	XB6.28	1	XC6.33	1
XA6.39	1	XB6.29	1	XC6.34	1
XA6.43	1	XB6.31	1	XC6.40	1
XA6.28	0	XB6.32	1	XC6.28	0
XA6.31	0	XB6.33	1	XC6.30	0
XA6.32	0	XB6.35	1	XC6.32	0
XA6.33	0	XB6.39	1	XC6.35	0
XA6.35	0	XB6.38	0	XC6.38	0
XA6.38	0	XB6.40	0	XC6.39	0
XA6.40	0	XB6.41	0	XC6.41	0
XA6.41	0	XB6.43	0	XC6.43	0

APPENDIX D

Variable correlation table after first elimination.

Table D.1: Variable Correlation Table after first elimination.

Variable	Correlation	Name of variable	relation	variable type
X1	1	MS	person	outcome variable
X9	0.14028827	age	person	predictor
X10	0.03605002	Sex	person	predictor
XA13.3	0.12103764	country16ageEspana	person	predictor
XB13.2	0.18849362	town16ageLares	person	predictor
XB13.3	0.14204419	town16ageSanGerman	person	predictor
XC13.2	0.1735622	age16age	person	predictor
XA15.4	-0.11401754	year tuberculosis	person	predictor
XA15.5	-0.11401754	year smallpox	person	predictor
XA15.8	0.12665783	year tetanus	person	predictor
XB15.4	-0.11401754	age tuberculosis	person	predictor
XB15.5	-0.11401754	age smallpox	person	predictor
XB15.8	0.11955989	age tetanus	person	predictor
XA16.1	1	MS	person	predictor
XA16.2	-0.21096325	fibromialgy	person	predictor
XA16.13	-0.11401754	hepatitis	person	predictor
XA16.20	-0.13072664	allergy	person	predictor
XA16.21	-0.16182413	glaucoma	person	predictor
XA16.35	-0.1140175	bipolar	person	predictor
XB16.1	-0.45398794	Ms mother	mother	predictor
XB16.45	-0.11401754	neuropathies	mother	predictor
XC16.1	-0.14122412	Ms father	father	predictor
XC16.10	0.14601109	diabetes	father	predictor
XC16.11	-0.11401754	migraine	father	predictor
XC16.17	-0.19891007	hernia esophagus	father	predictor
XD16.1	-0.1140175	Ms brother	brother	predictor
XD16.13	0.14212807	hepatitis	brother	predictor
XD16.14	-0.11401754	scleroderma	brother	predictor
XD16.19	-0.20270215	sinus	brother	predictor
XE16.1	-0.38917721	Ms sister	sister	predictor
XE16.9	-0.11401754	epilepsy	sister	predictor
XE16.11	-0.16068512	migraine	sister	predictor
XE16.12	0.14212807	osteoporosis	sister	predictor
XE16.20	-0.18959595	allergy	sister	predictor
XE16.35	-0.1140175	bipolar	sister	predictor
XE16.37	-0.11401754	osteoarthritis	sister	predictor
XE16.39	-0.11401754	Hernia ingle	sister	predictor
XE16.40	-0.11401754	ulcer	sister	predictor
XF16.1	-0.11401754	MS	father grandparents	predictor
XF16.2	-0.11401754	fibromialgy	father grandparents	predictor
XF16.12	-0.19891007	osteoporosis	father grandparents	predictor
XF16.19	-0.11401754	sinus	father grandparents	predictor
XF16.20	-0.11401754	allergy	father grandparents	predictor
XF16.37	-0.11401754	osteoarthritis	father grandparents	predictor

XF16.41	-0.16182413	Alzheimer	father grandparents	predictor
XG16.12	-0.15047772	osteoporosis	mother grandparents	predictor
XG16.14	-0.11401754	scleroderma	mother grandparents	predictor
XG16.16	0.16941854	tuberculosis	mother grandparents	predictor
XG16.19	-0.17851285	sinus	mother grandparents	predictor
XG16.23	0.12663373	cataract	mother grandparents	predictor
XG16.32	-0.11401754	depression	mother grandparents	predictor
XH16.1	-0.35833509	MS	daughter	predictor
XH16.2	-0.11401754	fibromialgy	daughter	predictor
XH16.15	-0.1140175	circulation problems	daughter	predictor
XH16.17	-0.11401754	hernia esophagi	daughter	predictor
XH16.25	-0.1140175	asthma	daughter	predictor
XH16.32	-0.1140175	depression	daughter	predictor
XH16.34	-0.1140175	anxiety	daughter	predictor
XH16.37	-0.11401754	osteoarthritis	daughter	predictor
XI16.1	-0.16182413	MS	son	predictor
XI16.5	-0.11401754	aids	son	predictor
XI16.13	-0.11401754	hepatitis	son	predictor
XI16.19	0.18498454	sinus	son	predictor
XI16.20	0.15028785	allergy	son	predictor
XI16.23	-0.11401754	cataract	son	predictor
XI16.34	-0.1140175	anxiety	son	predictor
X17.4	0.15976541	herpes labial	son	predictor
X17.10	-0.1140175	herpes genital	son	predictor
X18.1	0.16150665	chicken pox	age virus	predictor
X18.3	0.14557311	mononucleosis	age virus	predictor
X23	0.15592082	education	person	predictor

APPENDIX E

Variable correlation table after second elimination.

Table E.1: Variable Correlation Table after second elimination

Variable	Correlation	Name of variable	relation	variable type
X1	1	MS	person	outcome variable
X9	0.14028827	age	person	predictor
X10	0.03605002	Sex	person	predictor
XB13.2	0.18849362	town16age	person	predictor
XC13.2	0.1735622	age16age	person	predictor
XA16.2	-0.21096325	fibromialgy	person	predictor
XA16.21	-0.16182413	glaucoma	person	predictor
XB16.1	-0.45398794	Ms mother	mother	predictor
XC16.17	-0.19891007	hernia esophagus	father	predictor
XD16.19	-0.20270215	sinus	brother	predictor
XE16.1	-0.38917721	Ms sister	sister	predictor
XE16.11	-0.16068512	migraine	sister	predictor
XE16.20	-0.18959595	allergy	sister	predictor
XF16.12	-0.19891007	osteoporosis	father grandparents	predictor
XF16.41	-0.16182413	Alzheimer	father grandparents	predictor
XG16.16	0.16941854	tuberculosis	mother grandparents	predictor
XG16.19	-0.17851285	sinus	mother grandparents	predictor
XH16.1	-0.35833509	MS	daughter	predictor
XI16.1	-0.16182413	MS	son	predictor
XI16.19	0.18498454	sinus	son	predictor
XI16.20	0.15028785	allergy	son	predictor
X17.4	0.15976541	herpes labial	son	predictor
X18.1	0.16150665	chicken pox	age virus	predictor

APPENDIX F

Health conditions table for the final equation validation.

Table F.1: Final Equation Validation

	Final Equation Validation												
	Health Conditions												
Age	Fibromialgy person	Mother MS	Sister MS	allergy, sister	Daughter, MS	son, sinus	Age chicken pox, person	ValidationEquation1		ValidationEquation2		ValidationElquation3	
X9	XA16.2	XB16.1	XE16.1	XE16.20	XH16.1	XI16.19	X18.1	Equation	p^	Equation	p^	Equation	p^
39	0	0	0	0	0	0	0	1.308	0.212822	1.50113	0.18226	1.02467	0.26412
41	0	0	0	1	0	1	0	2.206	0.099213	0.30352	0.4247	2.93177	0.05061
54	0	0	0	0	0	0	12	2.52288	0.07427	2.541624	0.07299	2.9777	0.04844
36	0	0	0	0	0	0	30	4.3452	**0.012803**	4.102364	**0.01626**	4.00366	0.01792
56	0	0	0	0	0	0	19	3.23156	0.037995	3.148578	0.04115	3.7997	0.02189
40	0	0	0	0	0	1	0	3.854	**0.020755**	1.50113	0.18226	2.88477	0.05291
55	0	0	0	0	0	0	12	2.52288	0.07427	2.541624	0.07299	3.0247	0.04632
42	0	0	0	1	0	0	0	-0.34	0.584191	0.30352	0.4247	1.16567	0.23764
66	0	0	0	0	0	0	0	1.308	0.212822	1.50113	0.18226	2.29372	0.09164
47	0	0	0	0	0	0	8	2.11792	0.107367	2.194792	0.10022	2.23268	0.09685
72	0	0	0	0	0	0	8	2.11792	0.107367	2.194792	0.10022	3.40773	0.03205
29	0	0	0	0	0	0	0	1.308	0.212822	1.50113	0.18226	0.55465	0.36479
43	0	0	0	0	0	0	18	3.13032	0.041874	3.06187	0.04471	3.08468	0.04374
35	0	0	0	0	0	0	0	1.308	0.212822	1.50113	0.18226	0.83666	0.30224
39	0	0	0	0	0	0	2	1.51048	0.180868	1.674546	0.15782	1.23267	0.22571
32	0	0	0	0	0	0	26	3.94024	**0.019073**	3.755533	**0.02285**	3.39965	0.03231
47	0	0	0	0	0	0	10	2.3204	0.089447	2.368208	0.08563	2.44068	0.08012
58	0	0	0	0	0	0	0	1.308	0.212822	1.50113	0.18226	1.91771	0.12812

47	0	0	0	0	0	0	0	1.308	0.212822	1.50113	0.18226	1.40068	0.19771
33	0	0	0	0	0	0	0	1.308	0.212822	1.50113	0.18226	0.74266	0.32242
41	0	0	0	1	0	0	6	0.26744	0.433536	0.823767	0.30496	1.74267	0.14897
44	0	0	0	0	0	0	6	1.91544	0.128371	2.021377	0.11698	1.88368	0.13197
41	0	0	0	0	0	0	14	2.72536	0.061493	2.715039	0.06209	2.57467	0.07079
50	0	0	0	0	0	0	9	2.21916	0.098043	2.2815	0.09267	2.47769	0.07744
58	0	0	0	0	0	0	0	1.308	0.212822	1.50113	0.18226	1.91771	0.12812
72	0	0	0	0	0	0	8	2.11792	0.107367	2.194792	0.10022	3.40773	0.03205
54	0	0	0	0	0	1	30	6.8912	**0.001016**	4.102364	**0.01626**	6.6628	0.00128
50	0	0	0	0	0	0	36	4.95264	**0.007015**	4.622611	**0.00973**	5.28569	0.00504
62	0	0	0	0	0	0	8	2.11792	0.107367	2.194792	0.10022	2.93771	0.05032
51	0	0	0	0	0	0	10	2.3204	0.089447	2.368208	0.08563	2.62869	0.06731

ValidationEquation4		ValidationEquation5		ValidationEquation6	
Equation	p^	Equation	p^	Equation	p^
1.3988	0.19801	1.18719	0.233762	1.27608	0.218218
0.3953	0.40244	1.30345	0.213585	1.27608	0.218218
3.53627	0.0283	3.28446	0.036108	2.34384	0.087557
4.35905	0.01263	4.0761	0.01669	3.94548	0.018975
4.38589	0.0123	4.11549	0.016056	2.9667	0.048953
1.45765	0.18883	1.24532	0.223511	1.27608	0.218218
3.59512	0.02672	3.34259	0.034139	2.34384	0.087557
0.45415	0.38837	1.36158	0.203984	1.27608	0.218218
2.98775	0.04798	2.7567	0.059709	1.27608	0.218218
2.70608	0.06262	2.46911	0.078052	1.98792	0.120477
4.17733	0.01511	3.92236	0.01941	1.98792	0.120477
0.8103	0.30783	0.60589	0.352997	1.27608	0.218218
3.51628	0.02885	3.25769	0.037052	2.87772	0.053266
1.1634	0.23805	0.95467	0.277947	1.27608	0.218218
1.60792	0.16688	1.39141	0.199183	1.45404	0.189381
3.70541	0.024	3.43514	0.031215	3.58956	0.026869
2.9152	0.05141	2.67333	0.064566	2.16588	0.102857
2.51695	0.07468	2.29166	0.091816	1.27608	0.218218
1.8696	0.13359	1.65223	0.160808	1.27608	0.218218
1.0457	0.26005	0.83841	0.30187	1.27608	0.218218
1.02266	0.26451	1.91611	0.128296	1.80996	0.140643
2.32041	0.08945	2.0905	0.110024	1.80996	0.140643
2.98034	0.04832	2.73299	0.061055	2.5218	0.074344
2.98719	0.04801	2.74561	0.060335	2.0769	0.111362
2.51695	0.07468	2.29166	0.091816	1.27608	0.218218
4.17733	0.01511	3.92236	0.01941	1.98792	0.120477
5.41835	0.00441	5.12244	0.005926	3.94548	0.018975
5.81031	0.00299	5.50258	0.00406	4.47936	0.011214
3.58883	0.02689	3.34106	0.034189	1.98792	0.120477
3.1506	0.04107	2.90585	0.051865	2.16588	0.102857