# QUANTIFYING FAMILY HISTORY FOR MENTAL ILLNESS

A Project

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Abstract

QUANTIFYING FAMILY HISTORY

FOR MENTAL ILLNESS

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Family history, in the context of medicine, is made up of information about various disorders which have been suffered by blood relatives of a patient. Family history is a strong predictor in the development of many chronic diseases. It can provide information (both genetic and environmental) which can guide prevention and treatment with relatively low expense. One of the main issues, however, is the method by which one may generate a family history score for the purpose of analysis. A dichotomous measure (which takes the value of 1 if any relative of the patient is affected with the disorder, 0 otherwise), count of affected relatives, proportion of relatives that are affected within a family and scores involving prevalence and expectation of developing a disorder have been proposed in the literature. This project compares six existing methods of quantifying family history and proposes one new method, and outlines the advantages and disadvantages of each. A longitudinal psychological data set on bipolar disorder (BD) is used to illustrate the methods. The data set consists of individuals at high-risk of BD since one of their parents has BD. The methods

are assessed and compared through exploratory data analysis and Cox proportional hazards modeling. The different score methods produced varying results emphasizing the importance of weighting, family size and age of relatives as variables within family score calculation. Implications and directions for future study are discussed.

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*To Mom and Dad.*

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# Chapter 1

# Introduction

## 1.1 Purpose and Overview of the Project

There is a strong need for reliable and valid tools that can be used to predict the onset, course and response to treatment of chronic diseases. Given the advances made in mapping the human genome, it would seem that genetic testing would serve this need and allow for accurate prediction and the eventual conquest of the numerous chronic illnesses which plague humanity, examples of these being cancer, cardiovascular disease, diabetes and mental illness. Single gene disorders such as Huntington's disease and cystic fibrosis are shown to be accurately predicted through genetic testing, however these types of illness only make up roughly 5 percent of the diseases within the population (Yoon et al. 2002). Unfortunately, genetic testing is not reliable when one steps outside of the single-gene realm. With a vast majority of diseases lying beyond the scope of a single gene cause, other methods of predicting illness must be employed. These methods must incorporate information from both the genetic side, which would include not just a single gene but a mixture of many genes responsible for a disease, and the environmental side of the coin. The simplest way to achieve this is by using family history (Yoon et al. 2002). Family history

of a patient involves information dealing with the disease history of that patient's blood relatives or family members. Family members tend to show similar disease risk patterns because they usually share genetic and environmental information (Valdez et al. 2010).

Many studies have shown that family history serves as a powerful predictor in many chronic diseases. Pharoah et al. (1997) summarize multiple varying studies where family history can be shown as a significant risk factor for breast cancer. For colorectal, prostate, lung, ovarian and other cancers, researchers have also demonstrated that family history is a valuable tool for assessing risk (Valdez et al. 2010). Cardiovascular disease and diabetes are two other examples of chronic illnesses which show a strong connection between family history and development/prognosis of the disease (Mansour-Chemaly et al. 2002). Family history of obesity, hypertension and diabetes was also shown by Hunt et al. (2000) to be a significant risk factor for the development of these ailments, together classified in the category of multiple metabolic syndrome.

When discussing mental illness, family history has also been seen as significant in measuring a person's susceptibility. Studies involving anxiety, mood disorders, schizophrenia and numerous other psychological diseases have demonstrated this relationship (Firestone and Marshall, 2000). Ostiguy et al. (2011) showed that subjects with a family history of affective disorders (major depression and bipolar disorder), are seen to have higher stress and cortisol levels which are major predictors of nearly all mental illnesses. Within bipolar youth, Hua et al. (2011) found that psychotic features were more common in those subjects with a history of psychosis in their

family. Verghese et al. (2011) conducted a large study (over 8,000 subjects) and found that those with a family history of mental illness including anxiety, mood disorder, schizophrenia and substance abuse, showed significantly higher risk of psychotic episodes such as delusions and hallucinations.

Across forms of chronic disease, family history has revealed itself as a useful tool for prediction, however, how do we measure family history of a disease? Many studies simply ask whether the subject has a family member with the disorder in question. Others use a more detailed criterion, which makes use of factors such as family size, age and sex to quantify family history. Should family history be treated as an indicator variable or should it be a continuous variable? The present study will seek to examine this issue by first discussing various methods of quantifying family history that have been proposed and utilized in the literature. Then these methods will be calculated from a longitudinal data set involving offspring of bipolar parents and the parents' family history of various mental disorders. The resulting scores will then be examined using exploratory data analysis as well as Cox regression (Allison, 2010) in order to model how the different family history scores predict mental illnesses in the offspring.

The objectives of this study are to:

1. compare the values of different score methods;

2. evaluate the importance of different factors involved in calculating family history, such as family size, genetic distance, and number of affected relatives;

3. use Cox regression to determine how family history of psychopathology predicts

the development of mental disorders including anxiety, and bipolar disorder;

4. determine a possible direction for future work in the study of family history.

The remainder of Chapter 1 will be dedicated to describing the data set. Chapter 2 will focus on describing the different family score methods, what information they make use of and how they are calculated as well as the results of recent studies comparing them. Chapter 2 will also outline the Cox proportional hazards model utilized in the present study. Chapter 3 will present the results and comparisons of the score methods including the Cox regression analysis and Chapter 4 will discuss the results and present ideas for future work.

## 1.2 Description of the Data

The data set used is a subset of a larger ongoing longitudinal database collected from families in Ontario and Halifax. The information regarding the data collection and content is taken from Duffy (2011). The purposes of the data are to map out the clinical stages of bipolar disorder as well as to identify risk factors in its development, including family history, which is the subject of the present study.

The data consist of 220 offspring, which will henceforth be referred to as probands. Proband, in this sense, is defined as the individual being studied or reported on (National Institute of Health, 2011). All probands were at high risk of bipolar disorder and information on their first and second degree relatives was also included in the data set. In this study, high-risk is defined as having one, and only one, parent meeting the criteria for a specific major mood disorder outlined by the Di-

agnostic and Statistical Manual of Mental Disorders, version 4 (DSM-IV). The reason for the definition of high-risk including only one affected parent, is to minimize the contribution of assortative mating, that is a sexually reproducing organism choosing to mate with other organisms possessing similar characteristics (Duffy et al. 2010). Bipolar diosrder has presented itself as a strongly heritable mental illness, therefore it is safe to say that children of bipolar parents should be at high-risk for bipolar disorder (Firestone and Marshall, 2000).

Families are identified from their involvement in an ongoing genetics study. This study includes patients with bipolar disorder and their adult relatives who complete The Schedule for Affective Disorders and Schizophrenia-lifetime version (SADS-L) interviews conducted by a research psychiatrist. Information from unavailable relatives is obtained through The Family History Research Diagnostic Criteria (FH-RDC) from at least two informants. A subject is included in the study if they have one parent meeting the criteria outlined above (diagnosed with a major mood disorder) and one parent unaffected with a lifetime psychiatric disorder (this includes major mood disorder, psychotic disorder, anxiety disorder, substance use disorder as well as bipolar disorder). The subject must also be aged 7-19 and consenting, as 7 has been determined as the earliest age where reliable information can be collected based on interviews. Those subjects who are not able to follow the study protocol are excluded from the data. An example of this would be a subject suffering from a developmental disorder. For each of the 220 subjects, the data contained information on the subject, their affected parent, and the affected parents' mother, father and siblings. This information included the dates of birth, whether they were diagnosed

with bipolar disorder, major and minor mood disorder, anxiety disorder, substance use disorder, and psychotic disorder and the age of onset of these diagnoses. The age at last assessment was also included for the second degree relatives. For the offspring and their affected parent, age at last assessment was taken to be age at 12/05/2011.

The data set was made up of only high risk probands and hence, did not include any controls. In addition, not all siblings of the probands were included in the data (only those that consented). This led to the need for certain assumptions, which will be discussed later. The implications of these characteristics of the data set will also be discussed in later chapters.

# Chapter 2

# Methods

## 2.1 Methods for quantifying family history

There is strong evidence for family history as a significant risk factor for many chronic diseases such as cancer, heart disease and diabetes. Properly quantified family history can serve as an accurate measure of risk and subsequently guide intervention and motivate behaviour. Advantages of family history include the fact that it is less expensive than retrieving genetic information and it also includes shared genetic and environmental factors (Valdez et al. 2010). There are many methods discussed in the literature to quantify family history. The methods utilized in the present study are described below.

### 2.1.1 Dichotomous method

The simplest and most common method to quantify family history is the dichotomous measure where family history score is set to one for a person that has at least one relative with the disease in question and set to zero otherwise (Murad et al. 2006). So the dichotomous measure for the $ith$ proband can be described as follows,

where $affected_i$ represents the number of affected relatives for the $ith$ proband:

$$Dichotomous_i = \begin{cases} 1 & \text{if } affected_i \geq 1 \\ 0 & \text{if } affected_i = 0 \end{cases}$$

This method however does not take into account family size and specifically how many affected relatives there are.

### 2.1.2 Count Method

To account for the number of affected relatives, there is a method which simply takes a weighted sum of all of the affected relatives that a person has for the disease in question. The weight for each relative is based on that relative's genetic distance from the person, for whom the score is being calculated. So a first degree relative (parent or sibling) may receive double the weight of a second degree relative (grandparent or uncle) (Murad et al. 2006). The count method can be shown by the following formula for the $ith$ proband with $n$ affected relatives:

$$Count_i = \sum_{j=1}^{n} w_{ij} \tag{2.1}$$

where $w_{ij}$ is the weight allocated to the $jth$ affected relative of the $ith$ proband.

### 2.1.3 Weighted Proportion Score

Van Esch et al. (1994) describe a method that expresses family history score in terms of proportion. This score was used in assessing risk for seizures (Silberberg et al. 1999). This method takes the number of relatives affected by febrile seizures

and divides by the total number of family members excluding the proband (Van Esche et al. 1994). In the Van Esche et al. (1994) study, only first degree relatives were used therefore because the present study includes both first and second degree relatives, the method presented in Van Esche et al. (1994) was modified to make use of weighting based on genetic distance. The resulting formula for the $ith$ person with $n$ affected and $m$ unaffected relatives is given in (2.2) and will be known throughout the remainder of the paper as Weighted Proportion (WP) such that

$$WP_i = \frac{\sum_{j=1}^{n} w_{ij}}{\sum_{j=1}^{n} w_{ij} + \sum_{k=1}^{m} w_{ik}} \tag{2.2}$$

where $w_{ij}$ is the weight allocated to the $jth$ affected relative and $w_{ik}$ is the weight allocated to the $kth$ unaffected relative, both for the $ith$ proband. This method is beneficial in that it makes use of both how many affected relatives there are and also family size.

### 2.1.4 Methods Involving Expectation

There are also numerous score methods described in the literature which make use of expected values. The first of these, that will be discussed, was proposed by Slack and Evans (1966). Expected value was calculated using age-specific prevalence rates from the general population for death from heart attack and multiplying them by person-years lived in the family. Observed value was calculated by summing the number of heart attack deaths in the family. The family history score was presented as a ratio of observed divided by expected values. Williams et al. (1984) used similar

methods for calculating observed and expected values for heart attacks in a family, however these observed and expected values were combined into the following formula where $O_i$ and $E_i$ are the total observed and expected number of affected relatives in a family $i$

$$Williams_i = \frac{(|O_i - E_i| - 0.5) * |O_i - E_i|}{\sqrt{E_i} * (O_i - E_i)} \tag{2.3}$$

Reed et al (1986) simplified formula (2.3), also to describe family history for heart disease. This resulted in the following formula for "Reed's score"

$$Reed_i = \frac{(O_i - E_i)}{\sqrt{E_i}} \tag{2.4}$$

Schwartz et al (1988) further modified formula (2.4) where instead of taking the aggregated observed and expected scores from a family, each family member $j$ was considered separately in the formula for family $i$.

$$Schwartz_i = \sum_{j=1}^{n} \frac{(O_{ij} - E_{ij})}{\sqrt{E_{ij}}} \tag{2.5}$$

One of the criticisms of this score method is that it tends to lose stability in smaller families. In other words, one subject may have too strong an effect on the score if family size is small (Murad et al. 2006).

### 2.1.5 Previous Comparison of Methods

Silberberg et al. (1999) compared the scores described in sections 2.1.1 to 2.1.4 to each other, using heart disease (affected or not) as the studied ailment. Previous use of the methods involving expectation for heart disease had used the number of heart attacks rather than whether the patient had heart disease or not. Silberberg

et al. (1999) proposed that different scores are more appropriate, in some situations, based on the structure of the data. For example, a small family size investigated by (2.5) would result in an affected relative with low expected risk overwhelming the score. For data including family members of varying degrees, Silberberg et al. (1999) suggest that one would have to use a score that weights family members based on their genetic difference from the proband. Murad et al. (2007) compared the score methods using heart disease through simulations and real data on two different families. They found the dichotomous score performed the worst, while there was no significant difference between the other methods. They conclude therefore that the simplest, non-dichotomous score method (weighted proportion) is justified.

Within the realm of psychology, the dichotomous, weighted proportion and Reed's methods were compared by Milne et al. (2008) using data for nine different psychological disorders. To assess the performance of the three methods, Milne et al. (2008) used the family history score to predict whether the subject was diagnosed with the disorder or not using logistic regression. The dichotomous method was again seen as the poorest with the other methods not showing strong evidence of being better than each other.

### 2.1.6 Verdoux and Wals Method

Another method for quantifying family history was created by Verdoux et al. (1996) and utilized by Wals et al. (2004) again within the psychological field. This method used age and prevalence rates to calculate a likelihood ratio for each relative and multiplied the ratios together to arrive at a family history score for each

subject. Verdoux et al (1996) developed this method to model schizophrenia and Wals et al (2004) then used the method to model bipolar disorder. The Verdoux and Wals method (VWM) is described, in detail, below.

The proband is considered a potential familial or sporadic case. The term proband refers to the family member for whom the family history score is calculated. All of the relatives of the proband within the study are used to calculate the score. Familial means that the proband has a strong history of the disorder studied within their family. Sporadic means that there is a weak or non-existent history of the disorder with the proband's family. If a proband is familial then they should have a greater chance of developing the disorder than if the proband were sporadic (Verdoux et al. 1996).

The assumptions made by Verdoux et al. (1996) are that the lifetime risk of schizophrenia is 0.10 for relatives of familial probands and 0.005 for relatives of sporadic probands. These assumptions are based on prevalence rate of the disorder. The overall prevalence of schizophrenia is approximately 0.01 (Firestone and Marshall, 2000), therefore the sporadic case must have a lower risk than 0.01 so 0.005 was chosen by Verdoux et al (1996). Schizophrenia tends to have its earliest onset in mid to late teens and onset is rare beyond 50 years of age (Firestone and Marshall, 2000). Therefore the age-range at risk was set from 15-50 years of age by Verdoux et al. (1996). The risk of schizophrenia was also assumed to increase linearly across the age range from 0 to lifetime risk. Given this information and these assumptions the probabilities that a relative of age $x$ is affected or not affected if the proband is

familial are given by the following formulas

$$P(affected) = \frac{0.1 * (x - 15)}{50 - 15} \tag{2.6}$$

$$P(unaffected) = 1 - \frac{0.1 * (x - 15)}{50 - 15} \tag{2.7}$$

And if the proband is sporadic the probabilities that a relative of age $x$ is affected or not affected are given by

$$P(affected) = \frac{0.005 * (x - 15)}{50 - 15} \tag{2.8}$$

$$P(unaffected) = 1 - \frac{0.005 * (x - 15)}{50 - 15} \tag{2.9}$$

The ratio for whether the proband is sporadic or familial given that a relative of age $x$ is affected is obtained by taking (2.6) divided by (2.8) which equals 20. The ratio for whether the proband is sporadic or familial given that a relative of age $x$ is unaffected is obtained by taking (2.7) divided by (2.9). It can be seen that this ratio will vary depending on the relative's age.

Each relative (affected or not) of a proband will have a separate ratio calculated and these ratios are multiplied together to arrive at a score for the proband. The natural log is then taken of the score to produce the familiality score. Verdoux et al. (1996) found, using their score method, that having a family history of schizophrenia predicted a greater likelihood of non-recovery than not having a family history of schizophrenia.

Wals et al. (2004) also made use of the VWM. Bipolar disorder was studied and the procedure for calculating the score was the same due, in part, to the similarity in prevalence of bipolar disorder and schizophrenia. The only difference

in methodology was that the age range was changed to 10-50 from 15-50. Family history for bipolar disorder was used by Wals et al. (2004) to predict various other psychological disorders such as unipolar disorder and anxiety. The present paper will follow a similar method to that of Wals et al. (2004).

In addition to a score calculated using the VWM, a score is also proposed in the present paper that adds weighting based on genetic distance to this method. The ratio for an affected second degree relative (grandparents, aunts and uncles) will remain unchanged, however for first degree relatives (parents and siblings), the ratio will be multiplied by 2 giving a value of 40 instead of 20. For unaffected relatives, again ratios will remain unchanged for second degree relatives. For first degree relatives the ratio will be divided by 2. The reasoning for this is that an unaffected relative decreases the overall score, so a first degree unaffected relative should decrease the overall score in a more substantial way than an unaffected second degree relative. Conversely, a first degree affected relative should increase the score with greater magnitude than a second degree affected relative, which is why the affected ratio is multiplied and not divided by 2. Silberbeg et al. (1999) and Murad et al. (2006) both stressed the importance of weighting in their comparisons, therefore weighting has been incorporated in the VWM.

### 2.1.7 Summary

To summarize, the present paper will make use of seven different score methods to quantify family history for BD, they are:

1) Dichotomous Method

2) Count Method

3) Proportion Method

4) Reed's score

5) Schwartz score

6) Verdoux and Wals method (without weighting)

7) Verdoux and Wals method (with weighting)

The scores will then be compared using summary statistics and also will be used as predictors in separate Cox PH models for bipolar disorder and anxiety disorder in the probands. If the scores do not differ greatly then a simpler score method would be preferred, however if the scores do show a difference in their results then weighting, family size and expectation may be required to arrive at the most correct family history score.

## 2.2 Cox Proportional Hazards Model

The Cox proportional hazards model, also known as Cox regression, was first proposed by Cox (1972). It is a method designed to deal with survival data with time to an event as the response while taking into account censoring and adjusting for numerous predictor variables in addition to time. One of the features that separate this model from the parametric methods used to describe survival data is that it is not fully parametric but semi-parametric. This means that one does not have to select a specific probability distribution to represent the response (Allison, 2010). This feature is possible because of the method by which parameters are estimated within

the Cox model, known as partial likelihood (Allison, 2010), which will be described in greater detail later.

The Cox model addresses the issue of relating predictor variables $z$ to the distribution of survival times $t$ (Cox, 1972). The simplest version of the Cox model can be described in the following formula:

$$\lambda(t; z) = \exp(z * \beta) * \lambda_0(t) \tag{2.10}$$

where $\beta$ is a vector of unknown parameters for the $p$ predictor variables and $\lambda_0$ represents the hazard of "failure" for the conditions $z$=0 (Cox, 1972) known as the baseline hazard function (Allison, 2010). The hazard function indicates the way the risk of failure changes over time. The hazard function is important because many factors affecting the risk of failure can change with a person's age and the hazard function allows one to adjust for these changes (Lawless, 2003). In parametric models, the approximate shape of the hazard function for a particular set of data is modeled by choosing a distribution that represents it best. For example the Weibull distribution is most commonly used to model lifetimes of people or manufactured items (Lawless, 2003). If we take equation (2.10) to compare the hazards of two individuals $i$ and $j$ we get:

$$\frac{h_i(t)}{h_j(t)} = \exp(\beta_1(z_{i1} - z_{j1})...\beta_k(z_{ik} - z_{jk})) \tag{2.11}$$

where $h_i(t)$ represents the hazard for individual $i$ and $h_j(t)$ represents the hazard for individual $j$. Hence, the hazard for any one individual is proportional to the hazard for any other individual (Allison, 2010). As mentioned previously, the Cox model does

not require choosing a distribution to model the hazard function because it makes use of the idea of partial likelihood.

Partial likelihood allows one to estimate the parameter coefficients within the Cox model without worrying about describing the baseline hazard function (Allison, 2010). The estimates obtained through partial likelihood are consistent and asymptotically normal however they lose a small, but manageable, amount of efficiency for the most part due to the information about $\beta$ lost in making the baseline hazard function arbitrary (Cox, 1972).

Partial likelihood is represented by the following formula where $\delta_i = 0$ if the observation is censored, where the event has not been observed, and $\delta_i = 1$ if the observation is uncensored, where the event has been observed (Allison, 2010):

$$L = \prod_{i=1}^{n} \left( \frac{\exp(\beta * x_i)}{\sum_{j=1}^{n} Y_{ij} * \exp(\beta * x_j)} \right)^{\delta_i} \tag{2.12}$$

where $Y_{ij} = 0$ if the $jth$ individual has already experienced the event or censoring at time $t_i$ and $Y_{ij} = 1$ if the $jth$ individual has not experienced the event or censoring at time $t_i$ and remains in the risk set.

The resultant log partial likelihood is given by:

$$log(L) = \sum_{i=1}^{n} \delta_i * (\beta * x_i - \log \sum_{j=1}^{n} Y_{ij} * \exp(\beta * x_j)) \tag{2.13}$$

In order to maximize the log partial likelihood function and obtain the parameter estimates, the Newton-Raphson algorithm is used in most cases and sometimes the algorithm does not converge producing unusable estimates of the coefficients

and standard errors (Allison, 2010). In the case of non-convergence, Firth's method of penalized partial likelihood estimates can be used (Allison, 2010). Briefly, In Firth's method a modification of the score function is employed to remove the first order term from the asymptotic bias of the maximum likelihood estimates (Firth, 1993). The bias, which could be inflated by all observations being censored at a particular level of the predictor variable, is then reduced to allow convergence (Allison, 2010). Such a method was required in the present analysis and will be discussed in the results section.

Until now, methods for dealing with only non-tied data have been considered. However, when two events occur at the same time the Cox model must be adjusted to account for this (Allison, 2010). There are various methods for accomplishing this such as the exact and discrete methods, which can be highly computationally intensive and are needed when there are many ties in the data (Allison, 2010) and Breslow's approximation method (Breslow, 1974) which is the default in SAS. These methods will all produce identical results when there are little or no ties in the data, as was the case in the present study.

A crucial element of the Cox model is the proportional hazards assumption. The Cox model is based on the notion that the effect of the predictor on the hazard is constant over time. If this effect changes with time it represents a violation of the proportional hazards assumption (Allison, 2010). There are numerous ways of testing the proportional hazards assumption. The method used in the present paper makes use of Schoenfeld residuals. This type of residual is unique because instead of computing a residual for each individual, a residual is found for each covariate for

each individual (Allison, 2010). The Schoenfeld residual is calculated by subtracting the expected value of a specific covariate for a randomly selected person in the risk set from the observed value of the same covariate for that person (Schoenfeld, 1982). The Schoenfeld residuals should be independent of time, therefore a plot of these residuals against time should show them scattered, contained and centered around zero. A chi-square goodness of fit test can be used to examine the Schoenfeld residuals empirically to see if they are independent of time (Schoenfeld, 1982).

It is sometimes necessary to account for clustering in the Cox model depending on the data. Examples of this situation are longitudinal data or individuals clustered within a family as is the case in the present study. One should account for clustering because failure to do so may result in deflated standard errors and overestimated significance (Fitzmaurice et al. 2004). In logistic regression or any other generalized linear model one could use generalized estimating equations (GEE) and produce sandwich estimators to account for clustering within the data. A marginal Cox model utilizes a robust sandwich estimator similar to that of the GEE, however applied to survival data (Lin and Wei, 1989). So the robust sandwich covariance matrix is used to model dependence of failure times of probands within families.

# Chapter 3

# Results

## 3.1 Score Calculation

Family history scores (using all seven methods) were calculated for both bipolar disorder and anxiety disorder using the data set described in Chapter 1. Scores were calculated using the SAS 9.2 programming language. It was unknown how many siblings the proband's parents had so it was assumed that a proband's family (both first and second degree relatives) only included those relatives which appeared in the data set. The data set also did not include information on the unaffected parent. It was therefore assumed that the unaffected parent was not diagnosed with anxiety or bipolar disorder and that the unaffected parent was the same age as their spouse (the affected parent). The consequences of these assumptions will be discussed in chapter 4.

Reed's and Schwartz's scores required measures for expected prevalences. The expected value for bipolar disorder was taken to be 1.2 percent or 0.012, as this was the US prevalence rate described by Firestone and Marshall (2000) for all relatives that were above the age of 10. If they were 10 or younger, then their expected value was taken to be 0. This was done because bipolar disorder should not be found in

someone under 10 years of age (Wals et al. 2004). For anxiety disorder, the US prevalence rate described by Merikangas et al. (2011) was 31.9 percent or 0.319. Therefore this was taken as the expected value for anxiety disorder for all relatives older than 7. Those 7 or under were given an expected value of 0. For Reed's and Schwartz's scores observed value was taken as 0 if a relative was not diagnosed with the disorder and 1 if they were diagnosed with the disorder. For Reed's score $O_i$ was calculated by summing the observed values for all relatives of the $ith$ proband and $E_i$ was calculated by summing all of the expected values for all relatives of the $ith$ proband. These values were then used in formula 2.4. Given age adjusted prevalence rates, the expected value of a relative of a certain age would be equal to the prevalence rate for the disorder within the age range that the relative fell.

For the weighted and unweighted VWM scores, no method of quantifying family history for anxiety was presented in Wals et al. (2004) or Verdoux et al. (1996) therefore anxiety was treated with the same age range and prevalence rates as for bipolar disorder, which was presented and described in Wals et al. (2004). The implications of this assumption will be discussed in Chapter 4. Calculation and other assumptions for the VWM method were discussed in detail in chapter 2.

## 3.2 Exploratory Analysis

After each of the seven score types for bipolar and anxiety were calculated for each subject, exploratory analysis was performed to examine how the scores looked in comparison to each other. Plots of scores for each subject can be seen in figure

3.1 for bipolar disorder and figure 3.2 for anxiety disorder. One would expect that if all of the scores were quantifying family history in the same way that one subject with a higher family history score than another using one method should continue that trend across all methods. This trend is maintained for the dichotomous, WP and count scores however for the VWM, Reed and Schwartz scores there seems to be a bit of disagreement as to which subjects should have higher family history scores for both disorders.

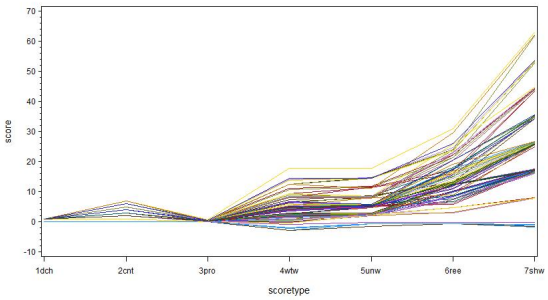


Figure 3.1: Trend plots of different family history scores for bipolar disorder

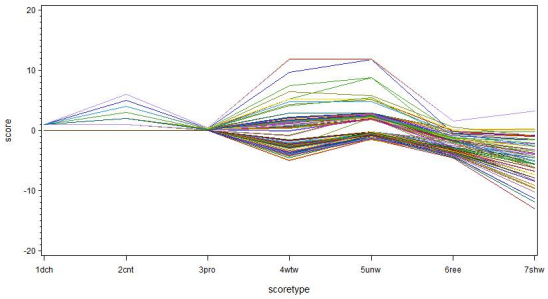


Figure 3.2: Trend plots of different family history scores for anxiety disorder

Two correlation matrices were produced, one for bipolar disorder and one for anxiety disorder, which display how the results of each score method relate to each other. They are shown below in tables 3.1 and 3.2:

Table 3.1: Correlations for different family history score methods for bipolar disorder

| Score | Count | WP | VWM(w) | VWM(uw) | Reed | Schwartz |
|---|---|---|---|---|---|---|
| Count | 1 | 0.764 | 0.946 | 0.924 | 0.927 | 0.999 |
| WP | 0.764 | 1 | 0.834 | 0.729 | 0.895 | 0.782 |
| VWM(w) | 0.946 | 0.834 | 1 | 0.968 | 0.917 | 0.952 |
| VWM(uw) | 0.924 | 0.729 | 0.968 | 1 | 0.817 | 0.925 |
| Reed | 0.927 | 0.895 | 0.917 | 0.817 | 1 | 0.934 |
| Schwartz | 0.999 | 0.782 | 0.952 | 0.925 | 0.934 | 1 |

Table 3.2: Correlations for different family history score methods for anxiety disorder

| Score | Count | WP | VWM(w) | VWM(uw) | Reed | Schwartz |
|---|---|---|---|---|---|---|
| Count | 1 | 0.940 | 0.948 | 0.946 | 0.843 | 0.662 |
| WP | 0.940 | 1 | 0.921 | 0.881 | 0.913 | 0.750 |
| VWM(w) | 0.948 | 0.921 | 1 | 0.952 | 0.908 | 0.798 |
| VWM(uw) | 0.946 | 0.881 | 0.952 | 1 | 0.791 | 0.656 |
| Reed | 0.843 | 0.913 | 0.908 | 0.791 | 1 | 0.936 |
| Schwartz | 0.662 | 0.750 | 0.798 | 0.656 | 0.936 | 1 |

All values were significantly different from 0 (p-value $< 0.001$). For bipolar disorder all scores seem to show very strong positive correlations with each other. This suggests that the scores, excluding the dichotomous score, resemble each other very strongly. For anxiety disorder, the same can be seen. All correlations are greater than 0.5 suggesting that the scores do resemble each other.

Mean plots were also generated for the mean scores for all seven methods. These plots can be seen in figure 3.3 and figure 3.4. The Schwartz method gives a much higher score when the observed frequency of the disorder is much higher than the expected prevalence rate, as is the case with bipolar disorder, whereas Reed's score by using the aggregated scores does not show as pronounced an effect. The effect is also seen in the plot for anxiety disorder, however in the negative direction due to the fact that the observed frequency of the disorder for anxiety was less than the expected prevalence rate for many subjects. Schwartz's score was described by Murad et al. (2006) to be more prone to inflation in either direction than Reed's score so this result is not unexpected. With regard to weighted vs unweighted VWM scores, it can be seen in the anxiety plots, that weighting makes a large difference in the score results though this effect is not seen in the bipolar plots, nor is it seen from the correlation matrices.

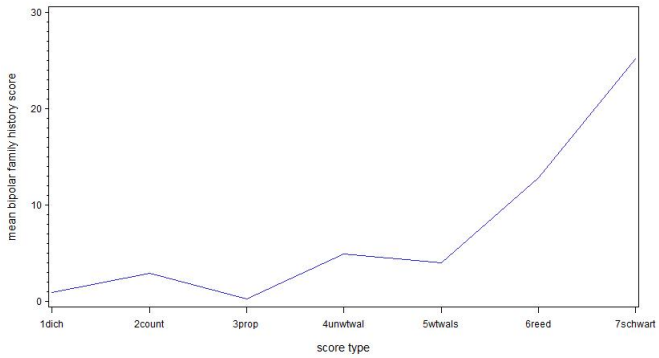


Figure 3.3: Mean plots of different family history scores for bipolar disorder

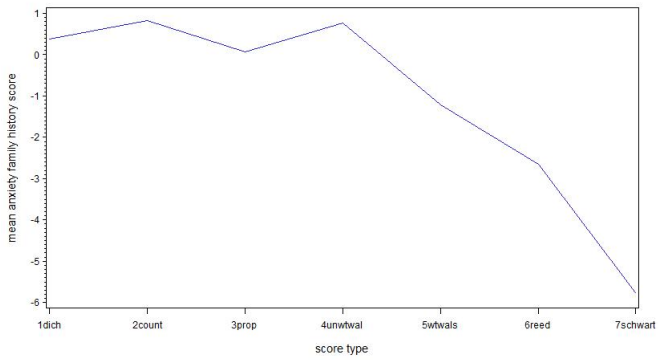


Figure 3.4: Mean plots of different family history scores for anxiety disorder

To examine how the scores are related to family size and weighted counts of affected relatives, graphs were generated plotting each score against family size and weighted count for both bipolar disorder and anxiety disorder. The plots can be seen in figures 3.5, 3.6, 3.7 and 3.8. As can be seen from figures 3.5 and 3.6 as well as the correlation matrices, all scores with the exception of the dichotomous score correlate strongly with the weighted count of affected relatives for both disorders. Figure 3.7 shows that, for bipolar disorder, having a larger family did not coincide

with significantly higher scores, suggesting that all scores were fairly robust to family size. In figure 3.8 however, Schwartz's score for anxiety seems to depend strongly on family size, more so than the other scores which echoes previous findings by Murad et al (2006).

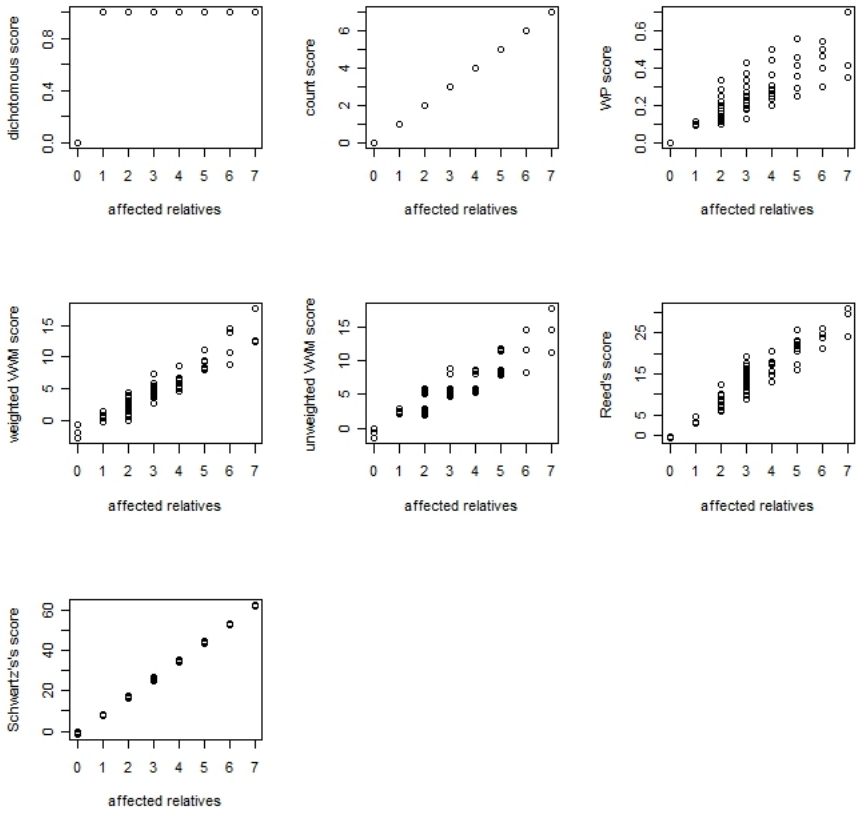


Figure 3.5: Plots of each different family history score for bipolar disorder against the weighted count of relatives affected with bipolar disorder

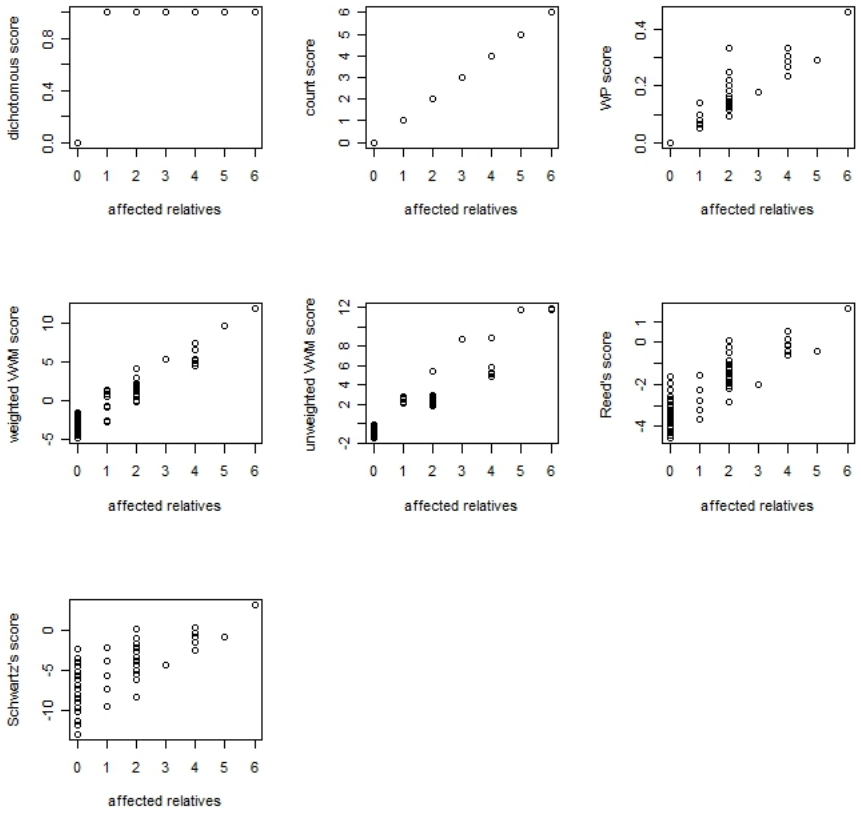


Figure 3.6: Plots of each different family history score for anxiety disorder against the weighted count of relatives affected with anxiety disorder

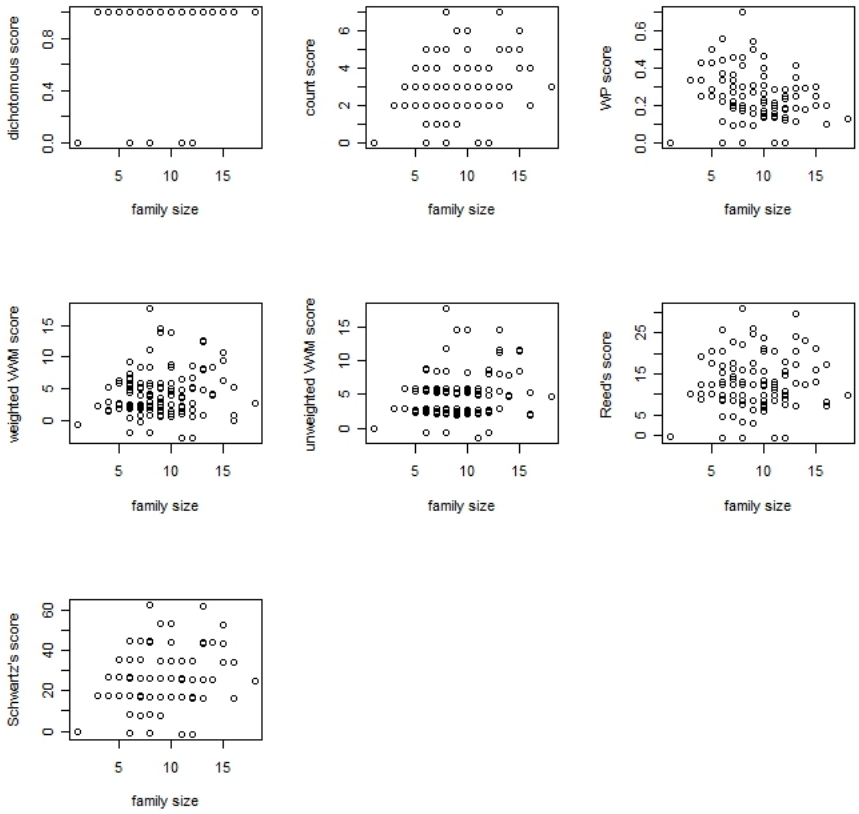


Figure 3.7: Plots of each different family history score for bipolar disorder against family size

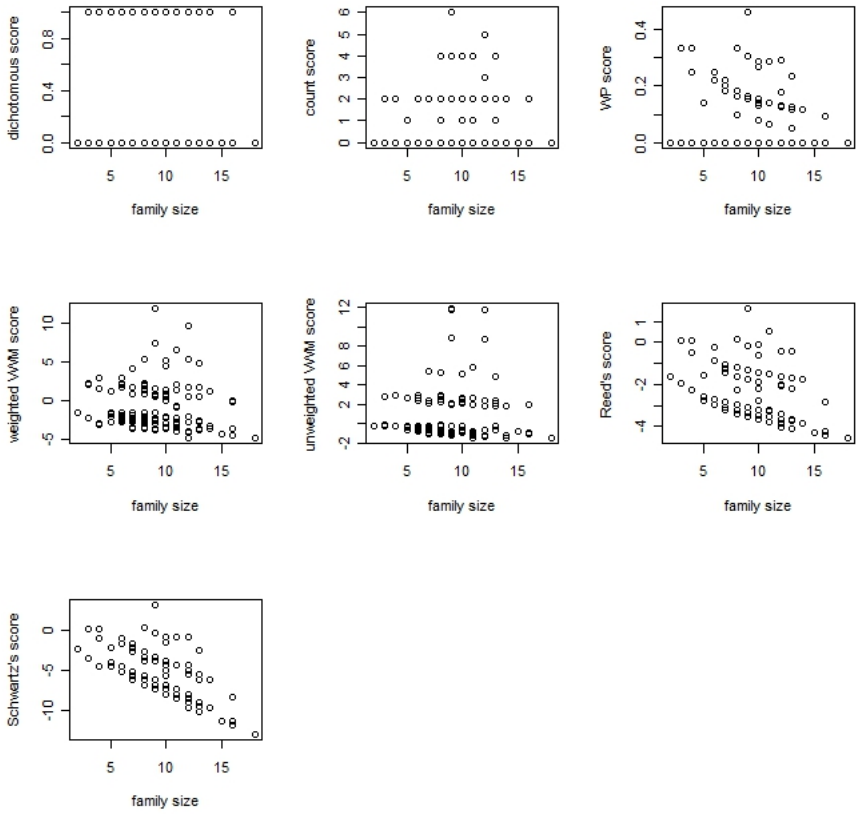


Figure 3.8: Plots of each different family history score for anxiety disorder against family size

Due to the fact that the score calculations operate under different conditions (continuous or discrete and with or without limits), each score was standardized by subtracting its mean and dividing by its standard deviation (where the mean and standard deviation were taken across all 220 individuals in the data set). This was done to make comparison of the scores more meaningful. This method was also used by Milne et al. (2008). The main purpose of calculating a family history score for a disease is to measure the susceptibility of a person to that disease. Therefore, it is necessary to see if a high family history score translates into the development of the disease in question. In order to examine this, first the means of the standardized scores for anxiety disorder were calculated for those offspring that were diagnosed with anxiety disorder and compared with the means for those offspring not diagnosed with anxiety disorder. Table 3.3 shows the results and a plot of these results can be seen in figure 3.9 where 0 represents offspring not diagnosed with anxiety disorder and 1 represents those diagnosed with anxiety disorder. The graph shows that for all types of scores a higher score was found for those diagnosed with anxiety disorder than those not diagnosed with the illness. The scores involving expected values (Schwartz and Reed) show the greatest difference. The weighted VWM score more closely resembles the Reed, Schwartz and WP scores, which also make use of weighting, whereas the unweighted VWM score is closer in proximity to the dichotomous score which does not factor in weighting, both of these scores show the smallest difference between those offspring with and without anxiety.

The same method was utilized with the bipolar family history scores. Table 3.4 shows the mean family history scores for those offspring with and without a bipolar

disorder diagnosis. The plot of these results can also be seen in figure 3.10. In the case of bipolar disorder, high family history score does not seem to coincide with diagnosis for the disorder, this result is somewhat surprising and will be discussed in chapter 5. When examining the scores individually, the unweighted VWM score again does not closely resemble the weighted scores and does not even resemble the dichotomous score in this case.

The bipolar family history scores were also compared to diagnosis of anxiety disorder in the offspring, as anxiety disorder has been implicated in a staging model for bipolar disorder (Duffy et al. 2010). The results can be seen in table 3.5 and in figure 3.11. Here there seems to be evidence that a family history of bipolar disorder correlates more strongly with a diagnosis of anxiety than a diagnosis of bipolar disorder. Again the unweighted VWM score is different, this time from all the other scores (the only case where the mean score was higher for those without the disorder). The other scores seem to cluster together in a pattern that does not resemble the other two analyses. The main common thread between the three plots is the unweighted VWM score demonstrating a difference from the weighted scores (and in two of the three plots from the dichotomous score).

Table 3.3: Means for standardized family history scores for anxiety disorder for probands with and without anxiety disorder diagnoses

| Score type | Anxiety Diagnosis | N | Mean Score |
|---|---|---|---|
| Dichotomous | Yes | 48 | 0.13 |
| Count | Yes | 48 | 0.17 |
| Proportion | Yes | 48 | 0.21 |
| Unweighted Wals | Yes | 48 | 0.15 |
| Weighted Wals | Yes | 48 | 0.24 |
| Reed | Yes | 48 | 0.28 |
| Schwartz | Yes | 48 | 0.30 |
| Dichotomous | No | 172 | -0.04 |
| Count | No | 172 | -0.05 |
| Proportion | No | 172 | -0.06 |
| Unweighted Wals | No | 172 | -0.04 |
| Weighted Wals | No | 172 | -0.07 |
| Reed | No | 172 | -0.08 |
| Schwartz | No | 172 | -0.08 |

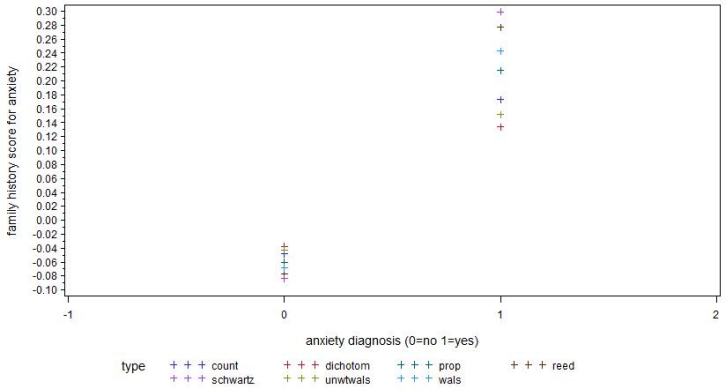


Figure 3.9: Plot of standardized family history scores for anxiety disorder for probands against anxiety disorder diagnosis in the proband

Table 3.4: Means for standardized family history scores for bipolar disorder for probands with and without bipolar disorder diagnoses

| Score type | Bipolar Diagnosis | N | Mean Score |
|---|---|---|---|
| Dichotomous | Yes | 35 | -0.18 |
| Count | Yes | 35 | -0.20 |
| Proportion | Yes | 35 | -0.14 |
| Unweighted Wals | Yes | 35 | -0.27 |
| Weighted Wals | Yes | 35 | -0.22 |
| Reed | Yes | 35 | -0.12 |
| Schwartz | Yes | 35 | -0.20 |
| Dichotomous | No | 185 | 0.03 |
| Count | No | 185 | 0.04 |
| Proportion | No | 185 | 0.03 |
| Unweighted Wals | No | 185 | 0.05 |
| Weighted Wals | No | 185 | 0.04 |
| Reed | No | 185 | 0.02 |
| Schwartz | No | 185 | 0.04 |

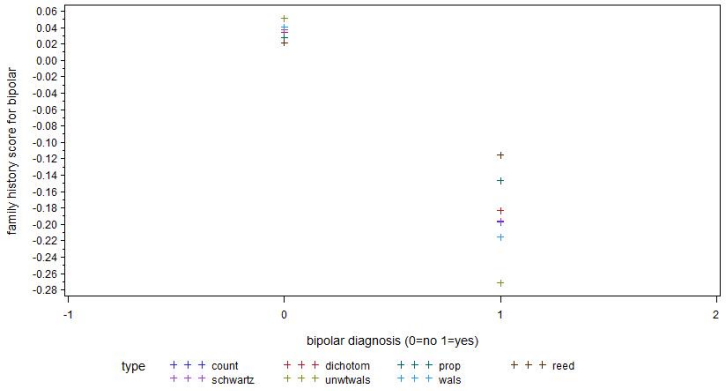


Figure 3.10: Plot of standardized family history scores for bipolar disorder for probands against bipolar disorder diagnosis in the proband

Table 3.5: Means for standardized family history scores for bipolar disorder for probands with and without anxiety disorder diagnoses

| Score type | Anxiety Diagnosis | N | Mean Score |
|---|---|---|---|
| Dichotomous | Yes | 48 | 0.17 |
| Count | Yes | 48 | 0.05 |
| Proportion | Yes | 48 | 0.22 |
| Unweighted Wals | Yes | 48 | -0.02 |
| Weighted Wals | Yes | 48 | 0.07 |
| Reed | Yes | 48 | 0.19 |
| Schwartz | Yes | 48 | 0.05 |
| Dichotomous | No | 172 | -0.05 |
| Count | No | 172 | -0.01 |
| Proportion | No | 172 | -0.06 |
| Unweighted Wals | No | 172 | 0.01 |
| Weighted Wals | No | 172 | -0.02 |
| Reed | No | 172 | -0.05 |
| Schwartz | No | 172 | -0.01 |

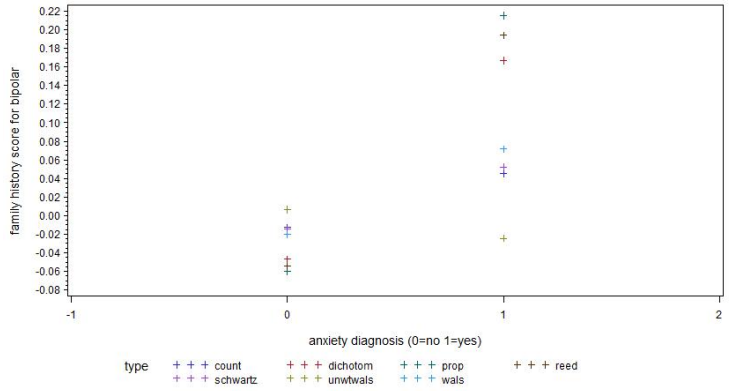


Figure 3.11: Plot of standardized family history scores for bipolar disorder for probands against anxiety disorder diagnosis in the proband

## 3.3 Cox Model Results

In order to test how the different family history scores predict mental illness in the offspring, the seven different scores were used as the lone covariate in seven Cox proportional hazards models. Time-to-event in the Cox models were represented using date of birth of the proband as the starting point in the study and the proband's age on 12/05/2011 as the end of the study (censoring) time. Milne et al. (2008) used logistic regression models in their analysis, however in the present study the data set included age of onset for all disorders in the probands, therefore the models could be adjusted for age and censoring could be taken into account. In addition to this, all models made use of sandwich estimators in order to control for clustering within a nuclear family, as there were many cases where siblings were included in the study. The proportional hazards assumption was tested using Schoenfeld residuals (example plots of Schoenfeld residuals can be found in appendix B). Of the 21 total models, one failed to satisfy the proportional hazards assumption.

The first set of models used the hazard of anxiety disorder in the offspring as the response and each of the seven family score calculations as predictors, each with their own separate model. The resulting hazard ratios and p-values can be seen in Table 3.6.

Though all hazard ratio estimates are greater than 1, indicating higher family history score for anxiety predicting anxiety, only Schwartz score is significant at $\alpha$=0.05 (p-value=0.03) with Reed's score showing moderate significance (p-value=0.08). This means that the risk or hazard of anxiety disorder in the proband is

Table 3.6: Hazard ratio estimates obtained from Cox PH models with family history score for anxiety disorder as the predictor and hazard of anxiety disorder in the proband as the response

| Score type | Hazard Ratio | 95% CI | P-value |
|---|---|---|---|
| Dichotomous | 1.16 | (0.81,1.67) | 0.42 |
| Count | 1.15 | (0.88,1.51) | 0.31 |
| Proportion | 1.22 | (0.90,1.65) | 0.20 |
| Unweighted Wals | 1.13 | (0.88,1.44) | 0.35 |
| Weighted Wals | 1.23 | (0.95,1.60) | 0.11 |
| Reed | 1.31 | (0.97,1.78) | 0.08 |
| Schwartz | 1.38 | (1.03,1.86) | 0.03 |

multiplied by 1.38 (95% CI=(1.03, 1.86)) for every one unit increase in standardized Schwartz score for family history of anxiety disorder. Similarly with Reed's score, the risk or hazard of anxiety disorder in the proband is multiplied by 1.31 (95% CI=(0.97, 1.78)) for every one unit increase in standardized Reed's score for family history of anxiety disorder. The weighted and unweighted VWM scores were both nonsignificant at $\alpha$=0.05 (p-value=0.11 and 0.35 respectively), however the weighted VWM score is much closer to significance than the unweighted VWM score. The dichotomous, count and WP scores were all not significant. The next set of models used family history score for bipolar disorder as the predictor and the response was hazard for bipolar disorder. The results for these seven models can be seen in Table 3.7.

As can be deduced from looking at the mean plots of the standardized scores, all of the hazard ratios are less than 1, however none of the models were significant at a significance level of 0.05. The closest one to significance was the unweighted VWM score (p-value=0.07), with all of the other family history scores showing p-values greater than or equal to 0.14. This is further evidence of the unweighted VWM score

Table 3.7: Hazard ratio estimates obtained from Cox PH models with family history score for bipolar disorder as the predictor and hazard of bipolar disorder in the proband as the response

| Score type | Hazard Ratio | 95% CI | P-value |
|---|---|---|---|
| Dichotomous | 0.87 | (0.70,1.07) | 0.18 |
| Count | 0.76 | (0.53,1.09) | 0.14 |
| Proportion | 0.87 | (0.60,1.27) | 0.47 |
| Unweighted Wals | 0.69 | (0.46,1.03) | 0.07 |
| Weighted Wals | 0.76 | (0.52,1.09) | 0.14 |
| Reed | 0.86 | (0.61,1.22) | 0.41 |
| Schwartz | 0.77 | (0.53,1.10) | 0.15 |

not really fitting in with the other scores, agreeing with the results shown in figures 3.9, 3.10 and 3.11.

The final set of models used the hazard of anxiety disorder in the offspring as the response and the family history scores for bipolar disorder as predictors. The results of these seven models can be seen in table 3.8. The dichotomous score shows significance. The dichotomous score, however, was an indicator variable with a high proportion of 1's. This is because there were a large number of affected parents with bipolar disorder. In this case, Firth's correction was required and even after it was applied, the proportional hazards assumption was violated. Table 3.8 includes the values obtained for the dichotomous score method using Firth's correction. These results, however, are unreliable due to the violation of the proportional hazards assumption. As for all of the other scores for bipolar disorder predicting anxiety in the offspring, the only one which was significant at $\alpha$=0.05 was the proportion score (p-value=0.05).

Table 3.8: Hazard ratio estimates obtained from Cox PH models with family history score for bipolar disorder as the predictor and hazard of anxiety disorder in the proband as the response, *violation of PHA

| Score type | Hazard Ratio | 95% CI | P-value |
|---|---|---|---|
| Dichotomous* | 1.20 | (1.03,1.41) | 0.02 |
| Count | 1.08 | (0.78,1.50) | 0.66 |
| Proportion | 1.30 | (1.00,1.70) | 0.05 |
| Unweighted Wals | 1.00 | (0.72,1.39) | 0.99 |
| Weighted Wals | 1.11 | (0.82,1.51) | 0.48 |
| Reed | 1.28 | (0.94,1.73) | 0.12 |
| Schwartz | 1.09 | (0.78,1.51) | 0.62 |

# Chapter 4

## Discussion and Future Work

The purpose of this project was to take six existing methods for quantifying family history plus one modified version of an existing method and use them to analyze psychological time-to-event data. The seven methods were presented, illustrated and compared using data dealing with the occurrence of anxiety and bipolar disorder in families from Ontario and Halifax. Exploratory analysis and Cox proportional hazards models, with the family history scores as covariates were used to perform these comparisons. In some cases, the scores were shown to produce differing results despite being designed to measure the same thing and being used on the same data.

Silberberg et al. (1999) described what was thought as desirable properties of a family history score. According to them, a score should consider the risk profile of a family, factoring in covariates such as age and sex. A score should also be robust to family size, consider the relationship of relatives (weighting) and not be inflated by a single individual. In the present study, unfortunately the only covariate which could be controlled for in Cox regression with family history score as the independent variable was age as it was the only information aside from disease status that was known (despite having to make assumptions). Reed's score, Schwartz's score and the two VWM scores account for this. Reed's and Schwartz's scores also make use of

information based on sex, therefore it would have been ideal to have information on the sex of all family members.

It was not surprising that the results from the unweighted VWM score differed from the results from the other three scores, which accounted for age, as they were weighted and it was not. The differences within the other three scores can be attributed to perhaps Schwartz's score being inflated or deflated by one or two relatives, as some of the subjects in the study only had information on a small number of relatives. This is a major disadvantage of Schwartz's score as described by Murad et al. (2006). The dichotomous and count scores carry no information on family size and therefore pedigrees with different proportions of affected relatives may have identical scores (Silberberg et al. 1999). The WP scores produced quite different results from the Cox models than the count and dichotomous scores (not including the score which violated the proportional hazards assumption), this demonstrates that family size is important in score calculation. Incorporating expectation into the family history score made a large difference in the anxiety predicting anxiety model as all three weighted scores that considered prevalence rates were much closer to significance than the other scores. Calculating expectation, however, can be problematic as one must rely on prevalence or incidence rates that are not always agreed upon, especially with psychological illness as there has been a lack of empirical data on a wide range of DSM-IV disorders (Merikangas et al. 2010). In addition to this more information is required such as age at last assessment and ages of onset, sex and other possible contributors to the development of a disorder which may affect expected value.

In the present study, assumptions were made to fill in some of the informa-

tion required. With the VWM scores specifically, the ratio calculation should change for each disorder as prevalence rates are different and the assumption that there is a linear increase in risk of a disorder is simply not true for many mental and physical illnesses. The question is then, is generating scores using expected values worth making the necessary assumptions and possibly being mistaken or would a proportion score suffice?

Siberberg et al. (1999) suggest that the characteristics of the data should be what drives the decision. The more information available, the more one should use a score that makes use of expected values, however assumptions need to be made carefully and if too many are required then a proportion score or even a count score, if all families are of similar size, would serve the purpose. The VWM scores require too many assumptions and are not easily generalized across disorders and Schwartz's score seems to be too prone to inflation. Therefore, agreeing with Milne et al. (2008) and Murad et al (2006) in their support of Reed's score seems warranted provided there is enough data to accurately calculate it. Finally, when the data includes relatives of differing genetic distance from the proband, weighting should be used and the general agreement is that first degree relatives should be double the contribution of second degree relatives.

A more complete data set would be desirable in comparing the scores that includes information on sex as well as more complete information on age so that fewer assumptions would need to be made. The consequences of invalid assumptions are that the inferences may be biased. For example, the lack of information on relatives of the unaffected parent, specifically, generates bias in the sense that it may inflate

family history scores. If bipolar disorder is heritable, one would expect the relatives of the unaffected parent to have a lower proportion of the disorder. Hence, the inclusion of the unaffected parent's family in the data set should decrease the family history score for bipolar disorder.

Another issue with the data was the lack of controls. Each proband had one parent affected with a form of mood disorder, which resulted in family history for bipolar disorder being possibly over-represented. This may have contributed to the results involving family history for bipolar disorder described earlier in the paper. Essentially high family history of bipolar disorder was compared to extremely high family history of bipolar disorder, which is not indicative of the general population, Wals et al. (2004) encountered the same issue and referred to it as a "ceiling effect". High family history scores for everyone in the data set hindered our ability to assess how well they work in predicting various disorders. Having data that includes controls and is more reflective of the general population would be desirable in the future. Also having data that includes a greater number of relatives would be interesting however trying to obtain four or more generations worth of data on a specific disease status would prove to be very difficult, especially when age of onset information is required.

Aside from using real world data, a simulation study similar to that used by Murad et al. (2006) could be utilized to further test the validity of the different scores. They assumed that risk for a disease was dichotomous (either high or low-risk) and simulated 1000 families of each type from a hypothetical population. Familial information was then generated for each individual using truncated Poisson, multinomial and Bernoulli distributions. Logistic regression was then used to model

family history and the scores were compared using ROC curves with higher values indicating better prediction of familial risk of a disorder (Murad et al. 2006).

For the most part, the scores did agree on the fact that family history for bipolar disorder was not a significant predictor in the development of bipolar disorder. This result is actually not that surprising as the offspring were mainly adolescent age or younger and may not have developed bipolar disorder yet as it is generally late adolescence where bipolar disorder is widely diagnosed (Firestone et al. 2000). Also there is strong co-morbidity between bipolar disorder and mood disorders, anxiety disorder and psychotic disorder therefore family history for bipolar disorder may be a strong predictor for these other disorders (Merikangas et al. 1988). When the hazard for anxiety disorder was tested as the response, the proportion score showed significance so combining mood disorders, anxiety disorder and bipolar disorder together as one response may show family history for bipolar disorder as a significant predictor. In terms of family history for anxiety disorder, there were scores which approached significance when predicting anxiety disorder. Given the co-morbidity between anxiety and mood/bipolar/psychotic disorder (Merikangas et al. 1988) it would be beneficial as well to combine disorders into the response and see whether family history for anxiety disorder is a significant predictor in the development of anxiety, mood, bipolar or psychotic disorder. Anxiety, mood disorders and bipolar disorder have been implicated (in that order) in a staging model (Duffy et al. 2010), therefore treating them as a "bundle" seems legitimate and this may also explain why family history for bipolar disorder seemed to do a slightly better job predicting anxiety disorder than it did predicting bipolar disorder in the offspring.

# Chapter 5

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# Appendix A

## Appendix SAS and R code

```
*******************************************IMPORT DATA SET***************
PROC IMPORT OUT= WORK.fl2
            DATAFILE= "M:\fldatasafety.csv"
            DBMS=CSV REPLACE;
     GETNAMES=YES;
     DATAROW=2;
     GUESSINGROWS=1000;
RUN;

**MASTERS PROJECT CALCULATION OF FL SCORES EX:BIPOLAR**********************

data fl3;*/change bipolar for relatives to one type;
set fl2;
if aff_parent_primary_dx=1 then affpbd=1;
else if aff_parent_primary_dx=2 then affpbd=1;
else if aff_parent_primary_dx=3 then affpbd=0;
else if aff_parent_primary_dx=4 then affpbd=0;
else if aff_parent_primary_dx=5 then affpbd=0;
else affpbd=.;
age_naffparent=age_affparent;
if age_affparent ne . then naffpbd=0;
else naffpbd=.;
if aff_p_father_bd=2 then affpfbd=1;
else if aff_p_father_bd=3 then affpfbd=1;
else affpfbd=aff_p_father_bd;
if aff_p_mother__bd=2 then affpmbd=1;
else if aff_p_mother__bd=3 then affpmbd=1;
else affpmbd=aff_p_mother__bd;
if aff_p_sib_1__bd=2 then affps1bd=1;
else if aff_p_sib_1__bd=3 then affps1bd=1;
else affps1bd=aff_p_sib_1__bd;
if aff_p_sib_2__bd=2 then affps2bd=1;
else if aff_p_sib_2__bd=3 then affps2bd=1;
```

```
else affps2bd=aff_p_sib_2__bd;
if aff_p_sib_3__bd=2 then affps3bd=1;
else if aff_p_sib_3__bd=3 then affps3bd=1;
else affps3bd=aff_p_sib_3__bd;
if aff_p_sib_4__bd=2 then affps4bd=1;
else if aff_p_sib_4__bd=3 then affps4bd=1;
else affps4bd=aff_p_sib_4__bd;
if aff_p_sib_5__bd=2 then affps5bd=1;
else if aff_p_sib_5__bd=3 then affps5bd=1;
else affps5bd=aff_p_sib_5__bd;
if aff_p_sib_6__bd=2 then affps6bd=1;
else if aff_p_sib_6__bd=3 then affps6bd=1;
else affps6bd=aff_p_sib_6__bd;
if aff_p_sib_7__bd=2 then affps7bd=1;
else if aff_p_sib_7__bd=3 then affps7bd=1;
else affps7bd=aff_p_sib_7__bd;
if aff_p_sib_8__bd=2 then affps8bd=1;
else if aff_p_sib_8__bd=3 then affps8bd=1;
else affps8bd=aff_p_sib_8__bd;
if aff_p_sib_9__bd=2 then affps9bd=1;
else if aff_p_sib_9__bd=3 then affps9bd=1;
else affps9bd=aff_p_sib_9__bd;
if aff_p_sib_10__bd=2 then affps10bd=1;
else if aff_p_sib_10__bd=3 then affps10bd=1;
else affps10bd=aff_p_sib_10__bd;
if aff_p_sib_11__bd=2 then affps11bd=1;
else if aff_p_sib_11__bd=3 then affps11bd=1;
else affps11bd=aff_p_sib_11__bd;
run;
*/weighted wals score obtain ratio values for each parent and sibling*/;
data flscoreraw;
set fl3;
if affpbd=1 then scorepbd=40;
*/if the father has the disorder,
the ratio=20 for unweighted, if not remove 0.5*;
else if affpbd=0 then scorepbd=0.5*
((1-((0.1)*(age_affparent-10)/40))/(1-((.005)*(age_affparent-10)/40)));
else scorepbd=1;
if naffpbd=1 then scorenpbd=40;
*/if the father has the disorder,
the ratio=20 for unweighted,if not remove 0.5*;
else if naffpbd=0 then scorenpbd=0.5*
((1-((0.1)*(age_naffparent-10)/40))/(1-((.005)*(age_naffparent-10)/40)));
else scorenpbd=1;
if sib1bd=1 then score1bd=40;
```

```
*/if the father has the disorder,
the ratio=20 for unweighted, if not remove 0.5*;
else if sib1bd=0 then score1bd=0.5*
((1-((0.1)*(sib1age-10)/40))/(1-((.005)*(sib1age-10)/40)));
else score1bd=1;
if sib2bd=1 then score2bd=40;
*/if the father has the disorder,
the ratio=20 for unweighted, if not remove 0.5*;
else if sib2bd=0 then score2bd=0.5*
((1-((0.1)*(sib2age-10)/40))/(1-((.005)*(sib2age-10)/40)));
else score2bd=1;
if sib3bd=1 then score3bd=40;
*/if the father has the disorder,
the ratio=20 for unweighted, if not remove 0.5*;
else if sib3bd=0 then score3bd=0.5*
((1-((0.1)*(sib3age-10)/40))/(1-((.005)*(sib3age-10)/40)));
else score3bd=1;
if sib4bd=1 then score4bd=40;
*/if the father has the disorder,
the ratio=20 for unweighted, if not remove 0.5*;
else if sib4bd=0 then score4bd=0.5*
((1-((0.1)*(sib4age-10)/40))/(1-((.005)*(sib4age-10)/40)));
else score4bd=1;
if sib5bd=1 then score5bd=40;
*/if the father has the disorder,
the ratio=20 for unweighted, if not remove 0.5*;
else if sib5bd=0 then score5bd=0.5*
((1-((0.1)*(sib5age-10)/40))/(1-((.005)*(sib5age-10)/40)));
else score5bd=1;
if affpfbd=1 then scorefbd=20;
else if affpfbd=0 then scorefbd=(1-((0.1)
*(aff_p_father_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_father_age_last_assessment-10)/40));
*/if the father does not have the disorder,
use formula given in Wals for ratio where x=age last assessment*/;
else scorefbd=1;*/if there is no father data then set ratio=1,
for ease of multiplication later*/;
if affpmbd=1 then scorembd=20;
*/same process for mother and 11 siblings below as for father*/;
else if affpmbd=0 then scorembd=(1-((0.1)
*(aff_p_mother_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_mother_age_last_assessment-10)/40));
else scorembd=1;
if affps1bd=1 then scores1bd=20;
else if affps1bd=0 then scores1bd=(1-((0.1)
```

```
*(aff_p_sib_1_last_assessment_age-10)/40))
/(1-((.005)*(aff_p_sib_1_last_assessment_age-10)/40));
else scores1bd=1;
if affps2bd=1 then scores2bd=20;
else if affps2bd=0 then scores2bd=(1-((0.1)
*(aff_p_sib_2_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_2_age_last_assessment-10)/40));
else scores2bd=1;
if affps3bd=1 then scores3bd=20;
else if affps3bd=0 then scores3bd=(1-((0.1)
*(aff_p_sib_3_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_3_age_last_assessment-10)/40));
else scores3bd=1;
if affps4bd=1 then scores4bd=20;
else if affps4bd=0 then scores4bd=(1-((0.1)
*(aff_p_sib_4_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_4_age_last_assessment-10)/40));
else scores4bd=1;
if affps5bd=1 then scores5bd=20;
else if affps5bd=0 then scores5bd=(1-((0.1)
*(aff_p_sib_5_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_5_age_last_assessment-10)/40));
else scores5bd=1;
if affps6bd=1 then scores6bd=20;
else if affps6bd=0 then scores6bd=(1-((0.1)
*(aff_p_sib_6_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_6_age_last_assessment-10)/40));
else scores6bd=1;
if affps7bd=1 then scores7bd=20;
else if affps7bd=0 then scores7bd=(1-((0.1)
*(aff_p_sib_7_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_7_age_last_assessment-10)/40));
else scores7bd=1;
if affps8bd=1 then scores8bd=20;
else if affps8bd=0 then scores8bd=(1-((0.1)
*(aff_p_sib_8_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_8_age_last_assessment-10)/40));
else scores8bd=1;
if affps9bd=1 then scores9bd=20;
else if affps9bd=0 then scores9bd=(1-((0.1)
*(aff_p_sib_9_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_9_age_last_assessment-10)/40));
else scores9bd=1;
if affps10bd=1 then scores10bd=20;
else if affps10bd=0 then scores10bd=(1-((0.1)
```

```
*(aff_p_sib_10_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_10_age_last_assessment-10)/40));
else scores10bd=1;
if affps11bd=1 then scores11bd=20;
else if affps11bd=0 then scores11bd=(1-((0.1)
*(aff_p_sib_11_age_last_assessment-10)/40))
/(1-((.005)*(aff_p_sib_11_age_last_assessment-10)/40));
else scores11bd=1;
run;

data flscoreraw2;
set flscoreraw;*/set all ratios=1 if they are =.
because some parents and siblings have unuseable age data,
so they do not affect the multiplication*/;
if scorepbd=. then scorepbd=1; else scorepbd=scorepbd;
if scorenpbd=. then scorenpbd=1; else scorenpbd=scorenpbd;
if score1bd=. then score1bd=1; else score1bd=score1bd;
if score2bd=. then score2bd=1; else score2bd=score2bd;
if score3bd=. then score3bd=1; else score3bd=score3bd;
if score4bd=. then score4bd=1; else score4bd=score4bd;
if score5bd=. then score5bd=1; else score5bd=score5bd;
if scorefbd=. then scorefbd=1; else scorefbd=scorefbd;
if scorembd=. then scorembd=1; else scorembd=scorembd;
if scores1bd=. then scores1bd=1; else scores1bd=scores1bd;
if scores2bd=. then scores2bd=1; else scores2bd=scores2bd;
if scores3bd=. then scores3bd=1; else scores3bd=scores3bd;
if scores4bd=. then scores4bd=1; else scores4bd=scores4bd;
if scores5bd=. then scores5bd=1; else scores5bd=scores5bd;
if scores6bd=. then scores6bd=1; else scores6bd=scores6bd;
if scores7bd=. then scores7bd=1; else scores7bd=scores7bd;
if scores8bd=. then scores8bd=1; else scores8bd=scores8bd;
if scores9bd=. then scores9bd=1; else scores9bd=scores9bd;
if scores10bd=. then scores10bd=1; else scores10bd=scores10bd;
if scores11bd=. then scores11bd=1; else scores11bd=scores11bd;
run;
data flscorefinal;
set flscoreraw2;
rawflscorebd=scorepbd*scorenpbd*score1bd*score2bd*score3bd*
score4bd*score5bd*scorefbd*scorembd*scores1bd*scores2bd*scores3bd*
scores4bd*scores5bd*scores6bd*scores7bd*scores8bd*scores9bd
*scores10bd*scores11bd;
*/multiply all the scores of each family member together to
obtain one score for each subject(offspring)*/;
flscorebd=log(rawflscorebd);
*/take the log of each score to get fl score*/;
```

```
run;

*/calculate dichotomous score for bd;
data fldich;
set fl3;
if affpbd=1 or naffpbd=1 or sib1bd=1 or sib2bd=1 or sib3bd=1 or
sib4bd=1 or sib5bd=1 or affpfbd=1 or affpmbd=1 or affps1bd=1 or
affps2bd=1 or affps3bd=1 or affps4bd=1 or affps5bd=1 or
affps6bd=1 or affps7bd=1 or affps8bd=1 or affps9bd=1 or affps10bd=1 or
affps11bd=1 then fldich=1;
else fldich=0;
run;
*/calculate count score for bd need to eliminate
dots or sum wont work and must only count the 1s;
data flcount;
set fl3;
if affpbd=. then affpbd=0;
if naffpbd=. then naffpbd=0;
if sib1bd=. then sib1bd=0;
if sib2bd=. then sib2bd=0;
if sib3bd=. then sib3bd=0;
if sib4bd=. then sib4bd=0;
if sib5bd=. then sib5bd=0;
if affpfbd=. then affpfbd=0;
if affpmbd=. then affpmbd=0;
if affps1bd=. then affps1bd=0;
if affps2bd=. then affps2bd=0;
if affps3bd=. then affps3bd=0;
if affps4bd=. then affps4bd=0;
if affps5bd=. then affps5bd=0;
if affps6bd=. then affps6bd=0;
if affps7bd=. then affps7bd=0;
if affps8bd=. then affps8bd=0;
if affps9bd=. then affps9bd=0;
if affps10bd=. then affps10bd=0;
if affps11bd=. then affps11bd=0;
run;
data flcount;
set flcount;
flcount=2*affpbd+2*naffpbd+2*sib1bd+2*sib2bd+2*sib3bd+2*sib4bd+
2*sib5bd+affpfbd +
affpmbd + affps1bd + affps2bd + affps3bd + affps4bd + affps5bd +
affps6bd + affps7bd + affps8bd + affps9bd + affps10bd + affps11bd;
run;
*/calculate family sizes that werent included in the data set
```

```
for proportion score again eliminate dots but this time
0s and 1s will be counted towards family size;
data flsize;
set fl3;
if affpbd=. then affpbd=0;else affpbd=1;
if naffpbd=. then naffpbd=0;else naffpbd=1;
if sib1bd=. then sib1bd=0;else sib1bd=1;
if sib2bd=. then sib2bd=0;else sib2bd=1;
if sib3bd=. then sib3bd=0;else sib3bd=1;
if sib4bd=. then sib4bd=0;else sib4bd=1;
if sib5bd=. then sib5bd=0;else sib5bd=1;
if affpfbd=. then affpfbd=0;else affpfbd=1;
if affpmbd=. then affpmbd=0;else affpmbd=1;
if affps1bd=. then affps1bd=0;else affps1bd=1;
if affps2bd=. then affps2bd=0;else affps2bd=1;
if affps3bd=. then affps3bd=0;else affps3bd=1;
if affps4bd=. then affps4bd=0;else affps4bd=1;
if affps5bd=. then affps5bd=0;else affps5bd=1;
if affps6bd=. then affps6bd=0;else affps6bd=1;
if affps7bd=. then affps7bd=0;else affps7bd=1;
if affps8bd=. then affps8bd=0; else affps8bd=1;
if affps9bd=. then affps9bd=0; else affps9bd=1;
if affps10bd=. then affps10bd=0; else affps10bd=1;
if affps11bd=. then affps11bd=0;else affps11bd=1;
run;
data flsize;
set flsize;
familysize=affpbd+naffpbd+sib1bd+sib2bd+sib3bd+sib4bd+sib5bd+affpfbd +
affpmbd + affps1bd + affps2bd + affps3bd + affps4bd + affps5bd +
affps6bd + affps7bd + affps8bd + affps9bd + affps10bd + affps11bd;
weightedfamilysize= 2*affpbd+2*naffpbd+2*sib1bd+2*sib2bd+
2*sib3bd+2*sib4bd+2*sib5bd+affpfbd + affpmbd + affps1bd +
affps2bd + affps3bd + affps4bd + affps5bd + affps6bd + affps7bd +
affps8bd + affps9bd + affps10bd + affps11bd;
run;
*/combine all data sets into a set to calculate proportion score;
proc sort data=flcount;
by family_id high_risk__hr__offspring_person;
run;
proc sort data=flsize;
by family_id high_risk__hr__offspring_person;
run;
data flprop;
merge flcount flsize;
by family_id high_risk__hr__offspring_person;
```

```
run;
proc sort data=flprop;
by family_id high_risk__hr__offspring_person;
run;
data flprop;
merge flprop flcount;
by family_id high_risk__hr__offspring_person;
run;
*/calculate proportion score;
data flprop;
set flprop;
propscore=flcount/weightedfamilysize;
run;
*/create one master data set with all scores;
proc sort data=flscorefinal;
by family_id high_risk__hr__offspring_person;
run;
data masterscore;
merge flprop flscorefinal;
by family_id high_risk__hr__offspring_person;
run;
proc sort data=fldich;
by family_id high_risk__hr__offspring_person;
run;
data masterscore;
merge fldich masterscore;
by family_id high_risk__hr__offspring_person;
run;
*/now for reed and schwartz scores;
*/change offspring bipolar to one type instead of 3 ;
data masterscore;
set masterscore;
if hr_offspring_bd=2 then hr_offspring_bd=1;
else if hr_offspring_bd=3 then hr_offspring_bd=1;
else hr_offspring_bd=hr_offspring_bd;
run;
*/set expected value of bipolar to 1.2% as suggested by firestone,2000;
data masterscoreexp;
set masterscore;
if affpbd ne . then expaffp=0.012;
else expaffp=0;
if naffpbd ne . then expnaffp=0.012;
else expnaffp=0;
if sib1bd ne . and sib1age<=10 then expsib1=0;
else if sib1bd ne . and sib1age>10 then expsib1=0.012;
```

```
else expsib1=0;
if sib2bd ne . and sib2age<=10 then expsib2=0;
else if sib2bd ne . and sib2age>10 then expsib2=0.012;
else expsib2=0;
if sib3bd ne . and sib3age<=10 then expsib3=0;
else if sib3bd ne . and sib3age>10 then expsib3=0.012;
else expsib3=0;
if sib4bd ne . and sib4age<=10 then expsib4=0;
else if sib4bd ne . and sib4age>10 then expsib4=0.012;
else expsib4=0;
if sib5bd ne . and sib5age<=10 then expsib5=0;
else if sib5bd ne . and sib5age>10 then expsib5=0.012;
else expsib5=0;
if affpfbd ne . then expaffpf=0.012;
else expaffpf=0;
if affpmbd ne . then expaffpm=0.012;
else expaffpm=0;
if affps1bd ne . then expaffps1=0.012;
else expaffps1=0;
if affps2bd ne . then expaffps2=0.012;
else expaffps2=0;
if affps3bd ne . then expaffps3=0.012;
else expaffps3=0;
if affps4bd ne . then expaffps4=0.012;
else expaffps4=0;
if affps5bd ne . then expaffps5=0.012;
else expaffps5=0;
if affps6bd ne . then expaffps6=0.012;
else expaffps6=0;
if affps7bd ne . then expaffps7=0.012;
else expaffps7=0;
if affps8bd ne . then expaffps8=0.012;
else expaffps8=0;
if affps9bd ne . then expaffps9=0.012;
else expaffps9=0;
if affps10bd ne . then expaffps10=0.012;
else expaffps10=0;
if affps11bd ne . then expaffps11=0.012;
else expaffps11=0;
run;
*/calculate reeds score;
data masterscoreexp;
set masterscoreexp;
if affpbd=. then affpobs=0;
else affpobs=affpbd;
```

```
if naffpbd=. then naffpobs=0;
else naffpobs=naffpbd;
if sib1bd=. then sib1obs=0;
else sib1obs=sib1bd;
if sib2bd=. then sib2obs=0;
else sib2obs=sib2bd;
if sib3bd=. then sib3obs=0;
else sib3obs=sib3bd;
if sib4bd=. then sib4obs=0;
else sib4obs=sib4bd;
if sib5bd=. then sib5obs=0;
else sib5obs=sib5bd;
if affpfbd=. then affpfobs=0;
else affpfobs=affpfbd;
if affpmbd=. then affpmobs=0;
else affpmobs=affpmbd;
if affps1bd=. then affps1obs=0;
else affps1obs=affps1bd;
if affps2bd=. then affps2obs=0;
else affps2obs=affps2bd;
if affps3bd=. then affps3obs=0;
else affps3obs=affps3bd;
if affps4bd=. then affps4obs=0;
else affps4obs=affps4bd;
if affps5bd=. then affps5obs=0;
else affps5obs=affps5bd;
if affps6bd=. then affps6obs=0;
else affps6obs=affps6bd;
if affps7bd=. then affps7obs=0;
else affps7obs=affps7bd;
if affps8bd=. then affps8obs=0;
else affps8obs=affps8bd;
if affps9bd=. then affps9obs=0;
else affps9obs=affps9bd;
if affps10bd=. then affps10obs=0;
else affps10obs=affps10bd;
if affps11bd=. then affps11obs=0;
else affps11obs=affps11bd;
obstotal1st=affpobs+naffpobs+sib1obs+sib2obs+sib3obs+sib4obs+sib5obs;
obstotal2nd=affpfobs + affpmobs + affps1obs + affps2obs + affps3obs +
affps4obs + affps5obs + affps6obs + affps7obs + affps8obs +
affps9obs + affps10obs + affps11obs;
exptotal1st=expaffp+expnaffp+expsib1+expsib2+expsib3+expsib4+expsib5;
exptotal2nd=expaffpf+expaffpm+expaffps1+expaffps2+expaffps3+
expaffps4+expaffps5+expaffps6+expaffps7+expaffps8+expaffps9+
```

```
expaffps10+expaffps11;
reed=2*((obstotal1st-exptotal1st)/sqrt(exptotal1st))+
((obstotal2nd-exptotal2nd)/sqrt(exptotal2nd));
run;
*/for schwartz score need measures for
each relative in terms of observed and expected values;
data masterscoreexp;
set masterscoreexp;
if affpbd=. then affpbdsch=0;
else affpbdsch=affpbd;
if naffpbd=. then naffpbdsch=0;
else naffpbdsch=naffpbd;
if sib1bd=. then sib1sch=0;
else sib1sch=sib1bd;
if sib2bd=. then sib2sch=0;
else sib2sch=sib2bd;
if sib3bd=. then sib3sch=0;
else sib3sch=sib3bd;
if sib4bd=. then sib4sch=0;
else sib4sch=sib4bd;
if sib5bd=. then sib5sch=0;
else sib5sch=sib5bd;
if affpfbd=. then affpfbdsch=0;
else affpfbdsch=affpfbd;
if affpmbd=. then affpmbdsch=0;
else affpmbdsch=affpmbd;
if affps1bd=. then affps1bdsch=0;
else affps1bdsch=affps1bd;
if affps2bd=. then affps2bdsch=0;
else affps2bdsch=affps2bd;
if affps3bd=. then affps3bdsch=0;
else affps3bdsch=affps3bd;
if affps4bd=. then affps4bdsch=0;
else affps4bdsch=affps4bd;
if affps5bd=. then affps5bdsch=0;
else affps5bdsch=affps5bd;
if affps6bd=. then affps6bdsch=0;
else affps6bdsch=affps6bd;
if affps7bd=. then affps7bdsch=0;
else affps7bdsch=affps7bd;
if affps8bd=. then affps8bdsch=0;
else affps8bdsch=affps8bd;
if affps9bd=. then affps9bdsch=0;
else affps9bdsch=affps9bd;
if affps10bd=. then affps10bdsch=0;
```

```
else affps10bdsch=affps10bd;
if affps11bd=. then affps11bdsch=0;
else affps11bdsch=affps11bd;
sp=(affpbdsch-expaffp)/sqrt(expaffp);
snp=(naffpbdsch-expnaffp)/sqrt(expnaffp);
s1=(sib1sch-expsib1)/sqrt(expsib1);s2=(sib2sch-expsib2)/sqrt(expsib2);
s3=(sib3sch-expsib3)/sqrt(expsib3);s4=(sib4sch-expsib4)/sqrt(expsib4);
s5=(sib5sch-expsib5)/sqrt(expsib5);sf=(affpfbdsch-expaffpf)/sqrt(expaffpf);
sm=(affpmbdsch-expaffpm)/sqrt(expaffpm);
ss1=(affps1bdsch-expaffps1)/sqrt(expaffps1);
ss2=(affps2bdsch-expaffps2)/sqrt(expaffps2);
ss3=(affps3bdsch-expaffps3)/sqrt(expaffps3);
ss4=(affps4bdsch-expaffps4)/sqrt(expaffps4);
ss5=(affps5bdsch-expaffps5)/sqrt(expaffps5);
ss6=(affps6bdsch-expaffps6)/sqrt(expaffps6);
ss7=(affps7bdsch-expaffps7)/sqrt(expaffps7);
ss8=(affps8bdsch-expaffps8)/sqrt(expaffps8);
ss9=(affps9bdsch-expaffps9)/sqrt(expaffps9);
ss10=(affps10bdsch-expaffps10)/sqrt(expaffps10);
ss11=(affps11bdsch-expaffps11)/sqrt(expaffps11);
run;
*/need to ensure no dots or sum will not calculate then
get schwartz score by summing scores for relatives;
data masterscoreexp;
set masterscoreexp;
if sp=. then sp=0;
else sp=sp;
if snp=. then snp=0;
else snp=snp;
if s1=. then s1=0;
else s1=s1;
if s2=. then s2=0;
else s2=s2;
if s3=. then s3=0;
else s3=s3;
if s4=. then s4=0;
else s4=s4;
if s5=. then s5=0;
else s5=s5;
if sf=. then sf=0;
else sf=sf;
if sm=. then sm=0;
else sm=sm;
if ss1=. then ss1=0;
else ss1=ss1;
```

```
if ss2=. then ss2=0;
else ss2=ss2;
if ss3=. then ss3=0;
else ss3=ss3;
if ss4=. then ss4=0;
else ss4=ss4;
if ss5=. then ss5=0;
else ss5=ss5;
if ss6=. then ss6=0;
else ss6=ss6;
if ss7=. then ss7=0;
else ss7=ss7;
if ss8=. then ss8=0;
else ss8=ss8;
if ss9=. then ss9=0;
else ss9=ss9;
if ss10=. then ss10=0;
else ss10=ss10;
if ss11=. then ss11=0;
else ss11=ss11;
schwartz=2*sp+2*snp+2*s1+2*s2+2*s3+2*s4+2*s5+sf+sm+ss1+ss2+ss3+
ss4+ss5+ss6+ss7+ss8+ss9+ss10+ss11;
run;
data masterscoreexp2;
set masterscoreexp;
if reed=. then reed=2*((obstotal1st-exptotal1st)/sqrt(exptotal1st));
run;

**PREPARE DATA SET FOR COX MODELS IE GET AGES OF ONSET********************

*/calculate age onset bd;
data masterscoreexp3;
set masterscoreexp2;
offspring_age_bp_to_age=('12may2011'd-hr_offspring_bd_onset)/364.2425;
offspring_age_bp_onset=age_offspring-offspring_age_bp_to_age;
run;

*/calculate age onset of other disorders;
data masterscoreexp4;
set masterscoreexp3;
offspring_age_md_to_age=('12may2011'd-hr_offspring_md_onset)/364.2425;
offspring_age_md_onset=age_offspring-offspring_age_md_to_age;
offspring_age_minor_d_to_age
=('12may2011'd-hr_offspring_minor_d_onset)/364.2425;
offspring_age_minor_d_onset=age_offspring-offspring_age_minor_d_to_age;
```

```
offspring_age_sud_to_age=('12may2011'd-hr_offspring_sud_onset)/364.2425;
offspring_age_sud_onset=age_offspring-offspring_age_sud_to_age;
offspring_age_anxiety_to_age
=('12may2011'd-hr_offspring_anxiety_onset)/364.2425;
offspring_age_anxiety_onset=age_offspring-offspring_age_anxiety_to_age;
offspring_age_psychotic_to_age
=('12may2011'd-hr_offspring_psychotic_onset)/364.2425;
offspring_age_psychotic_onset=age_offspring-offspring_age_psychotic_to_age;
run;
*/create fage variables for all disorders;
data masterscoreexp5;
set masterscoreexp4;
if hr_offspring_bd=1 then fage_bd=offspring_age_bp_onset;
else fage_bd=age_offspring;
if hr_offspring_lifetime_md=1
then fage_md=offspring_age_md_onset;
else fage_md=age_offspring;
if hr_offspring_minor_d=1
then fage_minor=offspring_age_minor_d_onset;
else fage_minor=age_offspring;
if hr_offspring__sud=1 then
fage_sud=offspring_age_sud_onset;
else fage_sud=age_offspring;
if hr_offspring_anxiety=1 then
fage_anxiety=offspring_age_anxiety_onset;
else fage_anxiety=age_offspring;
if hr_offspring_psychotic=1 then
fage_psychotic=offspring_age_psychotic_onset;
else fage_psychotic=age_offspring;
run;

proc sort data=masterscoreexp5;
by family_id high_risk__hr__offspring_person;
run;

*merge data into one complete master set called completemasterscore
using proc merge*



**********STANDARDIZE SCORES AND COX MODELS BIPOLAR**********

/*standardize scores*/
data masterscorenormal;
set completemasterscore;
```

```
array mean{7} _temporary_
(4.9514955,4.0220481,0.9727273,2.9136364,0.2374533,25.2030385,12.8142795);
array sd{7} _temporary_
(3.3998688,3.5548475,0.1632485,1.4451289,0.1134204,13.0411499,5.8315847);
array score{7} flscorebdunweighted flscorebd
fldich flcount propscore schwartz reed;
array normalscore{7} unwtwals wals dich count prop schw rd;
do i=1 to 7;
normalscore{i}=(score{i}-mean{i})/sd{i};
end;
run;

**********************************PREDICT BIPOLAR**********************

ods graphics on;
proc phreg data=masterscorenormal COVS(AGGREGATE);
model fAge_bd*hr_offspring_bd(0)= dich/ties=breslow firth risklimits;
assess ph/resample;
title "dich score predict bd";
id nuclear_id__with_slibling_identi;
run;
proc phreg data=masterscorenormal COVS(AGGREGATE);
model fAge_bd*hr_offspring_bd(0)= count/ties=exact risklimits;
assess ph/resample;
title "count score predict bd";
id nuclear_id__with_slibling_identi;
run;
proc phreg data=masterscorenormal COVS (AGGREGATE);
model fAge_bd*hr_offspring_bd(0)= prop/ties=exact risklimits;
assess ph/resample;
title "prop score predict bd";
id nuclear_id__with_slibling_identi;
run;
proc phreg data=masterscorenormal COVS (AGGREGATE);
model fAge_bd*hr_offspring_bd(0)= wals/ties=exact risklimits;
assess ph/resample;
title "wals score predict bd";
id nuclear_id__with_slibling_identi;
run;
proc phreg data=masterscorenormal COVS(AGGREGATE);
model fAge_bd*hr_offspring_bd(0)= unwtwals/ties=exact risklimits;
assess ph/resample;
title "unweighted wals score predict bd";
id nuclear_id__with_slibling_identi;
run;
```

```
proc phreg data=masterscorenormal COVS(AGGREGATE);
model fAge_bd*hr_offspring_bd(0)= schw/ties=exact risklimits;
assess ph/resample;
title "schwartz score predict bd";
id nuclear_id__with_slibling_identi;
run;
proc phreg data=masterscorenormal COVS(AGGREGATE);
model fAge_bd*hr_offspring_bd(0)= rd/ties=exact risklimits;
assess ph/resample;
title "reeds score predict bd";
id nuclear_id__with_slibling_identi;
run;
ods graphics off;

**************************CORRELATION MATRIX BIPOLAR********************
proc corr data=completemasterscore;
var fldich flcount propscore flscorebd
flscorebdunweighted reed schwartz;
run;


***************EXPLORATORY ANALYSIS CREATING LONG DATA SETS BIPOLAR*******

data scores;
set completemasterscore;
keep subject hr_offspring_bd hr_offspring_lifetime_md
hr_offspring_minor_d hr_offspring__sud hr_offspring_anxiety
hr_offspring_psychotic familysize weightedfamilysize
flcount fldich propscore flscorebd flscorebdunweighted reed schwartz;
run;

data scoresnormal;
set masterscorenormal;
keep subject hr_offspring_bd hr_offspring_bd hr_offspring_lifetime_md
hr_offspring_minor_d hr_offspring__sud hr_offspring_anxiety
hr_offspring_psychotic familysize
weightedfamilysize count dich prop wals unwtwals rd schw;
run;

*data sets to get trend plots;
data scoreslong;
set scores;
scoretype='1dch'; score=fldich; output;
*perform calculations and output to new data set;
```

```
scoretype='2cnt'; score=flcount; output;
scoretype='3prop'; score=propscore; output;
scoretype='4wtwls'; score=flscorebd; output;
scoretype='5unwtwls'; score=flscorebdunweighted; output;
scoretype='6rd'; score=reed; output;
scoretype='7shw'; score=schwartz; output;
run;

*make trend plots for each subject;

goptions interpol=join;
proc gplot data=scoreslong;
title 'different score types for each subject for fl bipolar';
plot score*scoretype=subject/nolegend haxis=axis2 vaxis=axis1;
run;
goptions reset;

*get standardized scores data sets for mean plots;

data scoresnormal;
set masterscorenormal;
keep subject hr_offspring_bd hr_offspring_bd hr_offspring_lifetime_md
hr_offspring_minor_d hr_offspring__sud hr_offspring_anxiety
hr_offspring_psychotic familysize weightedfamilysize
count dich prop wals unwtwals rd schw;
run;

*get standardized score means;

proc means data=scoresnormal;
var count dich prop wals unwtwals rd schw;
class hr_offspring_bd;
run;

proc means data=scoresnormal;
var count dich prop wals unwtwals rd schw;
class hr_offspring_anxiety;
run;

*create mean data sets for bipolar pred bipolar, bipolar pred anxiety;

data scoremeansnormal;
input type mean offspringbd;
datalines;
dichotomous 0.0346164 0
```

```
dichotomous -0.1829735 1
count 0.0373193 0
count -0.1972592 1
prop 0.0277906 0
prop -0.1468927 1
unwtwals 0.0513343 0
unwtwals -0.2713387 1
wals 0.0407364 0
wals -0.2153208 1
reed 0.0217928 0
reed -0.1151904 1
schwartz 0.0371333 0
schwartz -0.1962761 1
;
run;

data scoremeansnormal;
input type meanbd bd  meananx anx ;
datalines;
dichotomous 0.0346164 0  -0.0466223 0
dichotomous -0.1829735 1  0.1670625 1
count 0.0373193 0  -0.0126546 0
count -0.1972592 1  0.0453456 1
prop 0.0277906 0  -0.0601312 0
prop -0.1468927 1  0.2154704 1
unwtwals 0.0513343 0  0.0068017 0
unwtwals -0.2713387 1  -0.0243727 1
wals 0.0407364 0  -0.0199808 0
wals -0.2153208 1  0.0715981 1
reed 0.0217928 0  -0.0542435 0
reed -0.1151904 1  0.1943724 1
schwartz 0.0371333 0  -0.0146143 0
schwartz -0.1962761 1  0.0523679 1
;
run;



****bipolar fl score************************************

goptions interpol=join;
proc gplot data=scoremeansnormal;
title 'different fl scores for bipolar against
offspring anxiety disorder diagnosis';
plot meananx*anx=type;
```

```
run;
goptions reset;

goptions interpol=join;
proc gplot data=scoremeansnormal;
title 'different fl scores for bipolar against
offspring anxiety disorder diagnosis';
plot meanbd*bd=type;
run;
goptions reset;

*****************USE R FOR SCHOENFELD RESIDUALS EX BIPOLAR************

familyloadingbd<-read.csv('m:masterscorenormal.csv')

#BIPOLAR TO PREDICT BIPOLAR#########################################

fldichcox<-coxph(Surv(fage_bd,HR_Offspring_BD)
~dich,data=familyloadingbd)
> flcountcox<-coxph(Surv(fage_bd,HR_Offspring_BD)
~count,data=familyloadingbd)
> flwalscox<-coxph(Surv(fage_bd,HR_Offspring_BD)
~wals,data=familyloadingbd)
> flunwtwalscox<-coxph(Surv(fage_bd,HR_Offspring_BD)
~unwtwals,data=familyloadingbd)
> flreedcox<-coxph(Surv(fage_bd,HR_Offspring_BD)
~rd,data=familyloadingbd)
> flschwartzcox<-coxph(Surv(fage_bd,HR_Offspring_BD)
~schw,data=familyloadingbd)
> flpropcox<-coxph(Surv(fage_bd,HR_Offspring_BD)
~prop,data=familyloadingbd)

schoendich<-cox.zph(fldichcox,transform='log')
 schoencount<-cox.zph(flcountcox,transform='log')
schoenprop<-cox.zph(flpropcox,transform='log')
> schoenwals<-cox.zph(flwalscox,transform='log')
> schoenunwtwals<-cox.zph(flunwtwalscox,transform='log')
> schoenreed<-cox.zph(flreedcox,transform='log')
> schoenschwartz<-cox.zph(flschwartzcox,transform='log')

 plot(schoendich,main="dichotomous")
> plot(schoencount,main="count")
> plot(schoenprop,main="proportion")
> plot(schoenwals,main="weighted wals")
> plot(schoenunwtwals,main="unweighted wals")
```

```
> plot(schoenreed,main="reed")
> plot(schoenschwartz,main="schwartz")
```

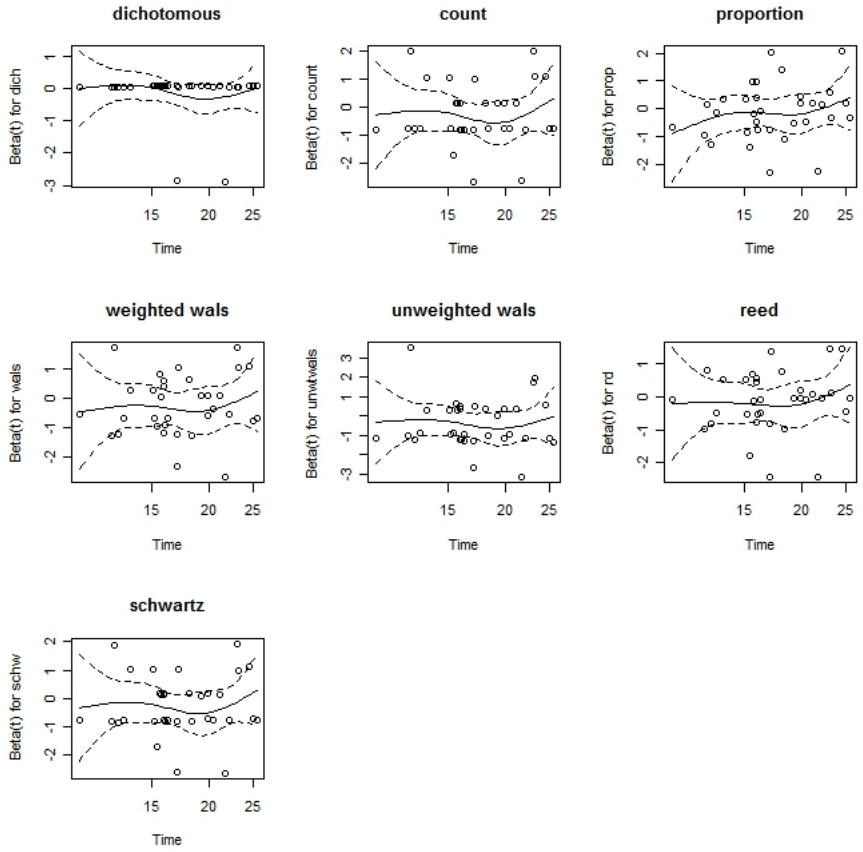


Figure A.1: Schoenfeld residual plots for Cox model with family history score for bipolar disorder as the predictor and hazard of bipolar disorder as the response