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The Familial Aggregation of Agoraphobia

by

Sylvie Rachelle Pappas

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the degree of Master of Science

Department of Psychiatry

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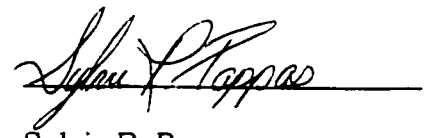

Sylvie R. Pappas
15016 131 St. N.W
Edmonton, Alberta
T6V 1K3

Sept. 1, 1999

University of Alberta

Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled *The Familial Aggregation of Agoraphobia* submitted by Sylvie R. Pappas in partial fulfillment of the requirements for the degree of Master of Science

Dr. Stephen C. Newman

Dr. Roger C. Bland

Dr. Peter H. Silverstone

Dr. Andrew J. Greenshaw

Dr. Don Schopflocher

Date: August 16, 1999

DEDICATION

To my husband Tom, for his unselfishness, his unrelenting desire to see me succeed and for showing me that true love does not consist of gazing into each other's eyes, but of gazing in the same direction.

ABSTRACT

A community based family study of agoraphobia (with or without panic disorder) in 2,386 first-degree relatives of 924 probands was conducted. All subjects were directly interviewed by non-clinician interviewers using the Diagnostic Interview Schedule (DIS). Diagnoses were made using DIS software with DSM-III criteria. There were 50 cases of lifetime agoraphobia in the probands and 75 cases in the relatives. The odds ratio for agoraphobia in probands *vs.* agoraphobia in relatives was 2.53. This was further confirmed with logistic regression (odds ratio=2.43) which included adjustment for gender of relatives, relationship to proband, depression in relatives, generalized anxiety disorder in relatives, simple phobia in relatives and social phobia in relatives. It was concluded that in a community sample DSM-III agoraphobia is familial after adjusting for comorbidity and demographic variables. Replication of these findings in twin and adoption studies is needed.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

1.1 GENETIC EPIDEMIOLOGY

Genetic epidemiology is a multidisciplinary field, which combines the fields of human genetics, molecular biology, statistics and epidemiology. Epidemiology is defined as the study of the distribution and determinants of disease frequency in human populations (Hennekens and Buring, 1987). Clearly, this definition encompasses genetic determinants. Yet, epidemiologists in the past have focused on the environmental causes of disease, and conversely geneticists have focused on heredity (Faraone and Tsuang, 1995; Susser and Susser, 1995). From recent discoveries in genetics, epidemiologists have now turned their attention to the key role of specific genes in the development of disease and at the same time geneticists have become increasingly aware of the importance of genetic and environment interaction. This departure from mutual exclusiveness has given rise to the field of genetic epidemiology which has been defined as "a science that deals with the etiology, distribution, and control of disease in groups of relatives and with inherited causes of disease in populations" (Faraone and Tsuang, 1995).

The chain of genetic epidemiology research follows a series of questions in a ratiocinative progression. The starting point is the phenomenon of familial aggregation – the tendency for relatives of individuals affected with a disorder to be at increased risk for that disorder. Put more simply, the first question

asked is "Is the disorder familial?". This question can be answered using the family study method, the focus of this thesis. Following the chain of progression, the second question asked is "What is the relative magnitude of genetic and environmental contributions to disease etiology and expression?". The tools to explore this question are twin and adoption studies. These are special types of family studies in which confounding by the environment is minimized. After establishing that the disorder is influenced by genetic factors, the next question asked is "What is the mode of transmission?." This next task uses segregation analysis to determine this information. Lastly, the research leads to questions related to "where the gene(s) are located? ". At this stage of inquiry, linkage and association studies are utilized (Cantor and Rotter, 1992; Faraone and Tsuang, 1995). The methodologies involved with family studies, twin and adoption studies, segregation analysis, and linkage studies will be discussed in more detail below.

1.1.1 Familial Aggregation

The primary purpose of a study of familial aggregation is to determine whether the disease prevalence in genetically related family members of affected individuals is increased over the prevalence of the disease in the general population. If genes are important to a disorder, then relatives of ill individuals (probands) should be at greater risk of the illness than the relatives of well individuals. It should be noted that evidence of familial aggregation from family studies does not imply that the disorder is genetic. Aggregation could result from both a shared common culture and common environment or

from shared genes (Tsuang and Faraone, 1990; Weissman et al., 1986). First-degree relatives are often investigated. Parents, children and siblings of probands are referred to as first-degree relatives as they share 50 percent of their genes with the proband (Cantor and Rotter, 1992 ; Tsuang and Faraone, 1990).

Family study data can serve several purposes. They can provide better understanding of and identification of homogenous diagnostic subgroups and can lead to the development of more precise clinical descriptions of the disorder. They can yield information on the early signs and childhood forms of the disorder and on the protective or risk factors in the development of the disorder (Weissman et al., 1986). Numerous family studies have demonstrated that some major psychiatric disorders such as depression, schizophrenia, and alcoholism are familial (Gershon et al., 1982; Goodwin, 1979; Kendler et al., 1984; Kendler et al., 1985; Schuckit, 1986; Tsuang and Vandermey, 1980; Weissman et al., 1984).

1.1.2 Family Study Methodology

The design of most family studies can be viewed as a cohort study. In a cohort study, subjects are classified on the basis of the presence or absence of exposure to a particular factor and then followed for a specified period of time to determine the development of the disease in each exposure group. In terms of a family study, relatives of the proband from the cohort and are classified on the basis of the presence or absence of 'exposure' to an ill proband. The

relatives are then 'followed' for a specified period of time to determine the development of the disorder in each exposure group. The follow up time is from the beginning of the risk period for the disease to the age at onset of disease for those individuals who developed the disease, and current age for those who did not develop the disease. In most family studies the 'follow-up' is retrospective and based in lifetime histories, as discussed below.

Since most psychiatric disorders have variable ages of onset (Thyer et al., 1985) they must be accounted for in the analysis. One way to adjust for the variable ages of onset is by computing the morbidity risk: the probability that the subjects being studied are susceptible to the disorder of interest. In other words, it is the probability that a person will manifest the disorder if he or she lives long enough in the absence of death from some other cause. Methods to estimate morbidity risk adjust the rate of illness in a sample to account for the well subjects who have not lived through the risk period. One approach to estimating the morbidity risk uses the concepts from survival analysis. Briefly, the age of onset of disease can be treated as a survival time, and the survival function presents the cumulative probability of being free from illness as a function of age. Censored cases are those subjects who do not develop the disease by the end of the follow-up period (Kahn and Sempos, 1989).

Ideally, in a family study, a prospective cohort study would be employed. More specifically, the ill probands would be restricted only to parents, and the population at risk would be their offspring who would be followed from birth over given period of risk. Selection that begins with the adult probands and

where psychopathology is studied among their offspring and other relatives has been termed the "top down " approach (Weissman et al., 1986). In this manner, the parents can be clearly defined as the 'exposure'. However, what is often done in practice is that the proband group is allowed to consist of a combination of parents, siblings and offspring. Thus, the source of exposure becomes ambiguous since the child can sometimes be the 'exposure' for the parent. Therefore, it is more comprehensible to define the exposure as the genetic material rather than the relationship to the proband. Furthermore, it is impractical to follow individuals over a lifetime to determine their risk of illness; consequently, a retrospective cohort study is commonly employed. In a retrospective study, both the exposure and outcome have already occurred. Information is obtained from the relatives based on recall. Although the retrospective method has the advantage of being less expensive and time consuming in comparison to the prospective approach, the reliance on the abilities of subjects to accurately recall lifetime symptoms can be called into question (Hennekens and Buring, 1987).

Another common design used in psychiatry is the family case-control study. In a classic case-control study a group of individuals are selected based on whether they do (cases) or do not (controls) have the disease in question. Groups are then compared with respect to the proportion having a history of exposure. In contrast to cohort studies, subjects are selected according to their disease status, rather than exposure status (Schlesselman, 1982) In family studies probands are often selected as cases and exposure is defined as a first-degree relative with the illness under investigation. In this design, only one

first-degree relative per proband can be included in the study to clearly distinguish between exposed and non-exposed proband groups. Ideally, the study is double blind in which the diagnoses of relatives are made independent of any knowledge of the proband's diagnostic status. Similar to cohort designs, variable age at onset in relatives must be adjusted for in the analysis (Faraone and Tsuang, 1995; Kendler et al., 1997; Cantor and Rotter, 1992; Weissman et al., 1986).

Individuals selected to comprise the exposed population in a cohort study often come from treatment settings, psychiatric or case registries. Generalizability may become an issue in such cases. Ideally, a community-based sample should be obtained. The comparison group of non-exposed individuals can be selected from several sources. For example, they can be selected from primary care facilities or from community samples. In the latter case, the subjects may include medically, but not psychiatrically ill relatives, normal, never psychiatrically ill, or they may have a psychiatric illness other than the one being studied. Groups being compared should be as similar as possible with respect to all other factors related to the disease except the disorder under investigation.

Sources of cases and controls are similar to cohort studies although there is debate regarding the ideal source of controls for psychiatric family studies. Some argue that the use of "super-normal" control groups (screened to eliminate all cases with any psychiatric disorder) are problematic. Since the exclusion often does not apply in the selection of cases, the relatives of the

super-normal control group will have lower risks for all excluded disorders than will relatives of the index probands; this will result in spurious evidence for coaggregation (Faraone and Tsuang, 1995; Kendler, 1990; Klein, 1993; Schwartz and Link, 1989). The way in which the "super-normal" control groups have been used in some family studies (Coryell and Zimmerman, 1987; Weissman et al., 1984) violates two basic principles of control selection: (1) the same exclusion criteria should be applied to cases and controls and (2) controls should be selected independent of exposure status (Rothman, 1986; Schlesselman, 1982). It has been suggested that gathering data on both screened and unscreened control groups will yield more generalizable results than either alone (Tsuang et al., 1988).

Family studies require practical methods to assess reliably the lifetime psychiatric status of possibly large numbers of individuals, many whom may never have been in treatment. There are two approaches for the evaluation of family members: the direct interview and family history method (Faraone and Tsuang, 1995). In general, the direct interview method is preferred since information is likely to be more accurate (Andreasen et al., 1977). Below are examples and descriptions of several interview instruments which have been used in the family studies.

1.1.3 Direct Interview

The Renard Diagnostic Interview is one of the first structured diagnostic interviews for systematically eliciting signs and symptoms of disorders in conjunction with a specified set of diagnostic criteria, the latter due to

Feighner et al., in 1972 (Robins et al., 1985). Next in line of development is Schedule for Affective Disorders and Schizophrenia (SADS) and the Research Diagnostic Criteria (RDC) (Spitzer and Endicott, 1977; Spitzer et al., 1978). The Feighner criteria were subsequently modified and elaborated by Spitzer et al., in 1978 and published as the RDC. The SADS and SADS-L (Spitzer and Endicott, 1977) are semi-structured interviews that allow diagnosis by RDC criteria. The SADS concentrates on current affective symptoms of subjects, while the SADS-L was designed for assessing lifetime disorders. Many investigators have used the SADS-RDC in large family studies (Fyer et al., 1990; Fyer et al., 1993; Fyer et al., 1996; Horwath et al., 1995; Lenane et al., 1990; Merikangas et al., 1985; Weissman et al., 1982; Weissman et al., 1984).

Another instrument is the Diagnostic Interview Schedule (DIS) which is the instrument used in the present family study. Only a brief description is presented here, a more detailed description is presented in section 2.3.2. The DIS is a combination of the Renard Diagnostic Interview and the SADS. Robins et al. (1981b) developed the DIS for the Epidemiologic Catchment Area Study. It is highly structured and can be used by lay interviewers. Although the DIS has been used in numerous studies as a diagnostic tool (Ahlberg et al., 1996; Borish et al., 1998; Gallo et al., 1998; Puura et al., 1998; Tomasson and Vaglum., 1998), few studies other than this present study have utilized the DIS in a family study (Kendler et al., 1992a; Kendler et al., 1995).

A commonly used instrument is the Structured Clinical Interview for the DSM (SCID) (Spitzer and Williams, 1985). The SCID is designed to enable clinically

trained interviewers to make major diagnoses based on Axis I and Axis II of the DSM. It is modeled on the typical clinical diagnostic interview in which an overview of the present illness and past episodes of psychopathology precedes the systematic inquiry about specific symptoms. A computerized version of the SCID is also available (Spitzer and Williams, 1985; First et al., 1996; First et al., 1997). The SCID has been utilized in several family studies (Kendler, 1992a; Kendler, 1992b; Reich and Yates, 1988).

Other instruments include the International Classification of Diseases (ICD)/ Present State Examination (PSE). The PSE, developed by Wing et al. (1974), is linked to the ICD which incorporates standard methods of defining, eliciting, and recording information on 140 symptoms in an interview format (Weissman et al., 1986). To date, only one family study has utilized the PSE (Sham et al., 1994).

More recently, the Composite International Diagnostic Interview (CIDI) was developed (Robins et al., 1988). It is a fully structured interview that combines elements of the DIS and PSE and is capable of generating DSM and ICD diagnoses. The CIDI is available in many different languages, is compatible with the European, US and other diagnostic schemes and takes into account international differences in psychiatric diagnosis, thus facilitating cross-national studies (Andrews and Peters, 1998; Robins et al., 1988). Similar to the PSE, the CIDI has been seldom used in family studies (Kendler and Gardner, 1997).

The only interview designed specifically for genetic studies is the Diagnostic Interview for Genetic Studies (DIGS). This instrument was developed and piloted as a collaborative effort by investigators from the National Institute of Mental Health. It was constructed for the assessment of major mood and psychotic disorders. The DIGS has the following features: (1) diagnoses can be made in multiple systems that include the RCD, DSM-III, DSM-III-R, DSM-IV and ICD-10; (2) it includes a detailed assessment of the course of illness, with particular attention to the comorbidity of substance abuse or dependence; (3) detailed sections are included to assess current and past occurrences of episodes of substance abuse; and (4) a detailed psychosis section is included for collecting data which carefully distinguishes schizophrenia, schizoaffective disorder and other psychotic conditions. The DIGS collects self-reported demographic and medical history data, and ratings are also available on several other psychiatric scales (Faraone and Tsuang, 1995; Nurnberger et al., 1994).

1.1.4 Family History

The second approach, the family history method, is utilized when direct interview is not possible due to proband or relative refusal, unavailability, geographic distance or death. The diagnosis is made based on the information provided about the relative by one or several informants of the family. Some of the specialized instruments available for this method include: (1) The Family History Research Diagnostic Criteria; (Andreasen et al., 1977); (2) the Family

Informant Schedule and Criteria (FISC) (Weissman et al., 1986) and (3) the Family Interview for Genetic Studies (FIGS) (Faraone and Tsuang, 1995).

The FIGS, like the DIGS was developed and piloted by principal investigators from the National Institute of Mental Health. Unlike the DIGS, the FIGS does not elicit self-report data. Subjects are asked to provide information about others. The instrument is administered in three ways: 1) a pedigree is drawn and reviewed with the informant; 2) general screening questions are asked about all known relatives; 3) one or more of 5-symptom checklists are completed for each first-degree relative or spouse. A particular checklist is completed based on the informants answers to the screening questions (National Institute of Mental Health, 1999: http://www.-grb.nimh.nih.gov/interviews.html.).

Research indicates that family history information is potentially unreliable and should be interpreted with caution. Specificity is the probability that a subject who is truly not ill will be assessed as not ill by the family study method. Sensitivity is the probability that a subject who is truly ill will be diagnosed ill by the family study method (Faraone and Tsuang, 1995). Comparison of diagnoses based on family history with diagnoses based on direct interview indicate that the specificity for the family history method is high but the sensitivity is low (Andreasen et al., 1977). Furthermore, family history data underestimates true rates of many psychiatric disorders in relatives (Andreasen et al., 1977; Orvaschel et al., 1982; Rimmer and Chambers, 1969). One exception is the diagnosis of antisocial personality disorder. Andreasen

(1986) found the family history rate of this disorder to be three times greater than the rate derived from the direct interview method. The family history method may be a viable choice when there are insufficient data to justify the expense of a direct interview family study and it may be a good choice for initial pilot phases of a genetic investigation (Faraone and Tsuang, 1995).

Several other ways of obtaining information include telephone interviews and psychiatric records. Interviews can be conducted via telephone when circumstances such as geographic distance prohibit direct interview with a family member. Several family studies have employed this method and it appears to have acceptable reliability compared to direct interviews (Crowe et al., 1980; Gershon et al., 1982; Weissman et al., 1986). Case records, when available, can supply data on symptoms, duration, and timing of illness. Generally, records should be regarded as supplemental information as they rarely contain enough information to arrive at a diagnosis in the absence of a family history or family study method (Kendler , 1997; Weissman et al., 1986).

Ideally, the diagnosis of the subject should be based on all sources of information: personal interview, family history with relatives who are familiar with the subject and medical records when available. This method has been called the "best-estimate diagnosis". The diagnosis is made by at least one clinician who is blind to the diagnostic status of the proband and who is not involved in direct interviews of any of the probands or relatives (Gershon and Guroff , 1984; Leckman et al., 1982). The "best-estimate diagnosis" has been commonly used in family studies (Fyer et al., 1995; Hein and Maier, 1995;

Horwath et al., 1995; Leckman et al., 1983; Merikangas et al., 1985; Weissman et al., 1982).

1.1.5 Statistics to Test for Familial Aggregation

The major outcome in a family study is rate of illness in relatives over their lifetime referred to as lifetime risk or morbid risk (Faraone and Tsuang., 1995). The first step in the analysis is reporting the test of association, usually the chi-square test. This is employed to determine whether there is an increased disease frequency in the family members of affected individuals as compared with controls. As shown in **Figure 1**, a 2 x 2 table is analyzed for a difference in proportions. In a case-control study, the rows in the table represent the presence or absence of disease in the relatives and the columns represent the cases and controls. In a cohort study, the rows in the table represent the presence or absence of disease in the proband, and the columns represent the presence or absence of disease in the relative. The usual chi-square test provides an approximate test of the hypothesis of no association between probands and relatives. It is computed as follows:

$$\chi^2 = [(ad - bc)^2 n] / [n_1 n_2 m_1 m_2]$$

If the chi-square statistic exceeds the $(1- \alpha)$ 100^{th} percentile of a chi-squared distribution with 1 degree of freedom, then the hypothesis of no association is rejected and it is concluded that there is an association between the variables (Schlesselman, 1982).

The second step is determining the degree of the association. Two common ways of estimating the magnitude of the association are the relative risk and the odds ratio. The relative risk is used in cohort studies, but the odds ratio can be used in both cohort and case-control studies. The relative risk measures increased risk of disease to members of the families of the affected individuals on a multiplicative scale. This statistic is calculated as the ratio of the disease rate in the relatives of the disease probands to that of control probands :

$p_1 = a/m_1 \qquad p_2 = b/m_2 \qquad RR = p_1 / p_2$

A relative risk greater than 1 indicates that the disease is more prevalent in the relatives of those with the disease compared to the relatives of those without the disease (Cantor and Rotter, 1992; Schlesselman, 1982).

The odds ratio is a measure of association between two dichotomous variables that is closely related to the relative risk. If the probability of an event is denoted by, p, then the ratio p/q, where $q = 1 - p$, is called the odds. The ratio of the odds of disease in exposed individuals relative to those unexposed is called the odds ratio. Referring to **Figure 1,** the odds ratio is calculated as ad/bc. Similar to the relative risk, an odds ratio greater than 1 indicates the disease is more prevalent in the relatives with the disease compared to relatives of those without the disease and likewise, no association implies the odds ratio is equal to 1 (Hillis and Woolson, 1995; Schlesselman, 1982).

1.1.6 Twin and Adoption Studies

The classic method to determine whether familial aggregation is due to common genetic or common environmental factors it to compare the concordance rates of the disease (whether one or both members of a twin pair is affected) in monozygotic and dizygotic twin pairs. The co-occurrence of a disorder in both twins is referred to concordance; if one twin has the disorder and the other does not, the twins are discordant for the disorder. Monozygotic twins have 100 percent of their genes in common. Thus, the difference between monozygotic twins must be environmental. In contrast, dizygotic twins have only 50 percent of their genes in common and since dizygotic twins are not genetic copies of each other, differences within a twin pair can be due to either gene or environmental influences. Thus, comparing the co-occurrence of a psychiatric disorder in the two types of twins provides information about the relative contributions of genetic and environmental influences in the etiology of the disorder. Other designs include studying monozygotic twins who have been reared apart since they do not share a common environment. Any phenotypic (observable trait) similarity must be due to genetic factors. As well, children of discordant monozygotic twins can be studied. If a disorder is caused by a genotype in combination with the environment, then the well member of a discordant monozygotic twin pair should carry the genotype. It is presumed that if they do not develop the disorder it is because they were not exposed to some common environmental factor. Therefore, children of the well twin should have the same risk for the disorder as the children of the ill twin (Faraone and Tsuang, 1995; King et al., 1992; Tsuang and Faraone, 1990).

Twin studies have provided extensive data for affective disorders, schizophrenia, and alcoholism (Carey and Gottesman, 1981; Gurling et al., 1981; Kendler et al., 1998; Kendler et al., 1997; Kendler et al., 1992b; Roy et al., 1995). One of the largest and methodologically sophisticated twin study was reported in Denmark by Bertelsen, Harvald, and Hauge in 1977 (Tsuang et al., 1990). They identified 220 twin partners through the Danish Psychiatric Twin Register for a study of manic-depressive psychosis and found a higher rate of concordance among monozygotic twins than dizygotic twins for the diagnosis of mood disorders (Tsuang et al., 1990). The Minnesota Twin Family study is another large twin research project initiated in 1983 within the Department of Psychology at the University of Minnesota. This family study is composed of several projects which in part investigate the development of alcoholism, schizophrenia, mood and anxiety disorders (Grove et al., 1992; Iacono and Grove, 1993; Iacono et al., 1998; McGue et al., 1992).

Adoption studies can also provide information regarding the genetic and environmental contributions to the familial aggregation of psychiatric disorders. Adoption separates individuals from their biological parents with whom they share genes and environment and moves them (with their genes unchanged) to a new environment. If the genes are important, then the familial transmission of the disorder should occur in the biologic but not the adoptive family. Likewise, if the source of transmission is environmental, then the familial transmission of the illness should occur in the adoptive but not the biological family (Faraone and Tsuang, 1995).

There are three common adoption study designs. One is the parent-as-proband design, which compares the rates of illness in the adopted offspring of parents with and without the disorder. It is expected that if the disorder is genetic, then the rates of illness should be greater in the adopted children of ill parents compared to the adopted children of well parents. A second design is the adoptee-as-proband design, which starts with ill and well adoptees and examines rates of illness in both biological and adoptive relatives. If the biologic relatives show higher rates of the disorder, then a genetic hypothesis is supported. A third design is the cross-fostering design, which compares the rates of illness for two groups of adoptees. One group has biologic parents who are not ill and are raised by ill adoptive parents and the other has ill biological parents and are raised by not ill adoptive parents. Higher rates of the disorder in the latter group would imply a genetic mode of illness transmission (Faraone and Tsuang, 1995; King et al., 1992; Tsuang and Faraone, 1990). Many adoption studies support the hypothesis that the familial transmission of mood disorders, and schizophrenia is due to genetic and not environmental factors (Cadoret et al., 1985; Kety et al., 1968; Rosenthal et al., 1975; Wender et al., 1986).

1.1.7 Transmission and Linkage Analysis

Once it is established that genetic factors play a role in the development of the disorder, the next step is to analyze data to arrive at a mode of inheritance for that disorder, such as a single locus model or the oligogenic/multifactorial model. In the former, one gene can account for most of the genetic

transmission of the disorder; in the latter, many genes may combine to cause the disorder. The statistical procedures used to model genetic transmission are prevalence analysis and pedigree segregation. In prevalence analysis, the data are reduced to a matrix that specifies the prevalence of the disorder in relatives of ill and control probands. Pedigree segregation analysis uses all information available in the pedigree and computes the likelihood of the pattern of illness in each family (Cantor and Rotter, 1992; Faraone and Tsuang, 1995; Tsuang and Faraone, 1990).

The next step is to locate the gene in the complement of human chromosomes. Statistical procedures conducted to accomplish this are referred to linkage analyses. Linkage studies are also useful for identifying the mode of inheritance; determining the specific biochemical abnormality and the pathogenesis of the illness; determining which environmental factors are relevant to the onset or course of illness; and determining gene-environment interaction (Cantor and Rotter, 1992; Weissman et al., 1986).

There are several issues in the study of psychiatric disorders that markedly reduce the power of linkage analysis and thus make progress in this research area much slower for psychiatric than for other human disorders. First, in Mendelian disorders, individuals who carry either one dominant or two recessive copies of the disease genes will always become ill. In contrast, the genetic risk factors for psychiatric disorders are not fully penetrant. Second, with most Mendelian disorders, there is no problem in differentiating the affected from the unaffected. This is not true for psychiatric disorders. For

example, should the offspring of a proband with dysthymia but no major affective depression be considered affected? Third, most genetic disorders cannot be mimicked by environmental factors. In contrast, some psychiatric illnesses can be caused by drug abuse and depressive illnesses can arise from psychological trauma without any prior vulnerability. Fourth, most genetic disorders are due to abnormalities of a single gene. It is speculated that it is unlikely that single genes are responsible for the broad range of behavioral syndromes in psychiatry. Other obstacles to linkage studies of psychiatric disorders include lack of standardization for systematically collecting pedigrees, a lack of reliability, and lack of specified diagnostic criteria (Kendler, 1997; Weissman et al., 1986).

However, some progress has been made and positive results are starting to emerge. There is some evidence for replicated linkages for bipolar disorder on chromosome 18 (Durner and Abreu, 1997; Haghighi et al., 1997; Margaritte-Jeannin et al., 1997; McMahon et al., 1997; Stine et al., 1995; Yoshikawa et al., 1997) and possibly 21(Detera-Wadleigh et al., 1997; Gurling et al., 1995; Straub et al., 1994;) and replicated linkages for schizophrenia on chromosome 6p (Brzustowicz et al., 1997; Moises et al., 1995; Schwab et al., 1995: S: Wright et al., 1998)., and also 8p (Blouin et al., 1998; Pulver et al., 1995) and 10p (Faraone et al., 1998; Schwab et al., 1998; Straub et al., 1998).

1.2 COMORBIDITY: POTENTIAL PROBLEMS WITH FAMILY STUDIES

Comorbidity refers to the co-occurrence of different diseases in the same individual (Blashfield, 1990). In psychiatry, there are alternative definitions of comorbidity which range from dual diagnoses to an emphasis on the increased likelihood of higher prevalence of a discrete disorder in the presence of another disorder in the same individual (Marshall, 1996). Population studies have found that 40-60% of respondents with a lifetime history of at least one disorder also have one or more other diagnoses (Boyd et al., 1984; Kessler et al., 1994; Robins et al., 1991). Comorbidity produces substantial problems in diagnosis, treatment, prognosis and in research methodology. For example, in a patient with two concurrent diagnoses, it may be unclear which disorder should be designated as the primary diagnosis and the other as the secondary diagnosis. Furthermore, it may be unclear if primary means etiologically responsible, temporally earlier, or it if is the diagnosis dominating the presentation. If the two disorders commonly co-occur, it raises questions about whether these disorders should even be considered separate conditions (Goisman et al., 1995a; Kash and Klein, 1996).

In the epidemiological analysis of data from family studies, there is an emphasis on the effect of various factors, such as comorbidity, on the risk of the disorder developing in the relatives. There are various methods available for controlling for possible confounding effects of extraneous factors while simultaneously investigating the risk factor of interest: (1) in the design of the study; matching and stratified sampling; (2) in the analysis through post-

stratification and regression and (3) through data restriction. Each of these methods will be explained and discussed in turn.

1.2.1 Design: Matching and Stratified Sampling

Matching and stratified sampling are two methods that can be used in the control of confounding factors. The use of matching or stratified sampling requires that one identify the variables to control in the selection process, before the analysis phase of the study. Matching is a selection process in which control subjects are selected for each individual of interest according to some comparable characteristics, which may play the role of a confounder. A confounder is a variable which can cause (or prevent) the outcome of interest, is not an intermediate variable and is not associated with the factor under investigation (Greenland and Rothman, 1998). As an example, in Weissman's et al. (1982) case-control study involving four proband groups, all probands were initially grouped matched by sex and as much as possible by age. Matching should be used cautiously as to avoid overmatching. Overmatching may occur if one matches on a factor that is associated with the disease but not exposure. Thus, variables selected for matching should have the strongest relationship to the study disorder and be least correlated amongst themselves (Kahn and Sempos, 1989; Schlesselman, 1982).

There are several advantages and disadvantages to matching. One of the advantages is that the process of matching is conceptually easy to comprehend and communicate. Secondly, it is assured that cases and controls

will be comparable with respect to each of the variables used for matching. Thirdly, matching eliminates the need to assume a specific functional relationship between the matching variable and the disease as would be needed to perform a multivariate analysis such as regression. Lastly, a matched design may be the only feasible way of investigating a specific hypothesis when the sample of cases is small. Disadvantages include the increased time and cost required to form matches, the loss of information on unmatched individuals and the loss of the opportunity to fully investigate interactions between other study factors and the matching variables (Jenick, 1995; Schlesselman, 1982).

Another method that identifies confounding variables before the analysis stage is stratified random sampling. Briefly, stratified sampling involves dividing the sampling frame into different strata such as age, sex or ethnic group, and then drawing simple random samples within each stratum. Controls are usually sampled so that every subgroup has the same ratio of cases and controls. Although the actual cases and controls may vary across the strata, the case to control ratio is typically held constant (Zahner et al., 1995; Schlesselman, 1982).

1.2.2 Analysis: Post-stratification

In the analysis phase of the study, post-stratification and regression are additional procedures commonly used to control confounding. Studies may be post-stratified according to disease gradient (stages of cancer, sites of cancer,

etc.), comorbidity, degree of exposure, etc. Once data are obtained in the study, they are catergorized using an ordinal or nominal scale and each stratum is then analyzed seperately. For example, lung cancer is known to be associated with smoking. To examine the association between air pollution and lung cancer, smoking would need to be controlled and so the population would be divided into strata according to smoking status. The association between air pollution and lung cancer would then be evaluated separately within each stratum (Hillis and Woolson, 1995).

An example in the family study setting is Horwath et al. (1995) who investigated the familial cotransmission between social phobia and panic disorder. The strength of the association between panic disorder and social phobia in the relatives was measured by the odds ratios calculated from 2 x 2 tables stratified by proband groups. The proband groups included panic disorder without depression, panic disorder with depression, early-onset depression and never mentally ill.

Once the strata have been analyzed individually, methods such as the Mantel-Haenszel procedure can be used to combine the odds ratios for the separate strata into an overall summary estimate of the odds ratio relating proband characteristics to the risk of developing disease in the relatives. It is also important to look at a related test of association. The Mantel-Haenzel chi-square test examines whether, all strata taken into consideration, exposure is related to disease (Kahn and Sempos, 1989).

There are some limitations to post-stratification. One, there is a loss of information resulting from subgroups in which only cases or controls occur. Second, the number of variables on which one can simultaneously stratify and the fineness of the classification are restricted by the number of cases and controls. However, post-stratification provides great flexibility as the variables on which stratification is based can be changed at any time in the analysis (Schlesselman, 1982).

1.2.3 Regression

Another approach to control for confounding and hence, comorbidity, is the use of a regression model. For a dichotomous outcome, the logistic regression model allows for simultaneous consideration of risk factors and possible confounders in family members when testing for familial aggregation. It evaluates whether there is evidence for familial aggregation even after the risk factors and confounders have been considered and adjusted for. The outcome variable is dichotomous but the independent variables can either be dichotomous, continuous or categorical (Hosmer and Lemeshow, 1988). As an example, Weissman et al. (1982) compared the relative frequency of psychiatric illness in first-degree relatives in three proband groups. Included in their logistic regression model, in addition to proband group status, were the following independent variables: sex of the relative, interview status, and categorical age (Hosmer and Lemeshow, 1989).

In logistic regression analysis, a logistic transformation of the dependent variable is made, which yields the logit or log odds. The measure of association between levels of the independent variables relative to the response variable is the odds ratio. As part of model construction, the significance of adding new terms to the model can be measured with the likelihood ratio test. At each step of the model building process, a log likelihood statistic is calculated. The change in log likelihood from one model to the next is monitored for any large statistically significant changes as variables are added.

The associated likelihood ratio statistic has approximately a chi-square distribution under the null hypothesis that there is no effect from the additional variables (Hosmer and Lemeshow, 1989; Khoury and Beaty, 1994).

1.2.4 Restriction

Data restriction is another means by which confounding factors may be eliminated or controlled for. In a restriction process, subjects having some potentially confounding characteristics are excluded from the study. Restriction makes subject selection more complex, sample sizes smaller, and decreases generalizability. However, such a process is frequently used in family studies (Fyer et al., 1990; Fyer et al., 1995; Maier et al., 1993; Reich and Yates, 1988). As an example, Horwath et al. (1995) excluded probands with comorbid social phobia from their analysis to eliminate the possibility that the higher rate of social phobia in relatives of probands with only panic disorder is due to the presence of social phobia in the probands.

CHAPTER 2

DIAGNOSIS AND EPIDEMIOLOGY OF AGORAPHOBIA

2.1 INTRODUCTION AND REVIEW OF THE LITERATURE

Anxiety disorders are a group of psychological problems whose key features include excessive fear and anxiety. These disorders are among the most prevalent of psychological problems in the general population and constitute a major group of psychiatric disorders (Antony & Swinson, 1996). Lifetime prevalence rates for experiencing any anxiety disorder had been reported to be anywhere from 10.4 % to 24.9 % (Bland et al., 1988; Bourdon et al., 1988; Kessler et al., 1994). Only alcohol disorders and major depression have a comparable prevalence with lifetime rates as high as 23.8% for alcoholic disorders in men and 12.6% for depression (Helzer et al., 1991; Joyce et al., 1990). According to the current edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM- IV) (American Psychiatric Association, 1994) the anxiety disorders include the following: social phobia, specific phobia, obsessive-compulsive disorder, generalized anxiety disorder, post-traumatic stress disorder, panic disorder with and without agoraphobia, and agoraphobia without a history of panic disorder.

2.1.1 Agoraphobia

Agoraphobia is categorized under the umbrella of phobic disorders along with simple and social phobia. In the DSM-III, (American Psychiatric Association,

1980) version of the DSM upon which the present study is based, phobic disorders are characterized by:

> "persistent avoidance behaviour secondary to
> irrational fears of a specific object, activity or situation ...
> the fear is recognized by the patient as irrational ,
> unreasonable and unwarranted by the actual
> dangerousness of the object , activity or situation..."

Phobia comes from the Greek word "phobos" meaning panic or terror and "agora", meaning a place of assembly or market-place. The term "agoraphobia" was first used by Westphal (1871) to describe complete avoidance of walking through certain streets or squares or extreme dread of doing so (Dick et al., 1994; Foa et al., 1984; Fyer & Klein, 1995; Tearnan et al., 1984). This disorder was also noticed a year earlier by Benedikt (1870) who thought the central feature was dizziness rather than anxiety and had suggested the name Platzschwindel, which did not endure (Mathews et al., 1981). From the definition elaborated by Westphal, this disorder began to be conceptualized as a type of specific phobia related to space and hence, as a counterpart to claustrophobia, the fear of enclosed spaces (Foa et al., 1984). Agoraphobia was introduced into the current classification by Marks (1970a) who distinguished it from social and specific phobia. The definition provided in the fourth edition of the DSM (1994) is:

> " The essential feature of Agoraphobia is anxiety about being in places or situations from which escape might be difficult or in which help may not be available in the event of having a Panic Attack or panic like symptoms. The anxiety typically leads to a pervasive avoidance of a variety of situations that may include being alone outside the home or being home alone; being in a crowd of people; travelling in a automobile, bus, or airplane; or being on a bridge or in an elevator."

Some other clinical symptoms observed in several studies include the fear of losing control, embarrassment, dying, fainting and the threat of bladder or bowel incontinence (Chambless , 1982; Tearnan et al., 1984).

2.1.2 Epidemiology of Agoraphobia

Agoraphobia has been reported to begin usually in young adults between the ages of 18 and 35 with a mean age in the mid to late twenties (Tearnan et al., 1984). According to Marks and Gelder (1966), the mean age of onset for agoraphobia is 23.9 years. Two peaks of onset were noted, one at age 20 and one at age 30 which corresponds to the onset of anxiety disorders. Although Mendel and Klein (1969) found a similar bimodal distribution, Thyer et al. (1985) found a unimodal pattern with a mean of 27.5 years. Likewise Sheehan et al. (1981) found a uniform distribution age of onset peaking in the mid-twenties and Ost (1987) reported similar onset with a mean of about 28 years.

Considerable variation has been found in prevalence rates of agoraphobia due to the differences in study population, instruments, and the definition of the disorder. Even after restricting to prevalence rates of agoraphobia from community studies using DSM- III criteria, variations still exist. In the Zurich survey in which 456 people aged 22-23 years were interviewed, the one year prevalence of agoraphobia with or without panic disorder was found to be 1.8 % (Angst & Dobler-Mikola, 1985). From the Epidemiologic Catchment Area Project, 6 month prevalence rates ranged from 2.7 % in St.Louis, to 5.8 % in Baltimore (Weissman, 1986). In Edmonton, the lifetime rate was reported to be 2.9 % and the 6 month rate was 1.9 % (Bland et al., 1988). In urban Taiwan, lifetime rates of agoraphobia were found to be a low 1.1 %, while in Puerto Rico a much higher rate of 6.9 % was reported (Canino et al., 1987; Hwu et al., 1989).

2.1.3 Classification of Agoraphobia & Panic Disorder

The classification of agoraphobia has been a subject of controversy from the time of its appearance (Horwath & Weissman, 1995; Noyes & Hoehn-Saric, 1998). According to the American view, agoraphobia is seen as secondary to repeated unexpected panic attacks and it is not a separate disorder but a more severe variant of panic disorder (Klein, 1981; Noyes & Hoehn-Saric, 1998; Perugi et al., 1998). Clinical and family studies have shown that patients with agoraphobia have an earlier onset, less frequent remissions and more severe symptoms compared to patients with panic disorder (Keller et al., 1994; Noyes et al., 1986; Noyes et al., 1987; Schneir et al, 1991). Furthermore, when

agoraphobia is present, there is a higher likelihood of one or more comorbid diagnoses (Marshall, 1996; Starcevic et al., 1992).

European investigators have questioned the temporal sequence and the causal role of panic attacks in the development of agoraphobia. According to the European view, panic attacks are not an essential feature of agoraphobia. Agoraphobia is a syndrome of many fears which may not include panic attacks (Marks, 1987). In a paper by Thompson et al. (1989) a total of 416 subjects were assigned one or more of the diagnoses of depression, panic or agoraphobia. Results showed that 83% showed major depression, 82% of these occurred in isolation and, specifically in the cases of agoraphobia, 60% occurred with no depression or panic. In summary, there were no cases of panic disorder and agoraphobia together when depression was not present and hence, it appears that panic disorder and agoraphobia are not associated unless the person has depression as well. In further defense of the European view, many population-based surveys using DSM-III criteria, have found that a substantial proportion of subjects with agoraphobia report no history of panic attacks. The percentage reported range from 29 to as high as 85 as compared to clinical samples where only 0% to 31% of patients with agoraphobia report no history of panic attacks (Angst and Dobbler-Mikola, 1985; Breier et al., 1986; Faravelli et al., 1989; Garvey and Tuason, 1984; Joyce et al., 1989; Kleiner & Marshall, 1987; Pollard et al., 1989; Torgersen, 1986; Thompson et al., 1989).

One explanation suggested for the discrepancy between the prevalence rates is that community studies may use structured interviews which are administered by less clinically experienced interviewers, thereby overestimating the prevalence of agoraphobia without a history of panic disorder in these samples (Goisman et al., 1995b; Horwath and Weissman, 1995). Horwath et al., (1993) in an attempt to resolve the clinical–community discrepancy reanalysed the Epidemiologic Catchment Area results. In this study, based on DSM-III criteria, 22 subjects were initially diagnosed with agoraphobia without a history of panic disorder. After reappraisal, only a single case of agoraphobia without panic was actually found. Furthermore, 87% of the cases had simple or social phobia rather than agoraphobia or had no DSM-III phobia at all. In fact, the reappraisal identified six more cases of panic disorder that had been missed initially. The authors concluded that epidemiologic studies such as the ECA may possibly overestimate the prevalence of agoraphobia without a history of panic disorder, in large part by including those subjects who should have been diagnosed with other phobias (Horwath et al., 1993).

Numerous changes have occurred in the grouping of agoraphobia since the DSM-III. The DSM-III classifies agoraphobia and panic disorder as two separate entities: panic disorder and agoraphobia with or without panic attacks (American Psychiatric Association, 1980). In 1987, the DSM-III-R reclassified agoraphobia as mainly a condition resulting from panic disorder. Panic disorder could present itself with or without agoraphobia (American Psychological Association, 1987). In the present DSM-IV, both the American and European views are reflected. Agoraphobia and panic disorder are treated

as two conditions that may at times co-occur. The DSM-IV lists three categories – panic disorder without agoraphobia, panic disorder with agoraphobia, and agoraphobia without a history of panic disorder (American Psychiatric Association, 1994).

2.1.4 Risk Factors in the Development of Agoraphobia

Many questions have been raised concerning factors contributing to the development of agoraphobia. The lifetime rates of agoraphobia have been found to be significantly higher for women in all community studies (Angst and Dobler-Mikola, 1985; Bland et al., 1988; Canino et al., 1987; Hwu et al., 1989). For example, in the ECA study, rates were two – fourfold higher in women than men and similarly in the Edmonton study, rates were threefold higher for women (Bland et al., 1988; Weissman, 1988). Several studies have shown no differences in socioeconomic standards between those with agoraphobia and controls, while in the ECA data, the lifetime prevalence of agoraphobia was higher among African–Americans than among whites or Hispanics (Horwath and Weissman, 1995; Solyom et al., 1974; Tearnan et al., 1984).

Other possible etiological factors proposed include poor parental relationships. Some studies have found families of those with agoraphobia compared to families of those with other disorders, to have had a more unstable childhood, to be more raised in overprotective families or lack maternal overprotection and have suffered parental loss or separation (Burns and Thorpe, 1977;

Goldstein and Chambless, 1978; Liebowitz and Klein, 1979; Snaith, 1968). However, other studies have found no differences in the childhood experiences between those with agoraphobia and those without. In fact, several investigators have found that subjects with agoraphobia tend to come from stable homes (Buglass et al., 1977; Marks et al., 1965; Snaith, 1968; Solyom et al., 1974).

The onset of agoraphobia seems to occur following a period of stress, or a major change in the person's life such as marriage, pregnancy, leaving home or a serious illness (Foa et al., 1984; Marks, 1970b; Tearnan et al., 1984). Goisman et al. (1995b) reported 30% of those with agoraphobia could identify a definite major life stressor and Sheehan et al. (1981) found 91% of a large sample of subjects with agoraphobia could identify precipitating causes. Similar findings have been reported by others (Bowen and Kohout, 1979; Solyom et al., 1974; Weekes, 1978).

Biological and physiological factors may also play a part in the development of agoraphobia. Early studies have centered on the abnormal arousal of those with agoraphobia. These researchers postulated that in normal individuals excess arousal is controlled by a physiological habituation mechanism, but in some individuals there is no dampening of arousal (Levin and Liebowitz, 1988). Another study showed that those with agoraphobia displayed spontaneous fluctuations in skin resistance and habituated more slowly to auditory stimuli than normal controls (Lader and Wing, 1966). More recently, cardiovascular disorders have been linked to agoraphobia and panic. Several

studies have reported a higher incidence of mitral valve prolapse in those with agoraphobia and panic when compared to the general population (Kantor et al., 1980; Liberthson et al., 1986). Recently, researchers (Jacob et al., 1996) have contended that vestibular dysfunction may contribute to the phenomenology of panic disorder and in particular to the development of agoraphobia in panic patients.

There is other evidence pointing to the role of biochemical factors in the development of agoraphobia. Findings from platelet, sodium lactate, yohimbine studies have led to speculation regarding a common biochemical basis for panic attacks (Ackerman and Sacher, 1974; Cameron et al., 1984; Kelly et al., 1971; Mathew et al., 1980). The contribution of genetic factors in the development of agoraphobia is presently limited. Most studies to date have shown support for genetic influences either by noting a higher prevalence of the disorder in first-degree relatives or by observing a higher correlation of anxiety symptoms between monozygotic twins compared to dizygotic twins. A detailed review of the existing literature is discussed next.

2.1.5 Family Studies of Agoraphobia

Although there is a general belief that agoraphobia runs in families, there is surprisingly little empirical evidence for this claim. Only a few twin studies have been published. Carey & Gottesman (1981) reported data on 21 twin pairs with mixed phobic symptoms and found the risk of phobic symptoms in the monozygotic co-twin to be double that of the dizygotic co-twin. The

concordance rate was 88% for monozygotic twin and 38% for dizygotic twins. Torgersen (1983) reported on 32 monozygotic and 53 dizygotic adult same – sexed twins where the index twin had agoraphobia with or without panic disorder. The concordance rate was 36% in monozygotic twins compared with 13% in dizygotic twins.

The existing family study literature reveals a trend towards familial aggregation of agoraphobia. Noyes et al. (1978) investigated the morbidity risk of anxiety neurosis and reported that the morbidity risk for anxiety neurosis among first-degree relatives to be 18% compared to 3% among control relatives, or a relative risk ratio of 6.0. The following family studies all based the diagnosis of agoraphobia on DSM–III criteria with all probands selected from hospital or clinic populations. Harris et al. (1983) compared rates of illness among the relatives of probands with agoraphobia, panic disorder only and controls. They found the morbidity risk for all anxiety disorders in first – degree relatives of patients with agoraphobia to be 32% vs. 15% for controls and the risk for agoraphobia was 8.6% vs. 4.2%. The relative risk for first-degree relatives of patients with agoraphobia was calculated to be 2.04. Moran and Andrews (1985) gathered data on the risk of agoraphobia in parents and siblings of 60 of probands with agoraphobia and found a morbidity risk of 12.5 % which was found to be significantly greater than the population incidence. Noyes et al. (1986) looked at 40 patients with agoraphobia, 40 with panic disorder, and 20 controls. They found the morbidity risk for agoraphobia to be 11.6 % ($p<..025$) in first- degree relatives of probands with agoraphobia compared to 4.2 % in relatives of controls giving a relative risk of 2.76. An

Italian study found a specific familial concentration of agoraphobia, a disorder which was exclusively clustered in first-degree relatives of those patients with agoraphobia. The morbidity risk was reported to be 1.46% for the general population, 10.1 % for the relatives of patients with agoraphobia giving a relative risk of 6.9 (Gruppo Italiano Disturbi d'Ansia, 1989).

In more recent studies, the diagnosis for agoraphobia is based on the DSM-III-R, where agoraphobia is seen as mainly a condition resulting from panic disorder. Hence, interpretation and comparison of results becomes more difficult. Maier et al. (1993) investigated the familial lifetime risks of 3 disorders: agoraphobia, and panic disorder with or without agoraphobia. These investigators found that agoraphobia was most common among the first-degree relatives of probands with agoraphobia (4.5 %) and was also increased by two-fold in families of probands with panic disorder without agoraphobia (2.6%) compared to healthy controls (1.2%). The relative risk for the first-degree relatives of probands with agoraphobia was 3.75. Fyer et al. (1995) included only probands who developed panic disorder with agoraphobia and found a relative risk of 3.0 ($p<.05$) among first-degree relatives of probands with agoraphobia compared to not ill controls.

Although there are some methodological differences among the studies, there is evidence of familiality with agoraphobia with consistency across the studies beginning to appear. This present study contributes to the already existing body of knowledge by exploring familiality among a large community sample with a standardized interview as opposed to using clinical samples as all other

previous studies have done. In addition, data generated from this study also include the diagnosis of a wide range of disorders which appeared to be lacking with previous similar studies. However, it is still not clear whether the aggregation results from genetic factors and/or shared environmental factors. To date, only one study has investigated this question looking specifically at agoraphobia. Kendler et al. (1992a), directly interviewed 2163 female twins and found that the familial aggregation of agoraphobia appeared to result from genetic and not from environmental factors.

CHAPTER 3

STUDY DESIGN

3.1 AIMS & HYPOTHESIS

The aim of this study was to determine if a lifetime history of agoraphobia is familial after adjusting for comorbid mental disorders and other possible confounding variables. The study hypothesis was that the odds for agoraphobia in relatives of agoraphobic probands will be increased compared with the odds among relatives of normal control probands.

3.2 METHODS

3.2.1 Data Collection

A prevalence study of community residents of Edmonton was conducted between December 1984 and February 1989. Subjects were selected using a two-stage design. First, households were systematically sampled from a computerized list of residential addresses supplied by the City of Edmonton. Only private dwellings were included in the sampling frame. Next, one occupant per household was chosen using a respondent selection grid. To be eligible for the survey, respondents had to be 18 years of age or older and a usual occupant at the address. Proxy interviews and respondent substitutions were not allowed (Orn et al., 1988).

Each interviewer was given a list of addresses. They made a minimum of four calls at various times and on different days before the addresses could be designated no contact. Experience from previous use of the DIS in Edmonton has shown the time required for an interview varies from a minimum of 25 to a maximum of 210 minutes with a median interview time of about 50 minutes (Orn et al., 1988).

Subjects signed a consent form permitting the researchers to contact them as part of a re-interview study. Re-interviews were conducted between April 1987 and April 1991. The methods were identical to the methods previously described. Re-interviews were conducted in a manner identical to the initial interviews. Subjects for the re-interview study were selected using systematic sampling, attempting to reinterview subjects in approximately the order in which they had been interviewed in the prevalence study. However, in order to ensure that a sufficient number of DIS-DSM III lifetime cases were present in the re-interview sample, subjects who had a lifetime history of major depression in the prevalence study were over-sampled.

The original interviewer did not reinterview respondents, even if that person was still working on the project. No special instructions were given to the respondent regarding the purpose of the interview. The interviewer was not aware of the case status of the respondent designated from the prevalence study (Newman and Bland, 1998).

Re-interview subjects were asked to provide consent to interview first-degree relatives for a family study. First-degree relative interviews were conducted between May 1987 and July 1991. The methods were identical to the methods previously described. First-degree relative interviews were conducted in a manner identical to the reinterviews.

3.2.2 Interview Instrument: Diagnostic Interview Schedule

For the present study, the main instrument used was the NIMH Diagnostic Interview Schedule (DIS), Version III (Robins et al., 1981b), a psychiatric questionnaire developed at the request of the Division of Biometry and Epidemiology of the NIMH for the Epidemiological Catchment Area (ECA) projects (Robins et al., 1981a). The DIS is a highly structured interview designed to make diagnosis by the following three systems: (1) DSM-III, published by the American Psychiatric Association in 1980; (2) Feigner criteria, from the Washington University in St.Louis in 1972; (3) the Research Diagnostic Criteria published by Spitzer et al., in 1978 (Robins et al., 1985).

Trained lay interviewers using version III of the DIS collected the data. The project manager who had been previously instructed in the use of the DIS (described below) at Washington University, St.Louis, trained all interviewers. Training sessions lasted approximately 42 hours over a seven-day period (Orn et al., 1988).

The DIS can be administered by trained lay interviewers thus limiting costs and offers the opportunity to computer generate diagnoses, as was done in this study, thereby ensuring consistent data interpretation across a large number of interviews. Reports on the validity and reliability of the DIS include comparisons of lay interviewers and psychiatrists using the DIS, investigations comparing the DIS to unstructured clinical interviews and specific studies involving various psychiatric disorders such as substance abuse, depression and schizophrenia. Generally, results showed moderate to good reliability based on kappa values (Anthony et al., 1985; Aktan et al., 1997; 1983; Goethe et al., 1995; Helzer et al., 1985; Regier et al., 1984; Robins et al., 1981a; Ross et al., 1995).

With regard to agoraphobia, Helzer and associates (1985) compared DIS diagnosis made by lay interviewers and physicians in a clinical sample and found sensitivity for agoraphobia to be 56% and specificity to be 95%. In a German study comparing psychiatric diagnosis using ICD-8 criteria with DSM/DSM III diagnoses, Wittchen et al. (1985) reported excellent sensitivity (100%) and specificity (90%) for phobia diagnoses in general populations and former psychiatric patients. Some studies have suggested that the DIS may lack generalizability. Matthey et al. (1997) reports the use of the DIS in determining rates of major depression in the Vietnamese and Arabic community in Australia questionable. North et al. (1997) found the DIS not suited for the homeless population as this method overestimates depression, underestimates antisocial personality disorder when compared to clinical assessment.

The DIS assesses the presence, duration, and severity of individual symptoms. First, whether the symptom ever occurred is determined. Next, its severity is assessed by several criteria; one, the degree to which it limits activity; two, whether a physician or other professional has been consulted; and finally, whether medication has been taken to treat it. Then the DIS asks whether every recurrence was explained by medical illness, or alcohol and other drug intake. Symptoms that meet the severity criteria and are not explained by medical illness or drug intake are grouped into patterns as designated by the DSM-III, Feighner, and the Research Diagnostic criteria. See Appendix 1 for the text of the DIS for agoraphobia (Boyd et al., 1984; Regier et al., 1984).

The phobia section of the DIS was designed to elicit diagnoses based on the DSM-III definition of phobic disorder, which is a "persistent and irrational fear of a specific object, activity, or situation. The fear is recognized by the individual as excessive or unreasonable in proportion to the actual dangerousness of the object, activity, or situation" (American Psychiatric Association, 1980). The DIS questions on phobias in general involve fifteen situations or stimuli. To meet a diagnosis for agoraphobia, at least one positive symptom from the following must be met:

A. Tunnels or bridges
B. Being in a crowd
C. Being on any kind of public transportation like airplanes, buses, elevators.
D. Going out of the house alone
E. Being alone

If a fear of a situation is reported, a series of questions is asked to ascertain whether the fear meets the criteria for a phobic level response. If the respondent told a doctor or other health professionals about the fear, or took medication for it more than once, or said that it interfered with his/her life, a phobic response is recorded. If the respondent answers no to all the probe questions and maintains that the fear did not interfere with "my life a lot because I avoid it", then the interviewer would then ask "Does having to avoid the situation interfere with your life or activities a lot? ". If the avoidance behavior is established, it is recorded at the phobic level. A phobic level response to one or more of the situations listed above results in a diagnosis of agoraphobia. In the present study, diagnoses were made by computer using DSM III criteria without hierarchical exclusions for other diagnosis (Robins et al., 1981b).

3.2.3 Data Entry

All interview schedules used in the survey were precoded except the small number of open-ended questions, which were recorded verbatim. Multiple editing was performed on all completed interviews. Information was transferred from the interview schedules into the computer using double entry followed by multiple edit cards (Orn et al., 1988).

3.2.4 Statistical Analysis

All of the statistical analyses were performed using the statistical analysis software SPSS, version 6.0 (SPSS Reference Guide, 1993). The preliminary analysis involved using the odds ratio as a measure of association. As described earlier, the odds ratio is defined as the ratio of the odds of disease in the exposed persons to the odds of disease in the non-exposed persons (Schlesselman, 1982). In the present study, the odds of a relative having agoraphobia given that the proband has agoraphobia is compared with the odds of the relative having agoraphobia given that the proband does not have agoraphobia. If the value of the odds ratio is significantly greater than 1, it can be concluded that familial aggregation is greater than that due to chance alone. As shown in **Figure 2,** a 2 x 2 contingency table shows the agoraphobia status of first-degree relatives cross-classified by the agoraphobia status of the probands.

Stratified analysis of the 2x2 table was performed to control for possible confounding variables. The Mantel-Haenszel estimate of the odds ratio was computed and the Miettinen's test-based procedure was used to compute 95% confidence intervals (Kahn and Sempos, 1989). Exact methods were used when the number in any cell was less than five. The primary risk variable of interest was the lifetime history of agoraphobia in the probands with or without panic disorder. Comorbidity studies have frequently found an overlap between agoraphobia and other anxiety disorders and a high comorbidity rate with depression, dysthymia and obsessive-compulsive disorder (Dick et al., 1994; Goisman et al., 1995a; Lepine and Pelissolo, 1996; Merikangas and

Angst, 1995; Magge et al., 1996; Schneier et al., 1992). Hence, the data were stratified by the following variables to control for possible confounding: *age of the relative, gender of relative, relationship of the relative to the proband, lifetime history of depression, generalized anxiety disorder, social phobia, simple phobia, obsessive–compulsive disorder*, and *dysthymia* in the relative. In addition, since the diagnosis for agoraphobia included those with or without panic disorder, the data was also stratified by the variable *panic disorder* in the relative.

It is also possible to control for the comorbid disorders in the proband in addition to or in place of the comorbid disorders in the relative. As shown in **Figure 3**, the question of primary interest is the relationship between agoraphobia in the proband and agoraphobia in the relative. The bold arrows illustrate where comorbid disorder relationships are already established and known. For example, simple phobia in the proband is highly comorbid with with agoraphobia in the proband or if a proband has depression, it is likely that the relative will also have depression. Therefore, in order to adjust for these comorbidities, either disorders of the proband and/or of the relative could be included in the model. However, as more variables are entered in the model, the greater the estimated errors become, and more numerically unstable the model becomes (Hosmer and Lemeshow, 1989) Hence, in order to seek the most parsimonious model that still explains the data, we choose to only include the comorbid disorders of the relatives.

Assessment of the homogeneity across the strata was based on an analysis using logistic regression. The p-value for each interaction term was analysed and p-values < 0.05 indicates no homogeneity across strata.

An unconditional multiple logistic regression was performed to further examine the variable *agoraphobia in probands* as a potential risk factor for agoraphobia in the relatives, while controlling for confounding variables. The general logistic model is as follows:

$$\ln (P/[1-P]) = B_o + B_1X_1 + B_2X_2 + \ldots . B_jX_j + e$$

Where P is the probability of a dichotomous outcome; P/[1-P] is the odds of the outcome. In this case the outcome is agoraphobia in the relative with or without panic, B_j is the coefficient of the j^{th} independent variable, and e is the independent error. The natural logarithms of independent variable coefficients, B_j ,are the odds ratios for these variables (Hosmer and Lemeshow, 1989).

The independent variables used in the model building process are presented below. All are dichotomous variables, except for the trichotomous variables *relationship* and *age*. The *age* category was broken down into meaningful age groups that would still ensure a reasonable number of subjects.

Agoraphobia in the proband
Gender of relative
Disorders in relative:
Simple phobia
Social phobia
Dysthymia
Obsessive compulsive disorder
Depression
Generalized anxiety disorder
Panic disorder
Age in relative:
18-30
31-49
50 +
Relationship to proband:
Parent
Sibling
Offspring

First, a preliminary analysis was conducted with each variable as a single main effect along with *agoraphobia in the proband.* This preliminary statistical assessment determined which variables would be included in the model building for multivariate analysis. An inclusion criteria based on the likelihood ratio (LR) test was used. For these preliminary regressions, a LR criterion of $p < 0.05$ was used.

Models were then built using a stepwise approach. Starting with 3 variables, one of which was always *agoraphobia in the proband,* the independent variables were entered or removed from the model on the basis of the significance of the LR test. A likelihood ratio criterion of $p < 0.05$ was used. This procedure was continued until a final model was reached.

The last step in the model building process was determining whether or not there was interaction in the data. We began with the main effects model and sequentially selected each of the variables from the final model and in turn formed an interacting with *agoraphobia in the proband* variable. An example of an interaction term would be *agoraphobia in the proband* x *gender of the relative*. The statistical significance of each interaction term was examined and a Wald's criterion level of $p < 0.05$ was used.

To control for potential confounding effects of depression with agoraphobia and panic disorder with agoraphobia, we conducted two separate analyses in which first-degree relatives with a history of depression or a history of panic disorder were excluded from the data set. This is an application of the method of restriction to control for confounding as studies have shown the two disorders depression and panic are highly comorbid with agoraphobia (Angst et al., 1985; Boyd et al., 1984; Kendler et al 1993; Sanderson et al., 1990; Schapira et al., 1970; Thompson et al., 1989). The elimination of first-degree relative with panic disorder adjusts for panic disorder that is included in the diagnosis of agoraphobia. Due to the comorbidity between depression, panic and agoraphobia these analyses almost certain over-adjust for confounding and hence produce conservative estimates of the familiality of agoraphobia. Nevertheless, these analyses are included for the sake of completeness. Due to small sample size, we analyzed the resulting data using the Mantel-Haenszel and Miettinen methods, as described above, but not logistic regression.

CHAPTER 4

RESULTS

4.1 THE SAMPLES

Of the 6,003 addresses randomly selected from the computerized residential listing for the prevalence sample, 5499 were eligible for the survey and 3956 (72%) were interviewed. **Table 3.1** shows the response rate of 71.9% for the prevalence study, defined as the number of interviews divided by the number of eligible addresses (Newman and Bland, 1998) The demographic composition and (unweighted) lifetime prevalence rates of the prevalence sample are shown in **Table 3.2.** Females are over represented, and the most common disorder was depression followed by simple phobia; the least common disorder of those considered was social phobia. Of the 3956 subjects in the prevalence sample, no attempt was made to contact 1156 (29%) of them, 264 (7%) had moved out of the province, and 54 (1.4%) had died (Newman and Bland, 1998).

The re-interview sample included 1964 subjects with a response rate of 79 % as shown in **Table 3.1**. From the 1964 subjects, 924 had first-degree relatives in Alberta who could be contacted. These 924 subjects are the designated probands for the family study. **Table 3.3** shows the demographic composition of the probands. Similar to the prevalence sample, females are over represented, and the most common disorder was depression followed by simple phobia; least common was social phobia. From the 924 probands, a total of 2386 first-degree relatives were interviewed for the family study with a response rate of 78.6% as shown in **Table 3.1.** The demographic composition

of the first-degree relatives is shown in **Table 3.4**. There are also proportionately more females than males and similarly, the most common disorders are depression and simple phobia.

4.2 CRUDE ODDS RATIO ANALYSIS

The crude odds ratio for agoraphobia among the first-degree relatives and probands is shown in Figure 2. The crude odds ratio of 2.53 shows that a proband with agoraphobia increases the odds of a relative developing agoraphobia by 2.53. The Mantel-Haenzel chi-square test is statistically significant, (p–value = .009) and the 95% confidence interval is (1.23, 5.21) which excludes 1. Thus there is a statistically significant association between agoraphobia in the relative and agoraphobia in the proband.

4.3 STRATIFIED ANALYSIS

In order to see if other variables account for the apparent effect of the study exposure, post-stratification was employed. **Table 3.5** shows the stratum-specific odds ratio, for each of the variables. It is evident from the table that the odds ratios between strata appear not to be different from each other as there is much overlap between the 95% C.I of each strata. For example, when looking at the *gender of relative* variable, the magnitude of the odds of a relative developing agoraphobia if the proband has agoraphobia is no different between males or females. However, one exception, is the *relationship to proband* variable. As shown in **Table 3.5** the *parent* category odds ratio is

considerably larger than the *sibling* or *offspring* categories. In fact, tests of homogeneity indicate that homogeneity exists between all stratum except for the *relationship* variable. Homogeneity does not exist between the strata of the *relationship* variable and thus the odds ratio for this variable should not be summarized. It appears that there is an increased odds of a relative developing agoraphobia by 16.73 times when the relative is in the *parent* category as compared to those in the *sibling* or *offspring* category which is only 1.39 or 1.55 times respectively. **Table 3.6** shows the Mantel-Haenzel odds ratio for each of the stratifying variables. After stratification, the odds ratios are not very different from the crude analysis. For example, after adjusting for *gender of the relative*, the summary odds ratio is 2.71 compared to the crude odds ratio of 2.53. Therefore, it appears that none of the variables are confounders of the relationship of agoraphobia in a proband to agoraphobia in a relative. Furthermore, the confidence intervals are wide and exclude 1,with the exception of *depression*, *dysthymia* and *age in relative* which therefore appear to be of less significance.

4.4 LOGISTIC REGRESSION

The logistic regression model, using *agoraphobia in the relative* as the outcome variable was developed using a forward stepwise approach. Variables were included in the model building process based on the significance of the likelihood ratio test. The preliminary analysis involved 2 main effects: *agoraphobia in the proband* and one other risk variable. Shown in **Table 3.7** are the likelihood ratio test results and corresponding p-values for each of the

resulting regression analyses. All analyses reached statistical significance with the highest p-value being .0014 for the *relationship to proband* combination.

In the next step, the analysis involved 3 main effects: *agoraphobia in the proband* and two other risk variables. Selection of the next variable was based primarily on the size of the Likelihood Ratio χ^2 test results since 6 of the 8 remaining variables all had p-values of < .0001. As shown in **Table 3.7,** again all analyses reached highly statistical significance when *agoraphobia in proband, simple phobia in the relative* and one other variable were included in the model. Similar to the two variables main effect combinations, *relationship to proband combination* had the highest p-value at .0006. Examination of the odds ratios also reveals similarity between the 2-variable and 3-variable models. Various combinations of all independent variables were tried with increasing model complexity.

The final logistic model is shown in **Table 3.8**. Only the variables *dysthymia in relative and age of relative*, were excluded from the model based on p-values of .078 and .070 respectively. Although the variable *age of the relative* can be deemed to be biologically significant, the variable *relationship to proband* can be considered a proxy for this variable. Spearman's correlation coefficient for *age of relative vs relationship to proband* produces a value of .60, a moderate correlation which is significant at the .01 level. Furthermore, as shown in **Table 3.9,** where we have replaced *relationship to proband* with *age of the relative* variable, the odds ratio for agoraphobia in the proband is 2.27 which is reduced slightly compared to the result in **Table 3.8**, and is still statistically

significant. All other odds ratios for the remaining variables have remained virtually the same from **Table 3.8** to **Table 3.9**.

In the final model, **Table 3.8**, the odds ratio of the risk factor *agoraphobia in the proband* is 2.43 which is not very different from the crude odds ratio of 2.53. In fact, the odds ratio for the risk factor agoraphobia in the proband did not change significantly with each addition of significant variable throughout the model building. The odds ratio ranged from 2.02 to 2.87 which is relatively close to the crude odds ratio of 2.53. Therefore, the variables included in the model can be viewed as predictors rather than confounders of the familial relationship. For example, being a male relative reduces your odds of developing agoraphobia compared to female relatives. In other words, being a female relative increases your odds of developing agoraphobia compared to being of the male gender. The final regression model reveals that the relatives of agoraphobia probands had more than a twofold increased odds of developing agoraphobia as compared with that for relatives of the not ill probands even after adjusting for social phobia, simple phobia, generalized anxiety disorder, depression, gender of relative and relationship to the proband.

As shown in **Table 3.10** even with the inclusion of the variable *panic disorder in the relative,* the odds ratio of the risk factor *agoraphobia in the proband* is 2.18 which is slightly smaller in magnitude to the final model, but still not very different from the crude odds ratio of 2.53. Since panic by definition may be part of the agoraphobia disorder, adjustment for panic will lead to

overadjustment and a reduction in the estimated odds ratio. Therefore, possibly due to the overadjustment of the *panic* variable, the p-value is greater than .05 and the confidence interval includes 1. From examination of Tables 3.8 and 3.9 where the former, panic disorder was excluded and the latter, panic disorder was over-adjusted; it would suffice to say that the true odds ratio for *agoraphobia in the proband* lies somewhere between these two values.

4.5 INTERACTION

After examining each of the interaction terms (*agoraphobia in the proband* X each of the main effect variables from **Table 3.8**), all were found to be not statistically significant and consequently the final model contains only the previously identified main effects.

4.6 RESTRICTION

The data were reexamined after excluding from the data set first-degree relatives with depression to remove the effects of co-morbidity. The restricted sample included 2100 first-degree relatives since 287 first-degree relatives had a lifetime diagnoses of depression. 41(2%) of the first-degree relatives had agoraphobia without depression, compared to the unrestricted sample where 75 (3.1%) of the relatives had agoraphobia with depression. Based on the crude odds ratio, probands with agoraphobia increase the odds of the first-degree relatives of developing agoraphobia by 1.60, thus there appears to be a familial relationship. However, as expected due to possible over-adjustment,

the 95% confidence interval is .484 to 5.265 which includes 1 and the result of the chi-square Mantel-Haenzel is not statistically significant (p= .438).

Additionally, the data was reexamined after excluding from the data set first-degree relatives with panic disorder so as to remove the effects of co-morbidity. The restricted sample included 2328 first-degree relatives. Of those, 58 (2.5%) of the first-degree relatives had a lifetime history of agoraphobia and no history of panic disorder. Additional analysis revealed that 43 (1.80%) of first-degree relatives had a lifetime history of panic disorder and no history of agoraphobia and 17 (.73%) had a history of both agoraphobia and panic disorder. Based on the odds ratio, probands with agoraphobia increase the odds of the first-degree relatives of developing agoraphobia by 1.77, thus again there appears to be a familial relationship. However, the 95% confidence interval is .69 to 4.26 which includes 1 and the result of the chi-square Mantel-Haenzel is not statistically significant (p=.221) due to over adjustment.

CHAPTER 5

CONCLUSION AND DISCUSSION

5.1 COMPARING RISK ESTIMATES

The present study sought to determine if a lifetime history of agoraphobia is familial after adjusting for comorbid mental disorders and other possible confounding variables. We hypothesized that the odds for agoraphobia in relatives of the agoraphobic probands would be increased compared to the odds among relatives of normal control probands. Our findings did indeed support our hypothesis. Our final logistic model revealed that the relatives of the agoraphobia probands had a 2.43 increased odds of developing agoraphobia as compared with that for relatives of the not ill probands. Although methodologies and statistical analyses differ among previous studies, there are some consistencies in the general direction of the published findings and the findings reported herein. The odds ratio of 2.43 is in keeping with other literature as other studies have reported relative risks in the range between 2.04 to 6.90. Odds ratios provide a valid estimate of the relative risk when the disease is rare, as it is in this case (Hennekens, 1987). Our estimate is at the lower end of the published range perhaps because, as previously mentioned, the DIS may overestimate the prevalence of agoraphobia without a history of panic disorder and, furthermore, the DIS may be over-inclusive with regard to DSM-III agoraphobia in general (Goisman et al; 1995b; Horwath and Weissman, 1995; Klein and Klein, 1989). Therefore, our prevalence rates may be overestimated and hence, our risk estimate may be underestimated.

5.2 RESTRICTION

After examination of the data with the exclusion of first-degree relatives with depression, probands with agoraphobia increased the odds of first-degree relative of developing agoraphobia by 1.60 which is a moderate decrease in risk from the initial result of 2.43. However, because of reduced sample size, the results were not statistically significant and thus must be interpreted with some caution.

Similar results were found after the exclusion of first-degree relatives with panic disorder. Probands with agoraphobia increased the odds of a first-degree relative of developing agoraphobia by 1.77, however, the results were not statistically significant due to small sample size.

5.3 LIMITATIONS OF THE PRESENT STUDY

Several limitations affect the interpretation of these data. One important limitation is lack of data on age of onset for agoraphobia. Variable age of onset can hinder any interpretation of simple rates of illness because these will depend on the age of the sample. For example, the rate among those in their early twenties, who have just only entered the period of risk, indicates a greater risk for agoraphobia than the rate among the 60 year olds who have lived through the risk period. To account for this, the age of the first-degree relatives was included in the regression model but was subsequently found to be not statistically significant.

A further limitation may be that the study relied solely upon the retrospective self-reports of subjects to obtain the diagnostic information. Responses may have been subject to errors such as inaccurate recall and/or reporting episodes of disorder. Although not always feasible, the information obtained on each relative should ideally be from multiple informants, clinical records and direct interview combined. An independent and experienced clinician should take into account the sources and quality of data, then apply uniform criteria and finally assign a "best-estimate" diagnosis to the relative (Gershon and Guroff, 1984; Kendler, 1996; Leckman et al., 1982).

5.4 STRENGHTS OF THE PRESENT STUDY

An important feature of this study was the use of a community-based sample which makes this study distinctive compared to all other published family studies examining agoraphobia. This offers two major advantages. First, the sample was not biased by treatment seeking. Hence, the sample comprised of individuals with varying severity of illness. Second, the findings can be generalized to the population of disordered individuals as a whole rather than to just a clinical population.

In summary, despite the methodologic limitations, these data in the context of previous studies strongly suggest that familial factors contribute to the development of agoraphobia.

5.5 FURTHER STUDIES

In the interpretation of our findings it must be remembered that, with a family study, we are unable to discern to what extent the familial nature of agoraphobia is truly heritable. More work is required to determine what the heritable component to agoraphobia. Perhaps, as proposed by Kendler (1990) the aggregation could be due to risk factors which run in families.

Other potentially useful areas of research may include investigating the possibility of the existence of subtypes of agoraphobia and the heritable implications of these findings. Interestingly, Eaton and Keyl (1990) revealed the existence of two subtypes of agoraphobia based on their sociodemographic and psychopathologic risk factors. They found a distinct pattern of risk for one particular form of agoraphobia which they have named 'classic'. This pattern shows an increased risk of onset for those aged 30 to 45 years, for those with lower educational levels, lower occupational status and for whites. From the analysis of prior psychopathology, a history of other phobias was related only to the second subtype, referred to as 'situational', and depression were related only to 'classic'. Future research involving the investigation of the familial aggregation of these two possible subtypes and others, has the potential to contribute toward a more appropriate classification of the disorder.

More generally, other future areas of research could include more large scale twin and adoption studies of children and adults with anxiety disorders in general to learn more about the risk factors, the course and pattern of these diseases.

Figure 1. 2 x 2 TABLE

Case-Control Study

		Cases	Control
Relative	Present	a	b
	Absent	c	d
		m1	m2

Cohort Study

Relative

		Present	Absent	
Proband	Present	a	b	n1
	Absent	c	d	n2

ODDS RATIO = ad/bc

Figure 2. CROSS TABULATION: AGORAPHOBIA

		Relative / Agoraphobia		
		Present	Absent	
Proband / Agoraphobia	Present	9	118	127
	Absent	66	2193	2259
		75	2311	

Total = 2386

ODDS RATIO = (9 x 2193) / (118 x 66) = 2.53

Figure 3. COMORBIDITY RELATIONSHIPS

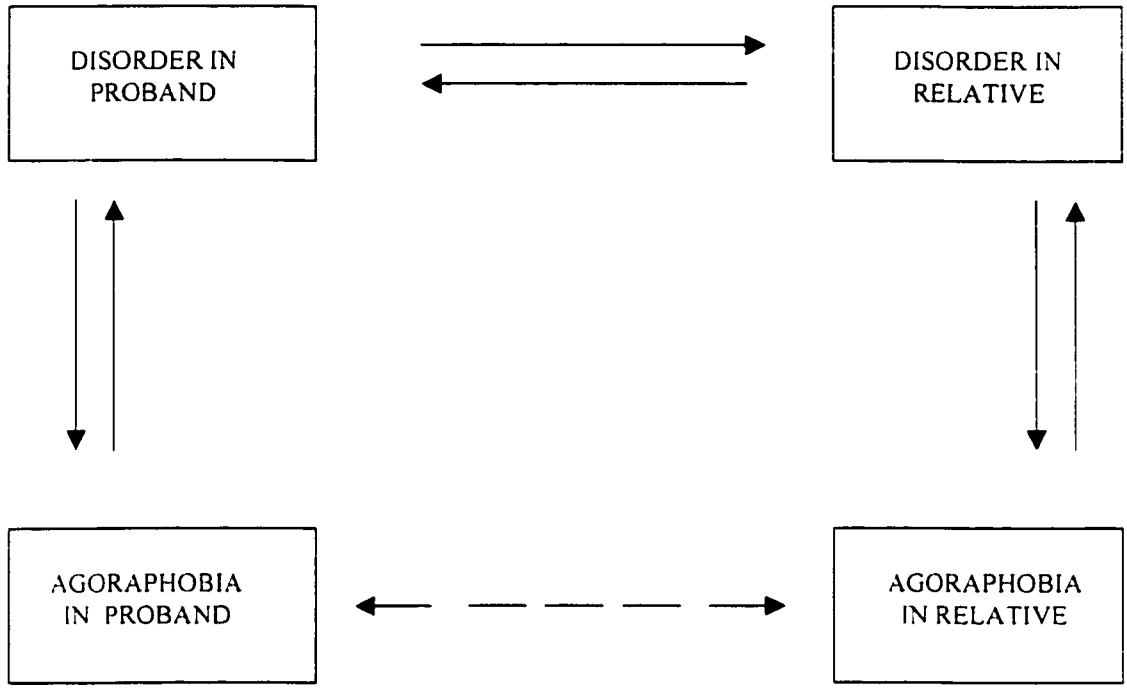

Table 3.1 RESPONSE RATE

PREVALENCE SAMPLE	
Total No. Interviewed	3956 (72%)
Refused	913 (17%)
* Other	630 (12%)
Response Rate	3956/5499 = 71.9 %
REINTERVIEW SAMPLE	
Total No.interviewed	1964 (79 %)
Refused	322 (13%)
* Other	198 (8%)
Response Rate	1964/ 2482 = 79.1%
FIRST-DEGREE RELATIVE SAMPLE	
Total No. interviewed	2386 (71.3%)
Refused	647 (19.3%)
*Other	312 (9.4%)
Response Rate	2386/3344 = 71.3%

* Unable to find someone home, interview not attempted because of language barrier, security problem or other reasons.

Table 3.2 CHARACTERISTICS OF PREVALENCE SAMPLE (N = 3956)

CHARACTERISTICS	N	%
Sex		
male	1488	37.6
female	2468	62.4
Lifetime prevalence (unweighted)		
Agoraphobia	73	1.85
Depression	552	13.95
Obsessive - compulsive	69	1.74
Panic	83	2.1
Simple Phobia	141	3.56
Social Phobia	29	0.73

Table 3.3 CHARACTERISTICS OF PROBAND SAMPLE (N = 924)

CHARACTERISTICS	N	%
Sex		
male	320	34.6
female	604	65.4
Lifetime prevalence (unweighted)		
Agoraphobia	50	5.4
Depression	212	22.9
Obsessive-compulsive	22	2.4
Panic	39	4.2
Simple Phobia	81	8.8
Social Phobia	17	1.9

Table 3.4 CHARACTERISTICS OF FIRST-DEGREE RELATIVES (N = 2386)

CHARACTERISTICS	N	%
Sex		
male	1028	43.1
female	1358	56.9
Lifetime prevalence (unweighted)		
Agoraphobia	74	3.1
Depression	286	12
Obsessive-compulsive	33	1.4
Panic	60	2.5
Simple Phobia	117	4.9
Social Phobia	33	1.4

Table. 3.5 STRATIFIED ODDS RATIO ANALYSIS OF AGORAPHOBIA IN PROBAND COMPARED TO AGORAPHOBIA IN RELATIVE

STRATIFIED VARIABLE		OR	95% CI		P-value X2 MH
Age of relative					
18-30		0.77	.10	5.88	0.8
31-49		2.25	.84	6.06	0.1
50-94		7.31	1.93	27.69	0.001
Gender of relative					
male		2.45	.55	11.27	0.22
female		2.78	1.21	6.37	0.01
Relationship to proband					
Parent		16.73	4.20	66.66	< 001
Sibling		1.39	32	5.97	0.66
Offspring		1.55	.46	5.29	0.47
Disorder in relative:					
Depression	Y	2.36	.87	6.33	0.08
	N	1.6	.48	5.26	0.44
Dysthymia	Y	1.51	.49	4.63	0.47
	N	1.75	.62	4.96	0.29
GAD	Y	2.23	.87	5.73	0.09
	N	1.98	.59	6.58	0.26
OCD	Y	0.38	.32	59.15	0.27
	N	2.88	1.40	5.95	0.003
Simple phobia	Y	1.46	.35	6.10	0.6
	N	2.71	1.13	6.53	0.02
Social phobia	Y	5.54	.66	46.5	0.16
	N	2.43	1.08	5.47	0.03
Panic disorder	Y	4.11	.81	20.78	0.09
	N	1.77	.70	4.50	0.22

Table 3.6 MANTEL-HAENZEL ODDS RATIOS OF AGORAPHOBIA IN PROBAND COMPARED TO AGORAPHOBIA IN RELATIVE

STRATIFYING VARIABLES	M-H OR	95% CI		X^2_{M-H}	P-values
Age in relative	2.31	.819	6.51	2.51	0.11
Gender in relative	2.71	1.34	5.44	5.64	0.018
Relationship to proband	2.52	1.25	5.04	6.83	0.009
Disorder in Relative:					
Depression	2.04	.951	4.38	3.35	0.067
Dysthymia	1.63	.762	3.48	1.58	0.21
GAD	2.13	1.03	4.41	4.16	0.04
OCD	2.3	1.19	4.41	6.21	0.013
Simple phobia	2.2	1.06	4.57	4.47	0.034
Social phobia	2.65	1.23	5.69	6.23	0.012
Panic disorder	2.23	1.01	4.93	3.93	0.047

Table 3.7 LOGISTIC REGRESSION MODEL WITH AGORAPHOBIA IN RELATIVES AS OUTCOME VARIABLE

MODEL		Exp (B)	Likelihood Ratio Test	
			X^2 Test	P-Value
UNIVARIABLE				
Agoraphobia in proband		2.53	5.20	.0226
2 VARIABLES - MAIN EFFECT				
Agoraphobia in proband +				
Age of relative	31 - 49	0.93	17.68	<.001
	50 - 94	3.08		
Male relative		0.31	18.9	< .001
Relationship to proband	Parent	2.88	18.36	< .001
	Sibling	2.15		
Depression in relative		6.53	51.68	<.001
Dysthymia in relative		9.05	50.39	<.001
GAD in relative		5.51	48.44	< 001
Simple phobia in relative		13.74	74.04	< 001
Social phobia in relative		32.63	62.6	< 001
3 VARIABLES - MAIN EFFECT				
Agoraphobia in proband + simple phobia +				
Age of relative	31 - 49	0.98	15.15	<.001
	50 - 94	3.02		
Male relative		0.37	12.6	<.001
Relationship to proband	Parent	3.21	14.72	<.001
	Sibling	2.33		
Depression in relative		4.79	33.26	<.001
Dysthymia in relative		6.57	33.59	<.001
GAD in relative		4.61	35.94	<.001
Social phobia in relative		24.54	46.73	<.001

Table 3.8 FINAL LOGISTIC MODEL WITH AGORAPHOBIA IN RELATIVES AS OUTCOME VARIABLE

VARIABLES	OR	95% CI		P-Value
Agoraphobia in proband	2.43	1.07	5.57	0.0346
Gender of relative (male)	0.39	.20	.73	0.0037
Relationship to proband				0.0018
Parent	2.95	1.30	6.67	0.0094
Sibling	2.47	1.40	4.32	0.0018
Depression in relative	2.23	1.25	3.98	0.0065
GAD in relative	3.11	1.80	5.40	0.0001
Simple phobia in relative	8.62	4.75	15.64	<.001
Social phobia in relative	14.59	6.18	34.44	<.001

Table 3.9 LOGISTIC MODEL WITH AGORAPHOBIA IN RELATIVES AS OUTCOME VARIABLE WITH AGE OF RELATIVE VARIABLE

VARIABLES	OR	95% CI		P-Value
Agoraphobia in proband	2.27	1.01	5.09	0.0466
Gender of relative (male)	0.39	.21	.74	0.0038
Age of relative	1.03	1.01	1.05	0.0023
Depression in relative	2.09	1.17	3.74	0.0126
GAD in relative	3.14	1.81	5.45	<.001
Simple phobia in relative	8.03	4.45	14.51	<.001
Social phobia in relative	14.7	6.1	35.21	<.001

Table 3.10 LOGISTIC MODEL WITH AGORAPHOBIA IN RELATIVES AS OUTCOME VARIABLE WITH PANIC VARIABLE

VARIABLES	OR	95% CI		P-Value
Agoraphobia in proband	2.18	.92	5.15	0.0751
Gender of relative (male)	0.41	.21	.77	0.0054
Relationship to proband				0.0037
Parent	2.81	1.22	6.44	0.0152
Sibling	2.36	1.34	4.18	0.0031
Depression in relative	1.91	1.04	3.47	0.0366
GAD in relative	2.61	1.46	4.63	0.0012
Simple phobia in relative	8.58	4.68	15.74	<.001
Social phobia in relative	12.57	5.22	30.26	<.001
Panic disorder in relative	3.69	1.64	8.33	0.0016

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APPENDIX 1: DIAGNOSTIC INTERVIEW SCHEDULE (PHOBIC DISORDERS)

INTERVIEWER: FOR EACH "2" OR "5" CODED, RECORD AN EXAMPLE.

INTERVIEWER:IF RESPONSE TO "2" PROBE IS : "IT DOESN'T INTERFERE WITH MY LIFE A LOT BECAUSE I AVOID IT,: ASK:
" Does having to avoid (CATEGORY) interfere with your life or activities a lot?

IF NO: CODE 2
IF YES: CODE 5

68. Some people have phobias, that is, such a strong fear of something or some situations that they try to avoid it, even though they know there is no real danger. Have you ever had such an unreasonable fear of (PHOBIA) that you tried to avoid (it/them)? REPEAT FOR EACH PHOBIA LISTED BELOW.

a. Heights ..... ① ② ⑤
Ex: _____ 08/

b. Tunnels or bridges ..... ① ② ⑤
Ex: _____ 09/

c. Being in a crowd ..... ① ② ⑤
Ex: _____ 10/

d. Being on any kind of public transportation like airplanes, buses, or elevators 1 2 5
Ex: _____ 11/

e. Going out of the house 1 2 5
Ex _____ 12/

f. Being in a closed place 1 2 5
Ex _____ 13/

g. Being alone ..... ① ② ⑤
Ex _____ 14/

h. Eating in front of other people (either people you know or in public) ..... ① ② ⑤
Ex: _____ 15/

i. Speaking in front of a small group of people you know ..... ① ② ⑤
Ex: _____ 16/

j. Speaking to strangers or meeting new people ..... ① ② ⑤
Ex: _____ 17/

k. Storms 1 2 5
Ex: _____ 18/

l. Being in water, for instance in a swimming pool or lake 1 2 5
Ex: _____ 19/

m. Spiders, bugs, mice, snakes or bats 1 2 5
Ex: _____ 20/

n. Being near any (other) harmless animal or a dangerous animal that couldn't get you 1 2 5
Ex: _____ 21/

o. Is there anything else you were unreasonable terrified to do or be near? ..... ① ② ⑤
SPECIFY _____ 22/

INTERVIEWER: DID R TELL A DOCTOR ABOUT ANY OF THESE PHOBIAS?

NO ..... ①
YES 5

INTERVIEWER: IF **ANY** "5's" CODED ABOVE: ASK QS 69-70
IF **NO** "5's" CODED ABOVE SKIP TO Q 72

CODE	
1= no	4 = med.exp.
2 = below crit.	5 = yes
3 = drugs or alc.	

69. How old were you the first time you were bothered by any of these fears(LIST ALL PHOBIAS CODED "5" IN Q.68)? (IF R SAYS "WHOLE LIFE":CODE 02)

ENTER AGE & GO TO Q.70 ☐☐ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨ ① ② ③ ④ ⑤ ⑥ ⑦ ⑧ ⑨

INTERVIEWER: IF "DK" AND R IS UNDER 40:CODE 01
IF "DK" AND R IS 40 OR MORE .ASK A

A. Would you say it was before or after you were 40?

Before 40.....(RECORD 01)
After 40.....(RECORD 95)
Still DK.....(RECORD 98)

69. How recently (has this fear/have any of these fears)been so strong that you tried to avoid the situation?

CODE MOST RECENT TIME POSSIBLE

Within last 2 weeks or current.....①
Within last month.....②
Within last 6 months.....③
Within last year.....④
More than 1 year ago.....⑤

IF MORE THAN A YEAR AGO:
A. How old were you then?

ENTER AGE: ☐☐ 1 2 3 4 5 6 7 8 9 1 2 3 4 5 6 7 8 9

INTERVIEWER: IF Q. 62 CODED "1" OR CODED "2-5"?
CODED "1".....(SKIP TO Q.72)..... 1
CODED "2-5"....(ASK Q.71)..... 5

70. You mentioned spells of feeling frightened or anxious when you (LIST UP TO 3 SYMPTOMS CODED "YES" IN Q.62). Did those spells occur only when you were(LIST ALL PHOBIAS CODED"5" IN Q.68) or did they occur at other times too?

only in phobic situations.....①
other times as well.....⑤