EMPIRIC RISK TO FIRST-DEGREE RELATIVES

OF ALZHEIMER DISEASE PATIENTS

by

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# Abstract

Kaplan-Meier risk estimates were generated and evaluated for 1867 first-degree relatives of 338 Alzheimer Disease (AD) index cases and 1873 first-degree relatives of 351 non-cognitively impaired, non-demented elderly controls. A cumulative lifetime risk of 26.73 ± 4.42% for first-degree relatives of AD cases, while significantly higher than the cumulative lifetime risk of 7.26 ± 2.74% found for first-degree relatives of controls, does not suggest that all cases of AD are due to a single autosomal dominant gene(s), but is evidence that a genetic component to the etiology of the disease exists. Female and male first-degree relatives of AD cases as well as parents and sibs of AD cases showed higher cumulative risks throughout their lifetimes when compared to their analogous control subgroups. Equal cumulative lifetime risks between first-degree female and male relatives (28.97 ± 3.60%, 22.03 ± 8.29%) and between parents and sibs (27.67 ± 4.50%, 28.87 ± 8.92%) of AD cases, but significantly different lifetime risk curves suggest that non-genetic factors may affect the age-specific expression of AD in individuals with an identical genetic propensity. Equal risk between first-degree relatives of early-onset and late-onset AD cases does not support the suggestion that relatives of early-onset cases share a higher risk to develop the disease. These results are interpreted as being suggestive of a complex etiology with both genetic and environmental factors, as well as interactions between the two playing a role in AD expression.

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# 1 INTRODUCTION

## 1.1 Background

Alzheimer Disease (AD) is a progressive degenerative brain disease believed to be the most common cause of dementia. AD affects between 5 to 11% of the population aged 65 and older, and up to 47% of those aged 85 and above (Evans et al., 1989; Pfeffer et al., 1987; Schoenberg et al., 1985). AD was first described by the German psychiatrist Alois Alzheimer, who presented the case of a 51 year old woman with behavioral symptoms and memory problems. When a then, newly developed silver stain technique (Bielschowsky method) was used at autopsy, abnormal nerve cells containing tangles of nerve fibres (neurofibrillary tangles) and collections of degenerating nerve ends (neuritic plaques) were found in the affected woman's brain (Alzheimer, 1907).

Blessed et al. (1968) first recognized that all individuals with AD had characteristic histopathologic changes. Further study showed that these histopathologic changes were the result of the abnormal deposition of intracellular cytoskeletal filaments in neurofibrillary tangles, and the accumulation of extracellular deposits of ß-amyloid protein collecting in the form of plaques in the hippocampus, cortex, and temporal lobe areas of the brain (Glenner and Wong, 1984; Terry and Katzman, 1983). The major component of these senile plaques is a 39-43-amino-acid peptide (ßA4) which is part of a larger molecule encoded by the amyloid-precursor-

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protein (APP) gene mapped to the long-arm of chromosome 21 (Goldgaber et al., 1987; Kang et al., 1987; Robakis et al., 1987; Tanzi et al., 1987a).


## 1.2 Diagnosis

Dementia is now recognized to result from several different causes including vascular disease, multiple infarcts (strokes) as well as AD (Table 1.1). Dementia is defined in the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) (American Psychiatric Association, 1987) as "the impairment of cognition severe enough to interfere with daily functioning". This impairment can affect different areas of cognition such as short-term memory (e.g. the ability to learn new information); long term memory (e.g. the ability to remember birthplace); abstract thinking (ability to understand conceptual information); judgement (e.g. ability to make rational plans); aphasia (language disorder); apraxia (impaired motor activity); agnosia (impaired recognition of objects despite having intact sensory function); constructional ability (e.g. ability to draw a 3-dimensional object); and personality. The National Institute of Neurological and Communicative Disorders and Strokes (NINCDS) and the Alzheimer Disease and Related Disorders Association (ADRDA) Work Group Criteria (McKhann et al., 1984) consider behaviour *in addition* to cognitive impairment in the definition of AD. NINCDS-ADRDA criteria define dementia as a decline of memory and other cognitive abilities from a previous level of functioning. This definition allows the inclusion of

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individuals with both high and low levels of intellectual functioning, including those with mental handicap (e.g. Down syndrome).

NINCDS-ADRDA diagnostic criteria (McKhan et al., 1984) for "definite" AD, "probable" AD, and "possible" AD are as follows:

i) *"Definite" AD*: This diagnosis can only be made after clinical criteria for "probable" AD are met (see below) and histopathologic material from biopsy or autopsy is examined for the classic neuropathologic signs. Large numbers of neuritic plaques and neurofibrillary tangles in the hippocampus and temporal lobes would be definitive signs of AD, however the accumulation of a few plaques and tangles is within the range of normal aging.

ii) *"Probable" AD*: This is the most definitive clinical diagnosis and criteria include dementia established by clinical examination with an insidious onset, a progressive decline in two or more areas of cognition including memory and the absence of all other conditions which could impact an individuals cognitive functioning (see Table 1.1).

iii) *"Possible" AD*: This diagnosis requires that an individual meet the clinical criteria for AD (i.e. "probable" AD) which is confounded by a concurrent condition possibly affecting cognitive functioning.

Clinically, the disease is best characterized by an insidious onset, a progressive course and deterioration in two or more areas of cognition. AD generally has its onset in the sixth or seventh decade of life, but individuals can become affected as early as the third or fourth decade. Based on clinical examinations, these NINCDS-

ADRDA diagnostic criteria provide an inter-clinician reliability of approximately 95%

(Forette et al., 1989). Studies using strict diagnostic criteria find good to excellent

agreement between clinical and histological diagnoses (70%-100%) (Burns et al.,

1990; Jellinger, 1990; Tierney et al., 1988). Adherence to strict diagnostic criteria

results in an acceptable level of reliability for research purposes.

**Table 1.1 Major Causes of Dementia***

**1. Cerebral Neuronal Degenerations**
    Alzheimer Disease
    Pick Disease
    Parkinson Disease
    Huntington Disease
    Progressive Supranuclear Palsy
**2. Acquired Cerebral Disorders (some potentially reversible)**
    Vascular Dementia: Multi-Infarct Dementia, Binswanger Disease
    Multiple Sclerosis
    Intracranial Neoplasms
    Trauma (including Subdural Hematoma)
    Hydrocephalus
    Transmissible Spongiform Encephalopathies (e.g. Creutzfeld-Jakob Disease)
**3. Other Potentially Reversible Disorders**
    Metabolic Disorders: Hypothyroidism, Renal Dialysis
    Toxic/Nutritional Disorders: e.g. Chronic Drug Intoxication, Alcoholism,
    Malnutrition (e.g. vitamin $B_{12}$ deficiency)
    Infections: e.g. HIV, neurosyphillis, tuberculous or bacterial meningitis,
    cryptococcosis, acute viral encephalitis
    Major Depression

*This is not meant to be a comprehensive list, but is presented to illustrate the
etiologic heterogeneity of dementia.
Revised from Morris and Rubin, 1991.

Clinical (phenotypic) heterogeneity exists in AD. The presentation of the cognitive syndrome can vary and include any or all of the following: amnesia; aphasia; apraxia; agnosia. A wide variation in ages-of-onset occurs both within multicase families and among "sporadic" (non-familial) cases (Bird et al., 1983). Historically, AD has been separated into early-onset (onset before age 65), and late-onset (onset at or after age 65) subgroups. However, other than age-of-onset, no phenotype has been definitively recognized to differentiate early and late-onset forms of AD. Variation in myoclonus, extrapyramidal signs, brain cholinergic activity, and neuropathological changes are also evidence of diverse clinical expression of the disease (Chui et al., 1985; Freidland et al., 1988; Mayeux et al., 1985).

In summary, it has not yet been possible to correlate the wide variation in clinical phenotype with subgroups of AD (eg. early-onset versus late-onset; familial versus sporadic).

### 1.3 Etiological Heterogeneity

### 1.31 Risk Factors

### 1.31.1 Background

Heterogeneity in AD is not only restricted to the presentation of clinical symptoms. The etiology of AD is also now believed to be heterogeneous. A wide range of risk factors have been reported for AD. These include both genetic and environmental factors as well as interactions between the two. The most commonly reported risk factors are listed in Table 1.2. The singular most definitive risk factor

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appears to be age. Jorm et al. (1987) reviewed 22 studies and found that the prevalence of AD doubles approximately every 4.5 years until age 90. It is unclear whether the trend for increasing risk continues indefinitely with age. One study reported that the incidence of dementia actually decreased after age 90 in an isolated Swedish population (Hagnell et al., 1981). To date no age-related molecular level changes have been identified to explain the neuropathological changes seen in AD brains (reviewed by McLachlan et al., 1991).

Other than age, a family history of dementia is the only other widely recognized definitive risk factor. The elevated risk to first-degree and second-degree relatives of AD probands provides evidence for a genetic contribution to the disease etiology. Further evidence of a genetic component to the etiology of AD is provided by a possible increased risk to develop AD for individuals with a family history of Down syndrome. Both familial risks and the association between Down syndrome and AD will be discussed in detail later (1.32, 1.35).

### 1.31.2 History of Head Trauma

Head trauma has been reported as a risk factor for AD, but not all studies agree on the significance of a history of head injury. Head trauma may further deplete an individuals' natural age-related decline in the number of neurons. This loss of neurons may result in the decrease of brain function below the level required for normal activity (reviewed by McLachlan et al., 1991). A head injury may also damage the blood-brain barrier, resulting in the brain being exposed to environmental

**Table 1.2: Commonly Reported Risk Factors for Alzheimer Disease**

| Factor | Reference |
|---|---|
| Age | Reviewed by Jorm et al., 1987 |
| Family History of Dementia | Breitner and Folstein, 1984; Broe et al., 1990; Chandra et al., 1987; Graves et al., 1990; Li et al., 1992; Mendez et al., 1992; Mortimer, 1983 |
| Parental Age | Urakami et al., 1989; Rocca et al., 1991 |
| Family History of Down's Syndrome | Broe et al., 1990; Heston et al., 1981; Heyman et al., 1983; |
| Family History of Parkinsonsim | Heyman et al., 1983; Hofman et al., 1989 |
| Thyroid Disease | Ewins et al., 1991; Heyman et al., 1984; Li et al., 1992; Mortimer 1989 |
| Depression | French et al., 1985; Shalat et al., 1987; |
| Head Trauma | Amaducci et al., 1986; Heyman et al., 1984; Mortimer et al., 1985; Sullivan et al., 1987 |
| Organic Solvent Exposure | Freed and Kandel, 1988; Hein et al., 1990 |
| Female Gender | Henderson, 1988; Jorm et al., 1987; Rocca et al., 1986 |
| Aluminum Exposure | Flaten, 1987; Leventhal, 1986; Martyn et al., 1989; Still and Kelley, 1980; Vogt 1986 |

toxins and viruses normally present in the body, but from which the brain would otherwise have been protected. The destruction of the blood-brain barrier could also allow an abnormal interaction between the immune system and the central nervous system (Mortimer et al., 1985). Together, these data emphasize the complex interactions which may be important in the etiology of AD.

### 1.31.3 History of Aluminum Exposure

A history of aluminum exposure has been cited as a risk factor for AD. However, this is not a universal observation (Markesbery et al., 1981; 1983; McDermott et al., 1979). An elevated level of aluminum has been found in the core of senile plaques in the brains of AD patients (Crapper et al., 1973). A study of AD neocortex samples found the level of aluminum in a DNA fraction enriched for genes repressed in AD patients is nine times that of controls (Crapper et al., 1980; McLachlan et al., 1989). One hypothesis is that the increased electrostatic binding of aluminum to DNA-associated proteins results in altered chromatin structure and a decrease in gene transcription (reviewed by McLachlan et al., 1991).

Another possible mechanism for aluminum's putative effect on a susceptible individual's brain is the association between aluminum and stress response proteins. It has been reported that the level of heat-shock protein 17 (a stress response protein) is increased with temperature in the hippocampus of adult rats, but not aged rats. It has also been demonstrated that exposing neuroblastoma cells to aluminum can induce the production of heat shock proteins (reviewed by Lake et al., 1991).

Another interesting link between these pieces of evidence is in a recent report by Schellenberg et al. (1992) who reported a candidate gene for AD found in a subset of early-onset multicase families to be HSPA2 (a 70-kd heat shock protein) located on chromosome 14. It is hypothesized that HSPA2 could potentially be involved in protein assembly and degradation, thus affecting the accumulation of ß-amyloid protein in the brain. Further investigation is needed to determine the role of these mechanisms in AD neurodegeneration. However, these observations do serve to illustrate that complex interactions may play a part in the disease etiology.

### 1.31.4 History of Thyroid Disease

A history of thyroid disease has also been reported as a risk factor for AD (Ewins et al., 1991; Heyman et al., 1984; Li et al., 1992; Mortimer 1989), but this association again has not been confirmed by all studies (Ammaducci et al., 1986; Henderson et al., 1986; Rocca et al., 1986). Several lines of evidence suggest that thyroid hormone which has as essential role in brain function, may play a part in the deterioration of cognitive functioning. Adults deficient in thyroid hormone exhibit slowing of intellectual function, loss of initiative, confusion, disorientation, memory loss, slowing of speech, and lethargy (Jellinek, 1962; Karnosh and Stout, 1935). One form of thyroid hormone receptor ($T_3$ receptor) is normally found in high concentration in the cortex and hippocampal regions of the brain (Dussault and Ruel, 1987). These same regions are deteriorated in AD patients. It is therefore

hypothesized that altered or decreased response to thyroid hormone may be involved in the etiology of AD (reviewed by McLachlan et al., 1991).

Antibodies to thyroglobulin (an inactive supply form of thyroid hormone) have been found in the cerebrospinal fluid of AD patients (McRae-Degueruce et al., 1988). These antibodies may further decrease thyroid hormone levels, aggravating the age-related deterioration in cognitive functioning associated with AD (reviewed by McLachlan et al., 1991; Reinisch et al., 1991).

### 1.31.5 Female Gender

A female preponderance (up to twice the rate for males) has been reported in AD (Bachman et al., 1992). This sex-specific difference in risk may be related to differences in the expression of male and female hormones (androgens and estrogens). Several morphologic sex differences in the human brain have been identified. These include the size of the corpus callosum and hypothalamus as well as hemispheric brain organization (reviewed by Reinisch et al., 1991).

Studies on the central nervous systems of other mammals suggest that sex differences in brain structure and function are direct results of the early organizational influence of sex hormones. Areas affected include the nuclei of the hippocampus, cerebellum, amygdala and cerebral cortex. Differences in the morphologic dimensions of the brain including synaptic connections, dendritic field patterns and the size of brain nuclei have all been reported (reviewed by Reinisch et al., 1991). Hormones also exert an effect on the brain at a cellular level, impacting

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cell number and size. Androgens (male hormones) may increase the survival of particular spinal cord cells early in human development (Toran-Allerand, 1986). These hormonal effects on the brain are not limited to the prenatal period, and can continue into adulthood (Greenough, 1986).

Biochemical and physiological functions such as hormone regulation, glucose metabolism and neurotransmitter function (including cholinesterase activity) are affected by androgens and estrogens (reviewed by Reinisch et al., 1991). The deficiency of the neurotransmitter choline acetyltransferase has been reported in AD patients (reviewed by Beattie, 1992) . Several studies provide evidence that a depressed level of choline acetyltransferase is a central factor in the disease process (reviewed by Beattie, 1992). These hormones are also known to control the excitability of brain cells by modulating the action of neurotransmitters. Increased cholinergic and catecholinergic activity are noted in males while serotinergic activity is elevated in females (reviewed by Reinisch et al., 1991).

It is known that raised estrogen and progesterone levels correlate with epileptic seizures. Further, postmenopausal women with decreased estrogen levels suffer mood changes which can be alleviated by estrogen supplements, suggesting that naturally occurring hormone level fluctuations are sufficient to affect neuronal activity. Decreased estrogen levels may remove the protective effect this hormone is thought to exert on the brain (reviewed by McLachlan et al., 1991). Raised glutamate levels in the brain cause overexcitation of the neurons and eventually lead to cell death. Estrogen regulates glutametergic activity, but whether the decreased

level of estrogen found in post menopausal women is adequate to sufficiently raise glutamate levels to cause this overexcitation and disruption of neuronal activity is, as yet, unknown. Altered glutamate activity in the cerebral cortex and hippocampal regions may be associated with impaired short term memory usually found in AD patients.

### 1.31.6 Other Risk Factors

Other risk factors which have been reported include consanguineous marriages (Lowenberg and Wagoner, 1934), and ethnic and racial differences (Bird et al., 1988; Goudsmit et al., 1981, Hendirie et al., 1989). A recent case-control study done on a Chinese population found both left handedness/ambidexterity and a family history of psychotic disorders as well as previously more commonly reported factors increase an individuals risk for AD (Li et al., 1992). Advanced maternal age has been widely reported as a risk factor (Ammaducci et al., 1986; Rocca et al., 1991; Urakami et al., 1989), and provides one link for a possible association between AD and Down syndrome (see section 1.35). Another risk factor providing additional evidence of a link between AD and autoimmune thyroid disease is a high incidence of autoimmune thyroid disease among affected relatives of FAD families (Ewins et al., 1991). A higher incidence of autoimmune thyroid disease in individuals suffering from Down syndrome and also been previously reported (Burgio et al., 1966; Lobo et al, 1980). As it is known that the underlying cause of Down syndrome is trisomy 21, these results lend further support to the possible genetic contribution to both autoimmune

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thyroid disease and AD, with the possibility that the latter diseases are linked to chromosome 21 (see sections 1.31.4, 1.35). The large number of possible risk factors has lead some researchers to postulate polygenic interaction to explain clustering of AD in some families (Sjogren et al., 1952; Sulkava et al., 1979; Whalley et al., 1982).

## 1.32 FAD

A portion of individuals with AD are from families whose disease aggregation of AD suggests an autosomal dominant mode of transmission. Estimates of the proportion of the AD population showing this type of transmission range from 5% (Appel, 1981) to 100% (Breitner et al., 1988) (see Section 1.4). Such families are referred to as "Familial Alzheimer Disease" (FAD) (Feldman et al., 1963; St. George Hyslop et al., 1989). It has been hypothesized that an autosomal dominant gene(s) is responsible for all cases of the disease, but potentially "affected" individuals die from competing causes before the age-of-onset for AD. This results in a lower percentage of observed cases within families than predicted by the autosomal dominant model (ie. 50%). To date, phenotypic heterogeneity has not been shown to exist between FAD and non-FAD cases (Haupt et al., 1992; Swearer et al., 1992). This was interpreted as further evidence that "sporadic" cases of AD actually represent reduced penetrance of a single autosomal dominant gene with non-expression being due to "unaffected" family members not living long enough to exhibit symptoms (St. George Hyslop et al., 1989). The difficulty in assessing families affected by a disease with

such a late-onset led one researcher to comment "... perhaps Alzheimer's disease would be simpler to understand if we all lived to be 150 years old" (Davies, 1986).

## 1.33 Molecular Genetic Investigation

It was originally reported in 1987 that DNA markers on the proximal long arm of chromosome 21 segregated with AD in four early-onset FAD families (St. George-Hyslop et al., 1987). This led to a series of studies examining genetic linkage between a possible defect in the APP gene, already mapped to the same region on chromosome 21 and implicated in AD pathogenesis, and FAD. Further study detected several obligate crossovers between FAD and APP, suggesting the possibility of other FAD gene loci (Tanzi et al., 1987*b*, Van Broeckhoven et al., 1987). Continued study has not supported the hypothesis that all FAD families are the result of an autosomal dominant segregating mutation linked to the proximal long arm of chromosome 21 (Goate et al., 1991; St. George-Hyslop et al., 1990; St. George-Hyslop et al., 1987). Although a small subset of early-onset FAD families appear to be linked to chromosome 21, the majority of early-onset families and all late-onset families do not support proximal 21q linkage (Pericak-Vance et al., 1988; Schellenberg et al., 1991; St. George-Hyslop et al., 1990). Recently (October 1992) a study found evidence for an FAD locus on chromosome 14 in a subset of early-onset FAD families (Schellenberg et al., 1992). This finding has been confirmed by three later studies reporting linkage of a subset of early-onset FAD families to the long

arm of chromosome 14 (Mullan et al., 1992; St George-Hyslop et al., 1992; Van Broeckhoven et al., 1992).

It has been suggested that FAD is more often found among early-onset AD than late-onset AD (reviewed by Nalbantoglu et al., 1990). However, several studies have reported linkage of a late-onset subset of FAD families to the proximal long arm of chromosome 19 (Pericak-Vance et al., 1991a, 1991b; Roses et al., 1990; Schellenberg et al., 1992). These data provide evidence that the expression of FAD is not restricted to individuals exhibiting an early-onset form of the disease. They also further support nonallelic genetic heterogeneity in AD.

Further evidence of genetic heterogeneity is provided by investigations of several different APP mutations which have been reported to segregate with FAD (Chartier-Harlin et al., 1991; Goate et al., 1991; Karlinsky et al., 1992; Murell et al., 1991). The ß-amyloid sequence is coded by parts of exons 16 and 17 of the APP gene. These mutations reside within codon 717 in exon 17 and involve changing valine to isoleucine, phenylalanine or glycine. Investigations have also revealed further mutations in the APP gene outside codon 717 apparently resulting in the AD phenotype (Hendriks et al., 1992; Mullan et al., 1992). One involves a substitution of glycine for the native alanine at codon 692, which is also coded for in exon 17 of the APP gene. The other is a double mutation at codon 670 and 671 coded for in exon 16 of the APP gene. A more recent investigation reported a double mutation at codon 715 and 713 in one apparently sporadic case of AD and in four of her six

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unaffected sibs (two of which have passed the probands age-of-onset) as well as an unaffected aunt (Carter et al., 1992).

This evidence suggests that only approximately 3% of FAD cases are a result of mutations in the APP gene (Chartier-Harlin et al., 1991; Schellenberg et al., 1991; Van Duijn et al., 1992), and that additional factors (environmental or genetic) may be necessary for manifestation of the AD phenotype by the end of the human lifespan.

In conclusion, the results indicating that no sporadic and only an extremely small proportion of FAD cases segregate with these known mutations strongly point to heterogeneity in the etiology of AD.

## 1.34 Twin Studies

The study of twins lends additional evidence to the supposed etiologic heterogeneity of AD. If AD were purely a genetic disease, concordance rates among monozygotic twins (genetically identical individuals) would approach 100%. Further, if AD were a single gene trait, concordance rates for dizygotic twins (individuals who share 1/2 of their genes, as do non-twin siblings) would approach 50%.

A concordance rate of 42% for monozygotic twins and 8% for dizygotic twins was reported by Kallman et al. (1956). A follow up study found a concordance rate for monozygotic twins to be approximately 50% (Jarvik et al., 1971). However both these studies suffered from design problems such as insufficient follow-up time for a disease known to be characterized by widely variable ages-of-onset, as well as the absence of strict diagnostic criteria (these studies were prior to the NINCDS-

ADRDA criteria). A more recent study found concordance rates of approximately 40% for both monozygotic and dizygotic twins (Nee et al., 1987). To date, case reports of 40 twin pairs (either one or both individuals affected) have been published. Sixteen of 35 monozygotic twin pairs were concordant; 19 monozygotic twin pairs were discordant, even after follow-up of 20 years in some cases (Hunter et al., 1971; Karlinsky, 1993; Kumar et al., 1991; Nee et al., 1987; Renvoize et al., 1986). The five reported dizygotic twin pairs are all concordant (reviewed by Karlinsky, 1993).

These twin data represent many of the biases in twin studies that are not population based. These include over-ascertainment of monozygotic pairs (ie. 87% of twins reported were monozygotic, whereas in the North American and European populations from which these cases were drawn, only approximately 30% of twins are monozygotic) (Ebers et al., 1986; McFarland, 1993; Vogel and Motulsky, 1979). Non-population based series are also biased towards concordant pairs as seen by the fact that 100% of the published dizygotic twin pairs are concordant.

These studies in AD clearly demonstrate that monozygotic twin pairs are not 100% concordant and concordant pairs can have widely different ages-of-onset. It has also been reported that an increased familial rate for AD among first-degree relatives of concordant monozygotic twin pairs compared to first-degree relatives of discordant monozygotic twin pairs exists, lending further evidence that a single disease etiology is unlikely (Rappaport, 1991).

## 1.35 Association Between AD and Down Syndrome

The putated association between Down syndrome (DS) and AD further supports the genetic contribution to AD etiology. DS results from the duplication of a section of chromosome 21 containing a specific portion of the chromosomal material, usually through meiotic nondisjunction. Interestingly, chromosome 21 is the same chromosome to which the FAD linked APP gene mutations have been mapped. The resulting DS phenotype is presumed to be a result of an overproduction of the gene products coded by the duplicated genes (reviewed by Potter, 1991).

All individuals affected by DS show the neurohistologic signs of AD by age 40 and a proportion also exhibit clinical signs of dementia (reviewed by Breitner and Folstein, 1984; McLachlan et al., 1991). It was this association that led to the original investigations linking FAD and chromosome 21 (see section 1.33).

DS has been reported to occur in the families of AD probands more often than expected (Heston et al., 1981; Heyman et al., 1984), but more recent studies which strictly control for maternal age do not confirm this association (Sadovnick et al., 1992).

It is important to note that although all DS affected individuals who live long enough have been found to have plaques and tangles characteristic of AD on autopsy, only 15% to 30% (or even 45%) will develop dementia (reviewed by Ball, 1987). These data emphasize the relationship between the neuropathology and dementia, ie., AD neuropathology is associated with dementia, but may not account for the dementia.

Sanford et al. (1991) reported that a similar defect in DNA repair may cause the neurodegeneration seen in individuals with both AD and DS. Additional evidence of a link between AD and DS comes from the shared risk factor of advanced maternal age (Ammadduci et al., 1986; Rocca et al., 1991; Urakami et al., 1989), although this has not always been confirmed for AD (Hofman et al., 1990, Jouhan-Flahault et al., 1989). The increased risk due to advanced maternal age can be explained in DS by the dramatic increase of non-disjunction in the aged ova of the mother, resulting in a greater proportion of trisomic offspring (reviewed by McLachlan et al., 1991). Urakami et al. (1989) proposed that the association between AD and DS may be due to similar cytogenetic events occurring in both disease processes. Potter (1991) hypothesized that the accumulation of trisomy 21 cells developing over time due to unequal segregation during mitosis leads to AD by the same mechanism that DS individuals acquire the disease.

**1.4 Overview of Previous Studies Examining Empiric Risk to First-Degree Relatives of AD Cases and Controls Using Similar Methodologies**

Age specific risks for AD to first-degree relatives of AD cases and controls can be calculated into the eighth and ninth decades of life if the study population is sufficiently large. Assuming a fully penetrant autosomal dominant model of inheritance, the risk to first-degree relatives of AD cases should approach 50% by the ninth decade of life. Assessment of lifetime risk to first-degree relatives is one method to evaluate the contribution of an autosomal dominant gene(s) to the

etiology of AD (Breitner et al., 1988; Martin et al., 1988; Mohs et al., 1987).

However, a risk approaching 50% does not unambiguously prove that a single

autosomal dominant gene is responsible for the disease. Molecular genetic studies in

AD support etiologic (genetic) heterogeneity.

Table 1.3 summarizes studies in the literature which examined the risk to first-

degree relatives of AD cases and non-demented, cognitively unimpaired controls,

using similar methodologies to those in this study. With the exception of one early

study (Brietner and Folstein, 1984), all studies listed in Table 1.3 used NINCDS-

ADRDA criteria (or very similar criteria) for the diagnosis of AD cases. Most

studies find a cumulative lifetime risk to first-degree relatives (or parents and sibs

only, as including children in the analysis generally lends nothing to the final estimate

since few have reached the "at risk" onset age) of approximately 50% by the eighth or

ninth decade of life, as predicted by an autosomal dominant model of inheritance

(Breitner and Folstein, 1984; Breitner et al., 1988; Huff et al., 1988; Martin et al.,

1988; Mayeux et al., 1991; Mohs et al., 1987). However, two studies did not find this.

Farrer et al. (1989), using a method which weighted the accuracy of diagnosis in the

affected relatives, found a lower risk to all first-degree relatives of AD cases. They

reported a maximum risk of 39 ± 10%, but felt a value weighted for certainty of

diagnosis, 24%, was probably closer to the true risk. Sadovnick et al. (1989) studied

151 AD cases and their relatives and found a cumulative lifetime risk to parents and

sibs of AD cases of 23.3 ± 3.8%, a figure very close to the weighted value of 24%

reported by Farrer et al. (1989). Although the cumulative lifetime risks differ

between these two studies and the bulk of other analyses, all studies found a sharp increase in risk with age at approximately age 70.

Cumulative lifetime risks have been compared for different subgroups of first-degree relatives, but to date no significant differences have been found. The two major studies which examined the risk to female and male first-degree relatives of AD cases found no significant differences (Brietner et al., 1988; Farrer et al., 1989), however Breitner et al. (1988) suggested that the "tendency" for female first-degree relatives of AD cases to develop the disease at an earlier age was "notable". Several studies examined cumulative lifetime risk to parents and sibs of AD cases and reported no significant differences (Brietner et al., 1984; Breitner et al., 1988; Farrer et al., 1989). Finally, no significant differences in cumulative lifetime risk between first-degree relatives of early-onset and late-onset AD cases have been reported, although relatives of early-onset cases reportedly have a non-significant tendency to develop the disease at an earlier age (Breitner et al., 1988; Farrer at al., 1989; Huff et al., 1988;).

The cumulative lifetime risk estimates to first-degree relatives of non-demented, cognitively unimpaired controls were found to be significantly lower than those to first-degree relatives of AD cases in all studies, however these estimates vary widely (8.07 ± 5.97% to 23 ± 10.8%). An important factor in weighing the significance of these results is the number of first-degree relatives surviving to the last ages of life. At these late ages (age 80 to 90 years old), the standard error of the estimated risk tends to become quite substantial. Studies investigating significantly larger samples

## Table 1.3: Overview of Previously Reported Risk Estimates Using Similar Methodologies

| | Cases | | | |
|---|---|---|---|---|
| Reference | Basis of Diagnosis | No. | Subgroup | Risk Estimate (%) |
| Breitner and Folstein, 1984 | Clinical Exam (agraphia[*], aphasia[§]) | 39 | Siblings and Children | 55.3 ± 15[*]  57.6 ± 22[§] |
| Mohs et al, 1987 | NINCDS-ADRDA | 50 | First-Degree Relatives | 45.9 ± 9 |
| Breitner et al, 1988 | NINCDS-ADRDA | 79 | First-Degree Relatives | 49.3 ± 8 |
| | | | Parents | 43 ± 8 |
| | | | Siblings | 61.0 ± 24 |
| | | | Males | 34 ± 13 |
| | | | Females | 54 ± 10 |
| | | 27 | Relatives of Early-Onset Cases | 56 ± 14 |
| | | 52 | Relatives of Late-Onset Cases | 38 ± 9 |
| Huff et al, 1988 | NINCDS-ADRDA | 50 | Parents/Sibs | 45 ± 11 |
| | | | Relatives of Early-Onset Cases | 49 ± 16 |
| | | | Relatives of Late-Onset Cases | 40 ± 14 |

continued

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| | Cases | | | |
| Reference | Basis of Diagnosis | No. | Subgroup | Risk Estimate (%) |
| --- | --- | --- | --- | --- |
| Martin et al, 1988 | NINCDS-ADRDA | 22 | First-Degree Relatives | 40.8 ± 9 |
| Farrer et al, 1989[Y] | NINCDS-ADRDA | 114 | First-Degree Relatives | 24 to 39 ± 10 |
| | | | Parents | 21 to 35 ± 6 |
| | | | Sibs | 35 to 59 ± 29 |
| | | | Females | 35 to 56 ± 14 |
| | | | Males | 12 to 18 ± 4 |
| | | 57 | Relatives of Early-Onset Cases | 45 ± 15 |
| | | 57 | Relatives of Late-Onset Cases | 37 ± 14 |
| Sadovnick et al, 1989 | NINCDS-ADRDA | 151 | Parents/Sibs | 23.3 ± 3 |
| Mayeux et al, 1991 | NINCDS-ADRDA | 110 | First-Degree Relatives | 48.7 ± ?[æ] |

[Y]Risk estimates calculated by a weighting method. Estimates represent weighted risk estimates and maximum risk estimates.
[æ]Standard error not reported.

continued

| | Controls | | | |
|---|---|---|---|---|
| Reference | Composition | No. | Subgroup | Risk Estimate (%) |
| Breitner and Folstein, 1984 | Non-AD Institut- ionalized Resident | 33 | First- Degree Relatives | 8.1 ± 6 |
| Mohs et al, 1987 | Spouse/ Volunteer | 45 | First-Degree Relatives | 12.1 ± 7 |
| Breitner et al, 1988 | Spouse/ Volunteer | 61 | First-Degree Relatives | 9.8 ± 6 |
| Huff et al, 1988 | Spouse | 47 | First-Degree Relatives | 11 ± 4 |
| Martin et al, 1988 | Spouse | 24 | First-Degree Relatives | 23 ± 10 |
| Mayeux et al, 1991 | Volunteer | 59 | First- Degree Relatives | 20 ± ?[æ] |

¥ Risk estimates calculated by a weighting method. Estimates represent weighted risk estimates and maximum risk estimates.
æ Standard error not reported.

will facilitate more accurate risk estimation.

## 1.5 Canadian Study on Health and Aging

In response to advice from experts in various disciplines, Health and Welfare Canada provided funding for a country-wide collaborative study on AD in the Canadian population. The objectives of this study were: (i) to estimate the prevalence of dementia among elderly Canadians; (ii) to determine risk factors for AD; (iii) to determine the weight of responsibility and the need for support by caregivers of demented patients; (iv) to establish a database for future studies.

The study of the prevalence of AD in the Canadian population (age $\geq 65$ years), provided the unique opportunity to screen a large sample of elderly individuals living in British Columbia for cognitive decline. This screening process identified elderly cognitively unimpaired individuals; "control" index cases for the study of familial risks for AD.

The Canadian Study for Health and Aging (CSHA) was designed to screen a representative sample from the population aged $\geq 65$, including those living in the community ("community sample") and in care facilities ("institutionalized population"). In British Columbia (B.C.), the sampling frame for the "community sample" was based on the B.C. Provincial Health Care Registry compiled through the British Columbia Provincial Health Care Plan. The sample was divided into three age group strata (65-74; 75-84; 85 and above), and weighted using the optimal allocation method (reviewed by Armitage, 1971). The following procedure to select the sample was in accordance with guidelines established for the entire country:

(A) Community Sample

    1. Select individuals age 65 and over as of October 1, 1990.

    2. Exclude individuals living in institutions.

    3. Use postal codes to select individuals living in designated study areas.

    4. Create sequential sampling frames alphabetically for each Central Metropolitan area and Urban Area using postal codes.

    5. Sort the sample into the Central Metropolitan Areas and Urban Areas using postal codes.

    6. Sort the above samples into three age strata: 65-74, 75-84, 85+.

    7. Randomly select the number (2N) subjects required for each stratum. By selecting twice the required number per stratum, replacement cases are available.

    8. Within each stratum, the odd numbers constitute the sample, and the even numbers, the replacement sample.

(B) Institutionalized Sample

    1. Use the Central Registry of Continuing Care Facilities to obtain a list of all institutions within Vancouver, Victoria, Kelowna, Kamloops, Matsqui, Mission, Chilliwack and Nanaimo. Geographic location was identified by postal codes.

    2. Obtain a list of all individuals age $\geq 65$.

    3. Sort the list into three strata based on size (maximum number of beds) of institution: small (4-25 beds), medium (26-100 beds) and large ($>100$ beds).

    4. From each stratum collect a random sample of approximately 200 (to allow for

a final sample of 84 individuals per stratum with replacements).

## 1.6 The Modified Mini-Mental State Exam

The Modified Mini-Mental State Exam (3MS) (Teng and Chui, 1987) was selected as the screening procedure for the CSHA. The 3MS has been widely used for several years. Its administration is more standardized and the scoring system is more refined compared to the original Mini-Mental State Exam (MMSE) on which the 3MS is based. The 3MS assesses a subject's cognitive functioning, examining his/her orientation to time and place, instant recall, short term memory, and arithmetic ability (Teng and Chui, 1987). The test is scored by summing the points assigned to each task. The test-retest reliability of the original MMSE is excellent, with most studies finding 24 hour retest scores of approximately 0.85 to 0.90 (Anthony et al., 1982; Folstein et al., 1983; Uhlman et al., 1987) which suggests the more refined 3MS has adequate reliability for research purposes.

The 3MS has a sensitivity of 0.94; superior to the score of 0.88 reported for the MMSE. A cut-off point of 80 out of a possible 100 on the 3MS is roughly equivalent to a cut-off point of 24 out of a possible 30 on the MMSE. A score of 23 or less on the MMSE is believed to be an indication of some form of cognitive impairment (Kay et al, 1985). Scoring 80 or above on the 3MS should therefore identify a conservative number of individuals free of cognitive loss or dementia.

## 1.7 Clinic for Alzheimer Disease and Related Disorders, University Hospital-UBC Site

The Clinic for Alzheimer Disease and Related Disorders, University Hospital - UBC Site ("Alzheimer Clinic") serves the entire population of British Columbia. The clinic's main roles are: (i) to provide a diagnosis (often a second opinion) for individuals referred with memory or other cognitive impairment; (ii) to counsel family members of patients with respect to prognosis for the patient, and familial risk; (iii) to conduct research on AD and other dementing illnesses. The B.C. Health Care Plan gives all patients essentially equal financial access to the clinic's services, thus avoiding many socioeconomic biases which can exist in other countries.

Each patient is assessed by the multidisciplinary Clinic Team, composed of an internist/geriatrician, a neurologist, a neuropsychologist, a social worker, a geneticist, and a language pathologist. Each clinic patient also has an extensive laboratory screen. Diagnoses are assigned according to NINCDS-ADRDA Criteria (McKahn et al., 1984). Patients not meeting the criteria for a diagnosis of dementia are reassessed at regular intervals. Longitudinal follow-up of patients with dementia is done as appropriate.

A wide battery of tests are used to assess each patient, including a comprehensive array of blood tests and routine diagnostic procedures such as a CT head scan, chest x-ray, and electrocardiogram. Detailed neuropsychological tests are also given. These include: (i) the Multi-focus Assessment Scale which measures social behaviour, auditory and visual receptive language skills, expressive language

skills, orientation, mood and accessibility for testing (Coval et al., 1985); (ii) the Wechsler Adult Intelligence Scale (WAIS) Information, Digit Span, Similarities and Block Design subscales; age corrected scores (Wechsler, 1955); (iii) the Controlled Oral Word Association Test or Word Fluency test which measures the ability to generate words in response to stimulus letters (Benton 1968); (iv) Finger Tapping Test and Dynamometer, measures of fine motor speed and grip strength; (v) Item 227 (Visual Recall) from the Luria Nebraska Neuropsychological Battery, modified to include copy and delayed recall components (Golden et al., 1984); and the Cued Recall procedure for memory assessment (Buschke, 1984).

The Alzheimer Clinic provides an excellent resource for family studies in AD. As family histories are routinely collected for all consecutive unrelated patients (cases), many biases inherent in family studies where cases are ascertained by the solicitation of volunteers are avoided. Over the years a number of families have been referred to the Alzheimer Clinic specifically because of their family history. These cases have been identified and are not included in this population based database.


## 1.8 Relevance of Study

### 1.81 Magnitude of AD on the Canadian Population and Health Care System

The demographic change in North America is towards an increasingly aged population. In 1988, it was estimated that health care costs for institutionalized AD patients in the United States exceeded $50 billion (Yankner and Mesulam, 1991). In addition to these direct monetary costs, the impact on family caregivers must also be

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considered. The impact of the "baby boom" generation approaching age 65 could be a health care problem of serious consequence. In 1900 approximately 5% of the Canadian population was over the age of 65. It is estimated that approximately 12% of the Canadian population will be aged 65 and over by the year 2000. It is presently estimated that at least 250,000 Canadians suffer from dementia, with a projected annual incidence of 25,000 cases (Feher, 1992).

## 1.82 Familial Risks

Relatives of individuals with AD are becoming increasingly concerned about their own risk to develop the disease. Given the extremely small proportion of individuals for whom autosomal dominantly segregating genetic mutations have been shown to be the underlying cause of the disease, the exact etiologic role of genetic factors must still be resolved (see Section 1.3). At present, the most appropriate method of counselling concerned relatives of AD individuals with respect to their own risks to develop AD is to provide the most up to date empiric age-specific risk data. This study is the largest of its kind to date, is relatively unbiased in case and control ascertainment, and will provide the most representative risk data for the B.C. population.

Investigations into the epidemiology of AD may lead to the clarification of the relative roles of "nature" and "nurture". The calculation of age-corrected familial risks to first-degree relatives of AD patients is one way to evaluate the genetic contribution to the etiology of the disease. The goal of these investigations is to gain

sufficient insight into this debilitating and costly disease to enable treatment and prevention.

# 2 MATERIALS AND METHODS

## 2.1 Cases

Data on cases were collected from all consecutive unrelated persons (patients) attending the Alzheimer Clinic during the period August, 1985 to March, 1992. NINCDS-ADRDA criteria were used to assign a diagnosis of the likelihood of AD. As described previously (section 1.2), a diagnosis of "definite" AD can only be made after examination of histopathologic material (eg. at autopsy or in rare instances, biopsy). The most definitive clinical diagnosis is "probable" AD. The importance of neuropathological examination is discussed with clinic patients and their relatives. Many consent to this procedure at the appropriate time.

The analyses presented in this thesis include only cases with a diagnosis of "probable" or "autopsy confirmed". Ideally, only "autopsy confirmed" AD cases should be used. However, this is not feasible as sufficient numbers of cases needed to allow for meaningful analysis would be extremely difficult to obtain.

## 2.2 Relatives of Cases

Studies investigating the role of genetic factors in the etiology of a disease require detailed information about each case's relatives. Family history data were collected using modifications of the "family history" method. At least two, and often more, knowledgable informants were interviewed by the clinic's geneticist who collected and verified family data. The use of multiple informants has been shown to

greatly reduce errors from underestimation of the number of affected relatives (Andreasen et al., 1977; Silverman et al., 1986).

The "family history" method was used over the "family study" method which requires all family members to be assessed directly for several reasons. In a late onset disease such as AD, many of the case's relatives are deceased at the time of study. Given the demographics of the B.C. population, it is rare that family members live in geographic proximity. For these reasons, a family study could not be done. The methods used in this study have been proven reliable for the well recognized genetic database for the Multiple Sclerosis Clinic at the University Hospital-U.B.C. Site (Ebers et al., 1986; Sadovnick et al., 1992).

The "family history" method was also used over the study of health records alone because many important and updated details proffered by knowledgeable family informants are not noted on health records. Early clinicians were inclined to ascribe dementia to undocumented sources such as arteriosclerosis or even failed to recognise dementia as a clinical condition, calling it normal aging.

Since AD can affect the cases' ability to accurately recall family history data, the study required co-informants (in addition to the case) with knowledge of all aspects of the cases' life. If the disease was obviously impeding the case's ability to recall certain aspects of their family history an additional co-informant was sought. Spouses and siblings of cases were preferred co-informants rather than children as the latter may lack detailed knowledge of older relatives (ie. parents and sibs of case). Identification of a co-informant was not a problem as all patients attending the

Alzheimer Clinic were requested in advance to attend the interview with an individual knowledgable about the patient's family history.

Whenever possible, reportedly affected relatives of cases were assessed in a specialized dementia clinic. Arrangements were made for neuropathological examination at a later date whenever possible. If the relative was deceased and/or assessment could not be arranged, medical/autopsy records were obtained (with appropriate consent) and reviewed by appropriate members of the Alzheimer Clinic Team to determine the most likely diagnosis, taking into account current criteria. This study had the advantage that the Canadian Provincial psychiatric facilities, where many relatives of cases have been institutionalized keep detailed records indefinitely, and with appropriate consent, release these to the Alzheimer Clinic.

To increase the reliability of the "family history" method, a standardized "Family History Questionnaire" originally devised by Silverman et al. (1987) was given to informants in the case of an "affected" relative being unavailable for examination (see copy in Appendix A). The "Family History Questionnaire" was used in conjunction with medical records to determine possible causes for the reported dementia. The use of a structured questionnaire allows more uniform assessment of the nature and progression of symptoms of dementia (Silverman et al., 1987). Questionnaires on reportedly affected relatives were completed by appropriate next of kin for each relative, and usually not the co-informant for the case. Our experience has been that family members are very cooperative in aiding these inquiries.

For the purpose of the analyses, a family member was considered "unaffected" if there was any possible explanation for the dementia other than AD (see Table 1.1). Relatives for whom no other identifiable cause of dementia could be determined, and whose dementia was reported to be irreversible and progressive were considered "affected". In the absence of clinical documentation, the Dementia Questionnaire and informant interview(s) were carefully considered in assigning "affected" or "unaffected" status.

Offspring of cases were not included in the lifetime risk analysis, although the information they proffer can be useful in determining whether a family represents FAD (see section 2.62). Only parents and full sibs (common mother and father) were included in the present analysis.

## 2.3 Controls

The combined "community" and "institution" sample from the CSHA was screened using the 3MS (see section 1.6). Using a high cut-off point of 80, a conservative number of elderly subjects (age $\geq$ 65) showing no signs of cognitive loss and/or dementia were identified. A proportion of these individuals were then referred for a full clinical evaluation at the Alzheimer Clinic.

Since controls were collected from the CSHA, they should be relatively free of biases inherent by the solicitation of volunteers. The CSHA controls did not include individuals showing mild forms of cognitive loss and/or those in the very early stages of dementia which would be included if a screening process were not used. The

present study only included controls for whom data collection was complete at the time of analysis for this study (April 1992). Follow-up of CSHA controls and their relatives is still in progress.

## 2.4 Relatives of Controls

Control family history data were collected in a similar manner to case family history data, ie. a direct interview using standardized questionnaires, multiple knowledgable informants and followed-up by obtaining medical records when possible.

## 2.5 Analysis

### 2.51 Overview

The family history information collected for studies of this type represents lifetime data. In the majority of situations where the risk to develop a disease is being evaluated among family aggregates, the genotype of an unaffected individual is rarely in question. However, for a late-onset disease such as AD, some data must be "right-censored". For AD the "right-censored" data represent those individuals who are potentially susceptible but who either die before their predicted age-of-onset, or are studied before their age-of-onset. In other words, being unaffected does not necessarily reflect the genotype, but rather the timing of chance events, ie. time of study or age-of-death. The data cannot be properly analyzed without taking into account these "right-censored" individuals.

One method that has been widely used to calculate lifetime risk for diseases where the disease onset is relatively late in life is the Kaplan-Meier method. This method uses information from all individuals to estimate age-specific risks (Kaplan and Meier, 1958).

At the time the family histories were collected, some susceptible individuals (first-degree relatives) will already exhibit symptoms of AD, allowing the true risk function to be calculated. Individuals who represent "right-censored" data are also essential for the calculation of this risk function as they contribute to the age-specific risk estimates by representing the decreasing numbers of individuals "at risk" with increasing age. The risk of an unaffected, susceptible individual becoming affected represents the conditional probability for an individual to succumb to the disease at a particular age. A chain multiplication of conditional probabilities is necessary to determine the true risk, due to the decreasing number of "at-risk" individuals with increasing age. For example, under an autosomal dominant model of inheritance, a 50% risk to first-degree relatives of AD cases would not be expected to be consistently observed due to either deaths from competing causes prior to disease onset or study being "too early" for disease manifestation in some of these "at-risk" individuals.

The Kaplan-Meier method has several advantages for this study. The first is that it is a non-parametric risk estimation method, thus no assumption is made about the age-of-onset distribution among affected relatives. It is known that for AD, intra-familial ages-of-onset tend to be more similar than inter-familial ages-of-onset (Bird

et al., 1989). However, making the assumption that the age-of-onset distributions of all cases, all affected relatives of cases and all affected relatives of controls are identical may be incorrect if factors other than a simple autosomal dominant gene(s) play a role in disease etiology as is suggested by the evidence for heterogeneity in the etiology of AD. Another advantage of the Kaplan-Meier method is that it allows for a direct comparison of lifetime risk estimates with the lifetime risk estimates calculated by previous studies using similar/identical methods (Table 1.3).

The major disadvantage of utilizing the Kaplan-Meier method results from the use of a database constrained by the imprecision of assigning an age-of-onset for AD, a common problem with this disease because of the insidious, gradual onset. Age-of-onset is usually assigned retrospectively, after the repeated review of past medical records and questioning of knowledgable informants, as is the practice at the Alzheimer Clinic (see Section 2.2). When this proves impossible, a conservative method for estimating age-of-onset is to consider the individual unaffected to the latest possible age. This method has been successfully utilized previously (Sadovnick et al., 1989). Possible implications of this approximation are considered later in this thesis (see Section 3.8).

The Kaplan-Meier method of risk estimation should yield meaningful risk estimates based on the assumption that the sample analyzed contains an affected individual with an age-of-onset at the limit of the age-of-onset distribution (ie. the sample contains an individual becoming affected at the oldest age possible. The risk calculated for this oldest age-of-onset represents cumulative lifetime risk). The large

size of the sample in this current study minimizes the likelihood of violating this assumption.

## 2.52 Computational Formulas

The SAS statistical package (SAS, 1985) was utilized for data analyses. The age-specific risk estimate can be defined in the following terms: the data set contains observations on N relatives with M ordered, distinct onset times denoted as $(t_1 < t_2 < ... < t_M)$. The possibility of more than one onset at each $t_m$ is allowed with $d_m$ representing the number of onsets at $t_m$. There are also a number of censoring times, $e_m$, for individuals who do not display symptoms at the time of study or have died before their age-of-onset. Since there may be some censored observations in $[0, t_1]$, the total sample size is $N = e_0 + \Sigma_{m=1}^M (d_m + e_m)$. The total number of relatives at risk at $t_m$ is $n_m = \Sigma_{j=m}^M (d_j + e_j)$. The product-limit survivor function, or empirical survivor function, S(t), is therefore defined as:

$$S(t_m) = \prod_{j=1}^m \frac{n_j - d_j}{n_j}$$

where $n_j - d_j / n_j$ represents the fraction of those relatives at risk in each interval who do not become affected. If a censoring time $e_m$, and an onset time $t_m$ are recorded as equal, the censoring times are adjusted an infinitesimal amount to the right so that $e_m$ is considered to be infinitesimally larger than $t_m$. In other words, any relative with a censoring age equal to $t_m$ is included in the set of $n_m$ relatives at risk at $t_m$, as are

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relatives who become affected at $t_m$. The empirical cumulative distribution function, $F(t)$, is then $F(t) = 1 - S(t)$.

The estimated variance $\sigma^2$ of $S(t_m)$ can be calculated using Greenwood's formula (Kaplan and Meier, 1958), defined as:

$$\sigma_m^2 = S^2(t_m)\Sigma_{j=1}^m \frac{d_j}{n_j(n_j - d_j)}$$

Differences between independently estimated lifetime risk curves will be assessed for significance using the Mantel-Haenszel test, called a "log-rank" test in the survival context. This test has been used in several previous studies, and was selected for this study primarily because it places more weight on older onset ages. The log-rank test can be defined as follows. Assume two risk curves are defined for subgroup 0 and subgroup 1. Let $(t_1 < \ldots < t_M)$ be the distinct, ordered ages-of-onset for the two subgroups together. Let $d_{mk}$ be the number of onset times equal to $t_m$ in the subgroup k, k = 0, 1, and define $e_{mk}$ as the number of observations censored by death or study occurring before the age-of-onset from sample k in the interval $(t_m, t_{m+1})$. The number at risk from each subgroup is then $n_{mk} = \Sigma_{j=1}^m (d_{jk} + e_{jk})$. The total number of observations in each subgroup is $N_k = e_{0k} + \{\Sigma_{j=1}^I (d_{ik} + e_{ik})\}$. As well, the quantities $d_m = d_{m0} + d_{m1}$, $n_m = n_{m0} + n_{m1}$, and $N = N_0 + N_1$ for the combined subgroups are defined. The observations at each $t_m$ can then be displayed in a $2 \times 2$ contingency table with expressions representing those individuals at risk from each sample, and whether they become affected or remain unaffected:

At $t_m$

| Subgroup | Total Onsets | Total Unaffecteds | Total At Risk |
|---|---|---|---|
| 0 | $d_{m0}$ | $n_{m0} - d_{m0}$ | $n_{m0}$ |
| 1 | $d_{m1}$ | $n_{m1} - d_{m1}$ | $n_{m1}$ |
|  | $d_m$ | $n_m - d_m$ | $n_m$ |

The significance of an assumed constant odds ratio of relative risk from independent $2 \times 2$ tables can then be assessed. For example, the $O_{m1}$ observed number of onsets in subgroup 1 at $t_m$ is $d_{m1}$ whereas the expected number of onsets, assuming the risk is equal between the two subgroups, is $E_{m1} = (n_{m1} \times d_m/n_m)$ (the number at risk from the first sample multiplied by the risk estimated from the combined sample). The durations in these predictions are then summarized by adding over the tables for the distinct ages-of-onset $t_m$, the difference between the observed, $O_{m1}$, and expected, $E_{m1}$, number of disease onsets to obtain $O_1$-$E_1$ $=\Sigma_{m=1}^{M} (O_{m1}-E_{m1})$. The log rank test statistic is then $(O_1 - E_1)^2/V$, with the variance, $V$, defined as:

$$V = \Sigma_{m=1}^{M} \frac{n_{i0}n_{i1}d_i(n_i-d_i)}{(n_i)^2(n_i-1)}$$

the log-rank test, under the assumption of equal risk in the two subgroups, is distributed approximately as Chi-Square with one degree of freedom (df). Note that this statistic allows for differences between the lifetime risk curves in either direction (reviewed by Crowley, 1984).

Differences in the estimated cumulative lifetime incidence were assessed using a difference of proportions test. This difference can be assessed by the following statistic:

$$Z = \frac{|\hat{p}_2 - \hat{p}_1|}{\{(\sigma_1)^2 + (\sigma_2)^2\}^{1/2}}$$

where $\hat{p}_1$ and $\hat{p}_2$ are the two sample proportion estimates, and $(\sigma_1)^2$ and $(\sigma_2)^2$ are the estimated sample proportion variances. If Z exceeds the critical value obtained from the standard normal curve for a specified significance level $\alpha$, the proportions $p_1$ and $p_2$ are considered to be unequal (reviewed by Fleiss, 1981).

## 2.6 Risk Comparison

### 2.61 Overview

The comparison of lifetime risk curves and cumulative lifetime risks for various subgroups of first-degree relatives of cases and controls should provide insight into the genetic etiology of AD. If an age dependant autosomal dominant gene(s) which is fully penetrant by the end of the human lifespan is responsible for all cases of AD as has been suggested (see Table 1.3), cumulative lifetime risks and lifetime risk curves for female and male first-degree relatives, as well as parents and sibs of AD cases should be equal and should approach 50% by the oldest ages (age 80-90). These risk curves should resemble a sigmoid curve asymptotic to a final lifetime risk of 50% if: (i) the gene(s) is fully expressed within the age range of the sample and (ii) age-of-onset follows a normal distribution (St. George-Hyslop et al., 1989).

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Under the same model, first-degree relatives of controls should have a risk to develop the disease of approximately 0% (assuming the gene is rare). This 0% risk is purely hypothetical since the collection of a totally homogeneous potentially unaffected group of controls is highly unlikely. Alternatively, if AD is not strictly inherited in an autosomal dominant fashion, but a genetic component to the etiology of the disease does exist, then the risk to first-degree relatives of cases should be higher (but less than 50%) than that to first-degree relatives of controls.

## 2.62 Criteria and Analysis for FAD

The following criteria used by this study and the Alzheimer Clinic for accepting a family as representing FAD are recognized to be quite stringent and thus identify a relatively conservative group as FAD. This was done in an attempt to exclude those families in which non-genetic clustering occurs (ie. phenocopies), and appears to follow an autosomal dominant model of inheritance. The criteria are as follows:

1. Detailed family history must be available for at least the case's generation and the previous generation.

2. Good clinical documentation of dementia in relatives, preferably from at least two separate sibships within the family, must be available; and there must be no other possible explanation for the dementia (eg. infarcts, strokes, alcoholism, head injury, etc.).

3. Neuropathologic documentation of AD must be available for at least one

member of the family, but preferably for two or more.

4. Accurate information on ages of death and/or present ages of relatives must be available so that it is possible to assess the "significance" of being clinically unaffected.

Data on first-degree relatives of cases will also be analyzed according to how "affected" relatives are included. Families meeting the criteria for FAD will be included in the overall risk calculations for first-degree relatives of cases in order to directly compare risk estimates with those calculated for previous studies (see Table 1.3). These families will also be analyzed separately to assess whether the criteria used to distinguish FAD families results in a subset of AD families for which the lifetime risk is in fact compatible with an autosomal dominant model of transmission. Identifying these families is increasingly important as molecular genetic studies pursue linkage analyses.

## 2.63 Risk Comparisons for Sample Subgroups

The data on first-degree relatives represent relatively unbiased samples from the entire B.C. population. Therefore, results of analyses offer important information about lifetime risks to first-degree relatives of elderly individuals either affected or unaffected with AD. Subgroups of first-degree relatives of cases and controls can be identified and allow meaningful analyses due to the relatively large sample for this study. This sample represents the largest of its kind reported to date, and as a result,

estimation of risk to various subgroups will not have the large standard error of most previous studies (see Table 1.3).

Table 2.1 shows the subgroups for which age-specific and cumulative lifetime risks will be calculated and compared using the Kaplan-Meier estimates. Differences in lifetime risk curves will be assessed for significance using the log-rank test with differences being considered significant at $\alpha = .05$. Differences in cumulative lifetime risk estimates will be assessed for significance using a difference of proportions test. Results will also be considered significant at $\alpha = .05$.

Based on previous estimates, this study should provide adequate sensitivity in detecting significant differences between the cumulative lifetime risks to various subgroups of first-degree relatives. If it is assumed that the risk estimates for present data set will approximate those from the earlier study (23.3 ± 3.8% to first-degree relatives of AD cases) (Sadovnick et al., 1989), a difference in cumulative lifetime risk of approximately 15% will be detected at a significance level of $\alpha = .05$ and a power of 1-ß = .80. This level of sensitivity is believed to be more than adequate to detect differences between a hypothesized 50% cumulative lifetime risk to first-degree relatives of AD probands under an autosomal dominant transmission model and the previously calculated 23.3% risk (1-ß = .999 at a significance level of $\alpha = .05$). Since subgroups of first-degree relatives represent a smaller sample size than the entire sample of first-degree relatives, the detectable differences in cumulative lifetime risk between subgroups will be greater than the approximately 15% detectable when comparing the entire sample.

**Table 2.1: First-Degree Relative Subgroup Comparisons**

1) First-Degree Relatives of Cases vs First-Degree Relatives of Controls
2) Female First-Degree Relatives of Cases vs Female First-Degree Relatives of Controls
3) Male First-Degree Relatives of Cases vs Male First-Degree Relatives of Controls
4) Female First-Degree Relatives of Cases vs Male First-Degree Relatives of Cases
5) Female First-Degree Relatives of Controls vs Male First-Degree Relatives of Controls
6) Parents of Cases vs Parents of Controls
7) Sibs of Cases vs Sibs of Controls
8) Parents of Cases vs Sibs of Cases
9) Parents of Controls vs Sibs of Controls
10) First-Degree Relatives of Early-Onset Cases (onset age $<65$) vs First-Degree Relatives of Late-Onset Cases (onset age $\geq 65$)

# 3 RESULTS

## 3.1 Sample Analyzed

### 3.11 Cases

Table 3.1 summarizes the diagnosis of all 883 Alzheimer Clinic cases after full

clinical assessment. Informative and complete family histories were available for

three hundred thirty eight (38%) cases diagnosed as either "probable" AD (N=316)

or subsequent to clinic assessment as "autopsy-confirmed" (N=22) AD. Table 3.2

gives the number and percentage of affected relatives in each subgroup of first-degree

relatives of cases. The case family histories represent data on 1867 first-degree

relatives (parents=676, sibs=1191) of 338 index cases.

Eighteen of the families (5.36%) met the Alzheimer Clinic's criteria for FAD

and are included in the risk calculations for the entire sample of first-degree relatives

of cases as well as separately under the "FAD only" criteria. Under the "FAD only"

criteria, 30 of 106 first-degree relatives are considered affected.

### 3.12 Controls

Informative and complete family histories were available for 351 consecutive,

unrelated controls and 1873 of their first degree relatives (parents=702, sibs=1171)

from the CSHA at the time of analysis. Table 3.3 shows the number and percentage

of affected first-degree relatives of controls in each subgroup. Of the 351 controls,

only two were identified from the institution sample (0.57%). Eighteen of 351

**Table 3.1: Diagnosis for 883 Alzheimer Clinic Patients After Evaluation***

| Clinic Diagnosis | No. | % of Total |
|---|---|---|
| Demented, Alzheimer Unlikely | 67 | 7.59 |
| Demented, Possible Alzheimer | 230 | 26.04 |
| Demented, Probable Alzheimer | 357 | 40.43 |
| Autopsy Confirmed Alzheimer | 30 | 3.40 |
| Not Demented | 199 | 22.53 |
| Total | 883[¶] | 100.00 |

*Seen during period 1985 to 1991

[¶]Total number of patients for whom diagnosis was made at time of analyses

**Table 3.2: Number and Percent of Affected First-Degree Relatives in Each Case Subgroup**

| Relative | Total No. | No. Affected* | % Affected* |
|---|---|---|---|
| Females | 937 | 84 | 8.96 |
| Males | 930 | 30 | 3.23 |
| Parents | 676 | 72 | 10.64 |
| Sibs | 1191 | 42 | 3.53 |
| Relatives of Early-Onset Cases | 648 | 34 | 5.25 |
| Relatives of Late-Onset Cases | 1219 | 80 | 6.56 |
| All Relatives | 1867 | 114 | 6.11 |

*Numbers and percentages are not age-corrected risk.

controls, (5.13%), were given a full clinical examination as part of the CSHA after scoring 80 or above on the 3MS. None of these 18 individuals showed any signs of cognitive impairment and/or dementia after full clinical assessment.

**Table 3.3: Number and Percent of Affected First-Degree Relatives in Each Control Subgroup**

| Relative | Total No. | No. Affected[*] | % Affected[*] |
|----------|-----------|-----------------|---------------|
| Females | 955 | 17 | 1.78 |
| Males | 918 | 7 | 1.78 |
| Parents | 702 | 13 | 1.85 |
| Sibs | 1171 | 11 | .94 |
| All Relatives | 1873 | 24 | 1.28 |

[*]Numbers and percentages are not age-corrected risk.

**Table 3.4: Comparison of Cases and Controls**

| | Cases | Controls |
|---|-------|----------|
| Number of Females | 219 | 195 |
| Number of Males | 119 | 156 |
| Mean Age[§] | 72 ± 7.9[*] | 74.5 ± 6.3 |
| Mean Age-of-Onset of Dementia | 67 ± 8.4[*] | N/A |

[*]Standard Error.
[§]Mean age does not differ significantly ($t = .25$, $df = 687$, $p > .05$).

Table 3.4 shows a comparison of selected characteristics of cases and controls.

## 3.2 Risk Estimates for First-Degree Relatives of Cases and Controls

The Kaplan-Meier age specific risk estimates for first-degree relatives (parents and full sibs) of cases and controls are given in Table 3.5. The cumulative lifetime risk to first-degree relatives of cases is 26.73 ± 4.42% compared with 7.26 ± 2.74% for first-degree relatives of controls. This difference is statistically significant when evaluated with a difference of proportions test ($z=3.75$, $p<.001$). The lifetime risk curve for first-degree relatives of cases is significantly higher than that of first-degree relatives of controls after assessment by a log-rank test (Log Rank Chi-Square=87.13, $p<.001$). The lifetime risk curves for both groups of first-degree relatives are plotted in Figure 3.1. The risk for developing AD increases with age in both subgroups. Risk begins at an earlier age, and increases more rapidly for first-degree relatives of cases compared with controls, but the risk increases at greater rate at the later ages for both groups of relatives.

## 3.3 Risk Estimates for FAD

Table 3.6 gives the age specific lifetime risk estimates for first-degree relatives of cases under the "FAD only" criteria. These values are plotted in Figure 3.2. The cumulative lifetime risk for "FAD only" first-degree relatives increases more rapidly than when the total group of all first-degree relatives of cases is considered. The risk for the former reaches the expected 50% risk compatible with autosomal dominant

## Table 3.5: Age Specific Risks for First-Degree Relatives of Cases and Controls

| Age | Cases Risk (%) | S.E. | Controls Risk (%) | S.E. |
|-----|-----------|------|--------------|------|
| 35 | 0.00 | 0.00 | 0.00 | 0.00 |
| 36 | 0.06 | 0.06 | 0.00 | 0.00 |
| 37 | 0.06 | 0.06 | 0.00 | 0.00 |
| 38 | 0.12 | 0.08 | 0.00 | 0.00 |
| 39 | 0.18 | 0.11 | 0.00 | 0.00 |
| 40 | 0.24 | 0.12 | 0.00 | 0.00 |
| 41 | 0.24 | 0.12 | 0.00 | 0.00 |
| 42 | 0.24 | 0.12 | 0.06 | 0.06 |
| 43 | 0.24 | 0.12 | 0.06 | 0.06 |
| 44 | 0.31 | 0.14 | 0.06 | 0.06 |
| 45 | 0.31 | 0.14 | 0.06 | 0.06 |
| 46 | 0.31 | 0.14 | 0.06 | 0.06 |
| 47 | 0.31 | 0.14 | 0.06 | 0.06 |
| 48 | 0.31 | 0.14 | 0.06 | 0.06 |
| 49 | 0.31 | 0.14 | 0.06 | 0.06 |
| 50 | 0.37 | 0.15 | 0.06 | 0.06 |
| 51 | 0.37 | 0.15 | 0.06 | 0.06 |
| 52 | 0.44 | 0.17 | 0.06 | 0.06 |
| 53 | 0.57 | 0.19 | 0.06 | 0.06 |
| 54 | 0.57 | 0.19 | 0.06 | 0.06 |
| 55 | 0.57 | 0.19 | 0.06 | 0.06 |
| 56 | 0.57 | 0.19 | 0.06 | 0.06 |
| 57 | 0.71 | 0.21 | 0.06 | 0.06 |
| 58 | 0.78 | 0.23 | 0.06 | 0.06 |
| 59 | 0.86 | 0.24 | 0.13 | 0.09 |
| 60 | 1.08 | 0.27 | 0.13 | 0.09 |
| 61 | 1.16 | 0.28 | 0.13 | 0.09 |
| 62 | 1.39 | 0.31 | 0.13 | 0.09 |

continued

|       | Cases      |        | Controls   |        |
|-------|------------|--------|------------|--------|
| Age   | Risk (%)   | S.E.   | Risk (%)   | S.E.   |
| 63    | 1.47       | 0.32   | 0.13       | 0.09   |
| 64    | 1.64       | 0.34   | 0.13       | 0.09   |
| 65    | 1.89       | 0.37   | 0.13       | 0.09   |
| 66    | 2.08       | 0.40   | 0.13       | 0.09   |
| 67    | 2.36       | 0.42   | 0.13       | 0.09   |
| 68    | 2.46       | 0.44   | 0.22       | 0.13   |
| 69    | 2.67       | 0.46   | 0.40       | 0.18   |
| 70    | 3.43       | 0.54   | 0.50       | 0.20   |
| 71    | 3.68       | 0.56   | 0.60       | 0.23   |
| 72    | 4.30       | 0.63   | 0.70       | 0.25   |
| 73    | 5.11       | 0.70   | 0.82       | 0.28   |
| 74    | 5.97       | 0.78   | 0.94       | 0.30   |
| 75    | 7.03       | 0.87   | 0.94       | 0.30   |
| 76    | 7.57       | 0.92   | 1.22       | 0.36   |
| 77    | 8.16       | 0.97   | 1.37       | 0.39   |
| 78    | 9.00       | 1.05   | 1.37       | 0.39   |
| 79    | 9.97       | 1.14   | 1.56       | 0.43   |
| 80    | 13.03      | 1.41   | 1.56       | 0.43   |
| 81    | 14.86      | 1.56   | 1.56       | 0.43   |
| 82    | 15.86      | 1.65   | 2.80       | 0.70   |
| 83    | 16.59      | 1.71   | 2.80       | 0.70   |
| 84    | 17.01      | 1.75   | 3.10       | 0.76   |
| 85    | 18.99      | 1.97   | 3.10       | 0.76   |
| 86    | 18.99      | 1.97   | 3.54       | 0.87   |
| 87    | 19.87      | 2.14   | 4.06       | 1.01   |
| 88    | 23.07      | 2.74   | 4.06       | 1.01   |
| 89    | 23.07      | 2.74   | 4.76       | 1.22   |
| 90    | 23.07      | 2.74   | 4.76       | 1.22   |
| 91    | 23.07      | 2.74   | 4.76       | 1.22   |

continued

|      | Cases | | Controls | |
| --- | --- | --- | --- | --- |
| Age | Risk (%) | S.E. | Risk (%) | S.E. |
| 92 | 23.07 | 2.74 | 4.76 | 1.22 |
| 93 | 23.07 | 2.74 | 4.76 | 1.22 |
| 94 | 23.07 | 2.74 | 4.76 | 1.22 |
| 95 | 26.73 | 4.42 | 7.26 | 2.74 |

**Table 3.6: Age Specific Risks for First-Degree Relatives of Cases from FAD Families**

| Age | Risk (%) | S.E. |
|---|---|---|
| 35 | 0.00 | 0.00 |
| 36 | 1.01 | 1.00 |
| 37 | 1.01 | 1.00 |
| 38 | 2.04 | 1.43 |
| 39 | 3.07 | 1.75 |
| 40 | 4.10 | 2.01 |
| 41 | 4.10 | 2.01 |
| 42 | 4.10 | 2.01 |
| 43 | 4.10 | 2.01 |
| 44 | 5.16 | 2.25 |
| 45 | 5.16 | 2.25 |
| 46 | 5.16 | 2.25 |
| 47 | 5.16 | 2.25 |
| 48 | 5.16 | 2.25 |
| 49 | 5.16 | 2.25 |
| 50 | 5.16 | 2.25 |
| 51 | 5.16 | 2.25 |
| 52 | 5.16 | 2.25 |
| 53 | 6.34 | 2.51 |
| 54 | 6.34 | 2.51 |
| 55 | 6.34 | 2.51 |
| 56 | 6.34 | 2.51 |
| 57 | 8.91 | 3.03 |
| 58 | 10.25 | 3.27 |
| 59 | 11.61 | 3.49 |
| 60 | 14.33 | 3.88 |
| 61 | 14.33 | 3.88 |
| 62 | 15.81 | 4.08 |
| 63 | 15.81 | 4.08 |
| 64 | 17.34 | 4.28 |

continued

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| Age | Risk (%) | S.E. |
|---|---|---|
| 65 | 17.34 | 4.28 |
| 66 | 18.99 | 4.51 |
| 67 | 22.51 | 4.95 |
| 68 | 24.27 | 5.14 |
| 69 | 24.27 | 5.14 |
| 70 | 29.95 | 5.71 |
| 71 | 31.95 | 5.88 |
| 72 | 31.95 | 5.88 |
| 73 | 34.22 | 6.11 |
| 74 | 34.22 | 6.11 |
| 75 | 36.57 | 6.33 |
| 76 | 36.57 | 6.33 |
| 77 | 41.86 | 6.81 |
| 78 | 41.86 | 6.81 |
| 79 | 41.86 | 6.81 |
| 80 | 41.86 | 6.81 |
| 81 | 51.04 | 7.52 |
| 82 | 51.04 | 7.52 |
| 83 | 51.04 | 7.52 |
| 84 | 55.12* | 7.93 |

*Cumulative lifetime risk reaches predicted 50% by age 84.

Figure 3.1: Risk to First-Degree
Relatives of Cases and Controls
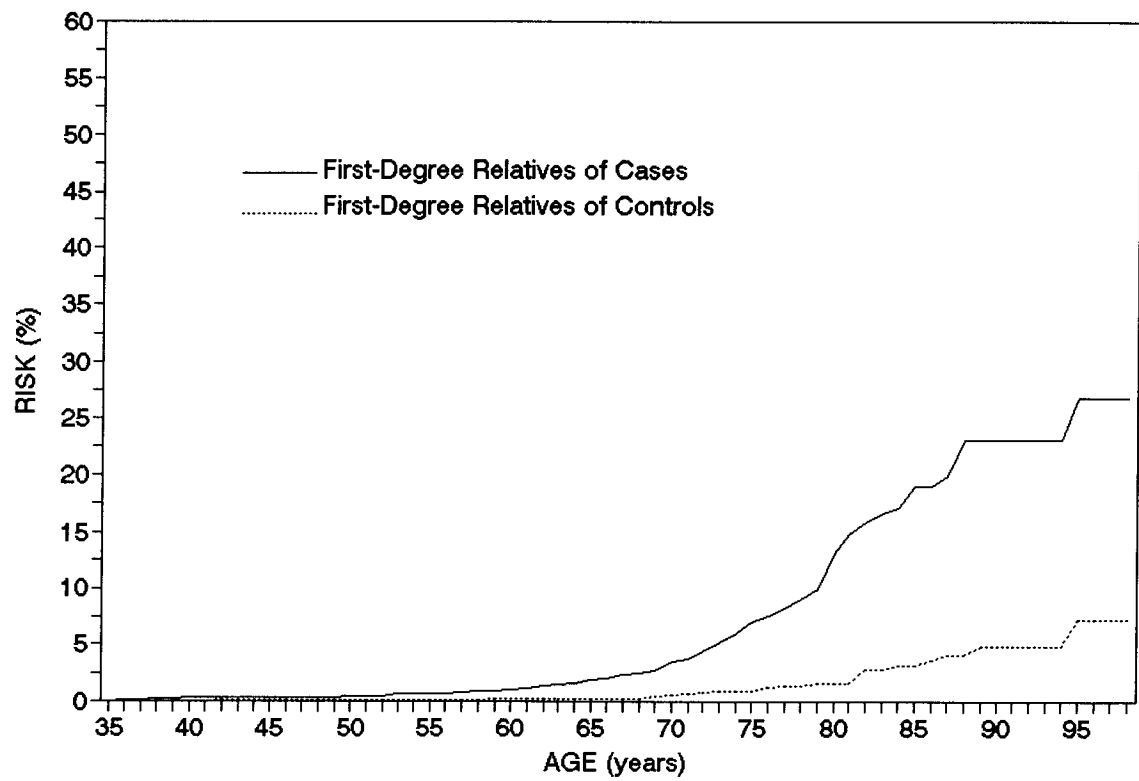
Figure 3.2: Risk to First-Degree
Relatives of FAD Families
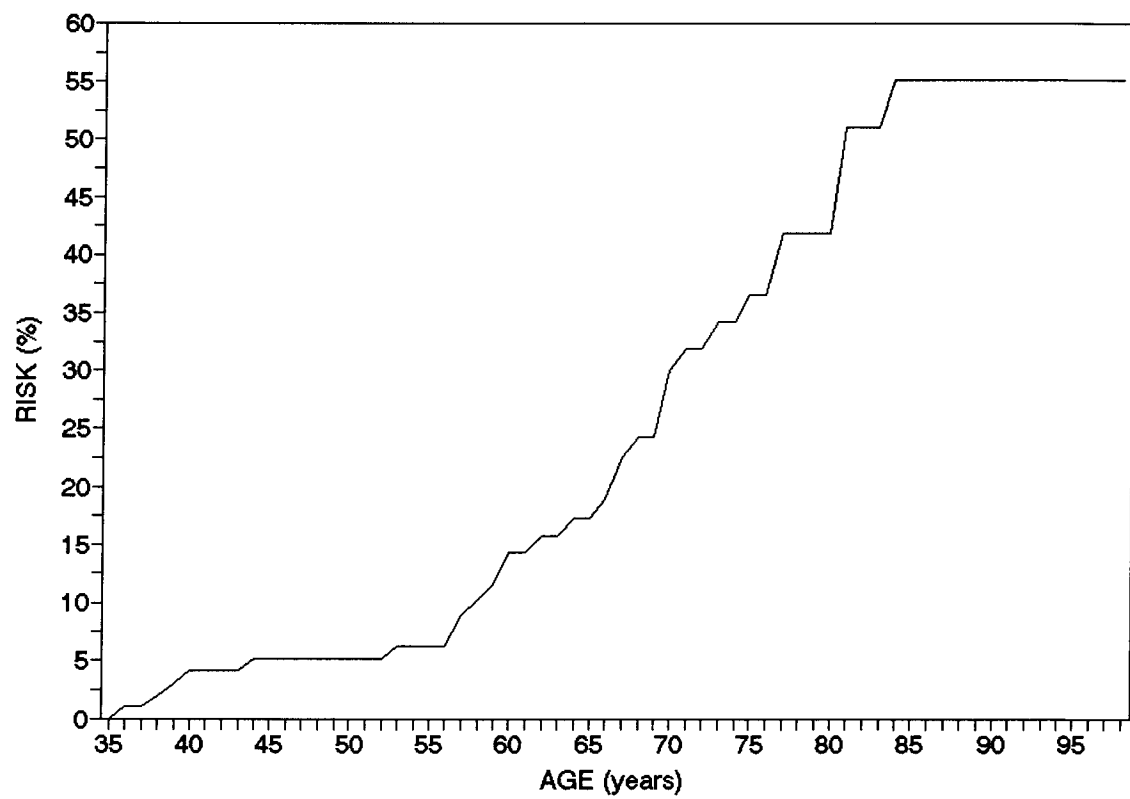
transmission by the late ages of life (age 84).

## 3.4 Risk Estimates for Female and Male First-Degree Relatives of Cases and Controls

### 3.41 Risk Estimates for Female First-Degree Relatives of Cases and Controls

Age specific risks for female first-degree relatives of cases and controls are given in Table 3.7. Female first-degree relatives of cases show a significantly higher cumulative lifetime risk than female first-degree relatives of controls (28.97 ± 3.60%, 6.14 ± 1.78%, z=5.72, p<.001). Figure 3.3 plots the lifetime risk curves for female first-degree relatives of cases and controls. The curves show that the risk for female first-degree relatives of cases is significantly higher than that to first-degree female relatives of controls throughout their lifetime (Log Rank Chi-Square=68.56, df=1, p<.001). The risk to female first-degree relatives of cases begins at an earlier age and increases more rapidly than the risk to first-degree relatives of controls.

### 3.42 Risk Estimates for Male First-Degree Relatives of Cases and Controls

The first-degree male relative subgroups of cases and controls also show an increase in risk with age. Male first-degree relatives of cases show a much higher, yet statistically non-significant cumulative lifetime risk when compared to male first-degree relatives of controls (22.03 ± 8.29%, 9.44 ± 6.79%, z=1.18, p<.23), as shown in Table 3.8. The large difference in cumulative risk estimates between the two male first-degree relative subgroups may be significant. However, due to the large

standard errors assumed by the cumulative lifetime risk estimates, even in a sample of this size, the possible significance in risk may not be detectable. This standard error reflects the extremely low number of males alive at the extreme older ages, which will, of course, result in very low number of affected males at these same ages. Canadian census data show 49.45% of the total Canadian population is male while this percentage drops rapidly to 44.08% by ages 70-74, 41.20% by ages 75-79, 37.61% by ages 80-84 and 30.32% by ages $\geq 85$ (Statistics Canada, 1986). Figure 3.4 shows that from age 82 to age 95, no male first-degree relatives of controls are considered to become affected. One individual has an age-of-onset at age 95, but this is an instance of using an individual's last known age when definitely affected in place of an unknown age-of-onset (see section 2.51). This single age-of-onset results in a very large increase in risk (2.47% to 9.44%) over a 1 year time interval. It would be safe to assume that this individual had a true age-of-onset before age 95. This would result in a decrease in the final cumulative lifetime risk estimate. For example, if this single individual had an age-at-onset 8.5 years before the family history was collected (the average for first-degree relatives of controls), the final cumulative lifetime risk for male first-degree relatives of controls could be calculated at 3.93 ± 1.81%. This lower cumulative lifetime risk estimate for male first-degree relatives of controls would be significantly lower than that for male first-degree relatives of cases (z=2.13, p<.04).

Although the final cumulative lifetime risk for the two male subgroups was not found to differ significantly in this sample, the lifetime risk to first-degree

**Table 3.7: Age Specific Risks for Female**
**First-Degree Relatives of Cases and Controls**

| | Cases | | Controls | |
| --- | --- | --- | --- | --- |
| Age | Risk (%) | S.E. | Risk (%) | S.E. |
| 37 | 0.00 | 0.00 | 0.00 | 0.00 |
| 38 | 0.12 | 0.12 | 0.00 | 0.00 |
| 39 | 0.24 | 0.17 | 0.00 | 0.00 |
| 40 | 0.24 | 0.17 | 0.00 | 0.00 |
| 41 | 0.24 | 0.17 | 0.00 | 0.00 |
| 42 | 0.24 | 0.17 | 0.00 | 0.00 |
| 43 | 0.24 | 0.17 | 0.00 | 0.00 |
| 44 | 0.36 | 0.21 | 0.00 | 0.00 |
| 45 | 0.36 | 0.21 | 0.00 | 0.00 |
| 46 | 0.36 | 0.21 | 0.00 | 0.00 |
| 47 | 0.36 | 0.21 | 0.00 | 0.00 |
| 48 | 0.36 | 0.21 | 0.00 | 0.00 |
| 49 | 0.36 | 0.21 | 0.00 | 0.00 |
| 50 | 0.48 | 0.24 | 0.00 | 0.00 |
| 51 | 0.48 | 0.24 | 0.00 | 0.00 |
| 52 | 0.61 | 0.27 | 0.00 | 0.00 |
| 53 | 0.86 | 0.33 | 0.00 | 0.00 |
| 54 | 0.86 | 0.33 | 0.00 | 0.00 |
| 55 | 0.86 | 0.33 | 0.00 | 0.00 |
| 56 | 0.86 | 0.33 | 0.00 | 0.00 |
| 57 | 0.99 | 0.35 | 0.00 | 0.00 |
| 58 | 1.13 | 0.38 | 0.00 | 0.00 |
| 59 | 1.13 | 0.38 | 0.13 | 0.13 |
| 60 | 1.42 | 0.43 | 0.13 | 0.13 |
| 61 | 1.42 | 0.43 | 0.13 | 0.13 |
| 62 | 1.86 | 0.49 | 0.13 | 0.13 |
| 63 | 2.01 | 0.52 | 0.13 | 0.13 |

continued

| | Cases | | Controls | |
|---|---|---|---|---|
| Age | Risk (%) | S.E. | Risk (%) | S.E. |
| 64 | 2.32 | 0.56 | 0.13 | 0.13 |
| 65 | 2.64 | 0.60 | 0.13 | 0.13 |
| 66 | 2.81 | 0.62 | 0.13 | 0.13 |
| 67 | 3.16 | 0.67 | 0.13 | 0.13 |
| 68 | 3.34 | 0.69 | 0.29 | 0.20 |
| 69 | 3.54 | 0.72 | 0.62 | 0.31 |
| 70 | 4.54 | 0.84 | 0.79 | 0.36 |
| 71 | 4.76 | 0.87 | 0.97 | 0.40 |
| 72 | 5.44 | 0.94 | 0.97 | 0.40 |
| 73 | 6.88 | 1.10 | 1.18 | 0.45 |
| 74 | 7.92 | 1.20 | 1.40 | 0.50 |
| 75 | 9.00 | 1.31 | 1.40 | 0.50 |
| 76 | 9.96 | 1.40 | 1.65 | 0.55 |
| 77 | 10.64 | 1.47 | 1.91 | 0.61 |
| 78 | 11.37 | 1.55 | 1.91 | 0.61 |
| 79 | 13.01 | 1.72 | 1.91 | 0.61 |
| 80 | 17.26 | 2.10 | 1.91 | 0.61 |
| 81 | 19.73 | 2.31 | 1.91 | 0.61 |
| 82 | 20.80 | 2.40 | 3.10 | 0.91 |
| 83 | 21.95 | 2.50 | 3.10 | 0.91 |
| 84 | 22.59 | 2.56 | 3.57 | 1.03 |
| 85 | 25.59 | 2.87 | 3.57 | 1.03 |
| 86 | 25.59 | 2.87 | 4.27 | 1.23 |
| 87 | 25.59 | 2.87 | 5.07 | 1.46 |
| 88 | 28.97 | 3.60 | 5.07 | 1.46 |
| 89 | 28.97 | 3.60 | 6.14 | 1.79 |

## Table 3.8: Age Specific Risks for Male First-Degree Relatives of Cases and Controls

| Age | Cases | | Controls | |
| --- | --- | --- | --- | --- |
| | Risk (%) | S.E. | Risk (%) | S.E. |
| 35 | 0.00 | 0.00 | 0.00 | 0.00 |
| 36 | 0.12 | 0.12 | 0.00 | 0.00 |
| 37 | 0.12 | 0.12 | 0.00 | 0.00 |
| 38 | 0.12 | 0.12 | 0.00 | 0.00 |
| 39 | 0.12 | 0.12 | 0.00 | 0.00 |
| 40 | 0.25 | 0.18 | 0.00 | 0.00 |
| 41 | 0.25 | 0.18 | 0.00 | 0.00 |
| 42 | 0.25 | 0.18 | 0.13 | 0.13 |
| 43 | 0.25 | 0.18 | 0.13 | 0.13 |
| 44 | 0.25 | 0.18 | 0.13 | 0.13 |
| 45 | 0.25 | 0.18 | 0.13 | 0.13 |
| 46 | 0.25 | 0.18 | 0.13 | 0.13 |
| 47 | 0.25 | 0.18 | 0.13 | 0.13 |
| 48 | 0.25 | 0.18 | 0.13 | 0.13 |
| 49 | 0.25 | 0.18 | 0.13 | 0.13 |
| 50 | 0.25 | 0.18 | 0.13 | 0.13 |
| 51 | 0.25 | 0.18 | 0.13 | 0.13 |
| 52 | 0.25 | 0.18 | 0.13 | 0.13 |
| 53 | 0.25 | 0.18 | 0.13 | 0.13 |
| 54 | 0.25 | 0.18 | 0.13 | 0.13 |
| 55 | 0.25 | 0.18 | 0.13 | 0.13 |
| 56 | 0.25 | 0.18 | 0.13 | 0.13 |
| 57 | 0.40 | 0.23 | 0.13 | 0.13 |
| 58 | 0.40 | 0.23 | 0.13 | 0.13 |
| 59 | 0.56 | 0.28 | 0.13 | 0.13 |
| 60 | 0.71 | 0.32 | 0.13 | 0.13 |
| 61 | 0.88 | 0.36 | 0.13 | 0.13 |
| 62 | 0.88 | 0.36 | 0.13 | 0.13 |

continued

| | Cases | | Controls | |
|---|---|---|---|---|
| Age | Risk (%) | S.E. | Risk (%) | S.E. |
| 63 | 0.88 | 0.36 | 0.13 | 0.13 |
| 64 | 0.88 | 0.36 | 0.13 | 0.13 |
| 65 | 1.06 | 0.40 | 0.13 | 0.13 |
| 66 | 1.26 | 0.45 | 0.13 | 0.13 |
| 67 | 1.47 | 0.49 | 0.13 | 0.13 |
| 68 | 1.47 | 0.49 | 0.13 | 0.13 |
| 69 | 1.70 | 0.54 | 0.13 | 0.13 |
| 70 | 2.18 | 0.64 | 0.13 | 0.13 |
| 71 | 2.44 | 0.69 | 0.13 | 0.13 |
| 72 | 3.00 | 0.79 | 0.37 | 0.27 |
| 73 | 3.00 | 0.79 | 0.37 | 0.27 |
| 74 | 3.64 | 0.91 | 0.37 | 0.27 |
| 75 | 4.66 | 1.07 | 0.37 | 0.27 |
| 76 | 4.66 | 1.07 | 0.69 | 0.42 |
| 77 | 5.12 | 1.16 | 0.69 | 0.42 |
| 78 | 6.12 | 1.34 | 0.69 | 0.42 |
| 79 | 6.12 | 1.34 | 1.14 | 0.62 |
| 80 | 7.38 | 1.60 | 1.14 | 0.62 |
| 81 | 8.17 | 1.77 | 1.14 | 0.62 |
| 82 | 9.04 | 1.95 | 2.47 | 1.11 |
| 83 | 9.04 | 1.95 | 2.47 | 1.11 |
| 84 | 9.04 | 1.95 | 2.47 | 1.11 |
| 85 | 9.04 | 1.95 | 2.47 | 1.11 |
| 86 | 9.04 | 1.95 | 2.47 | 1.11 |
| 87 | 11.37 | 2.99 | 2.47 | 1.11 |
| 88 | 14.23 | 4.03 | 2.47 | 1.11 |
| 89 | 14.23 | 4.03 | 2.47 | 1.11 |
| 90 | 14.23 | 4.03 | 2.47 | 1.11 |
| 91 | 14.23 | 4.03 | 2.47 | 1.11 |

continued

| | Cases | | Controls | |
| --- | --- | --- | --- | --- |
| Age | Risk (%) | S.E. | Risk (%) | S.E. |
| 92 | 14.23 | 4.03 | 2.47 | 1.11 |
| 93 | 14.23 | 4.03 | 2.47 | 1.11 |
| 94 | 14.23 | 4.03 | 2.47 | 1.11 |
| 95 | 22.03 | 8.29 | 9.44 | 6.79 |

Figure 3.3: Risk to Female First-Degree
Relatives of Cases and Controls

Figure 3.4: Risk to Male First-Degree
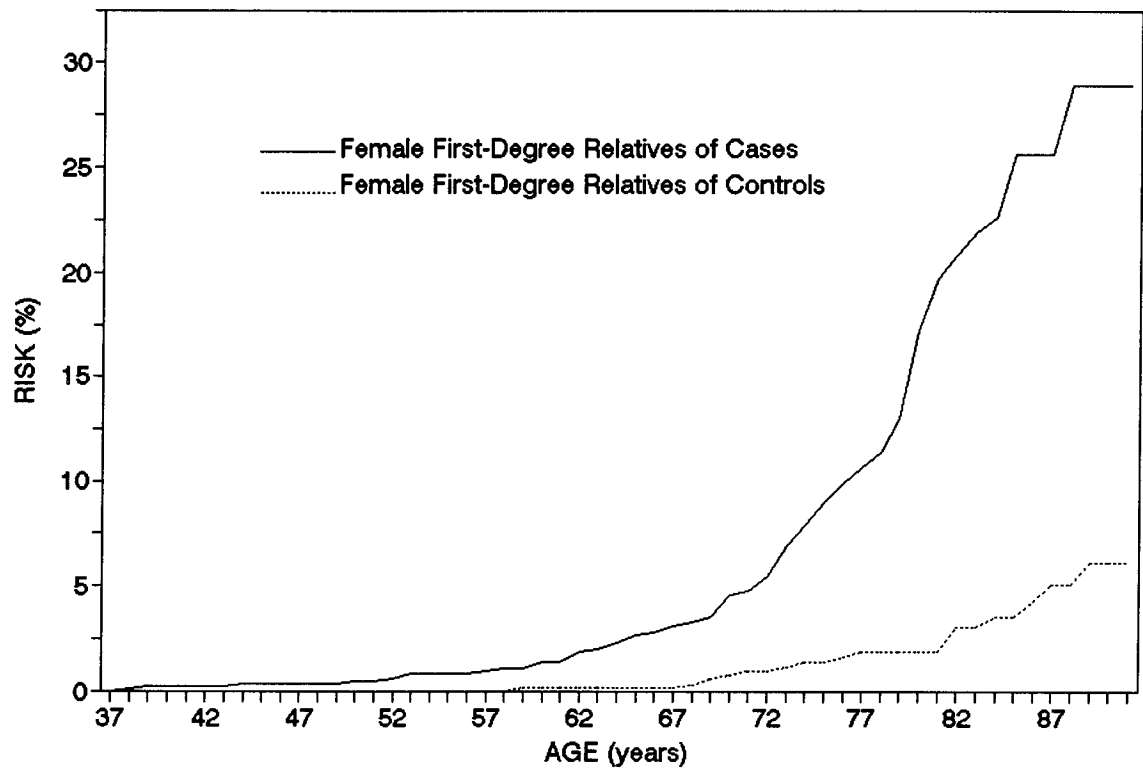Relatives of Cases and Controls

——— Male First-Degree Relatives of Cases
············ Male First-Degree Relatives of Controls
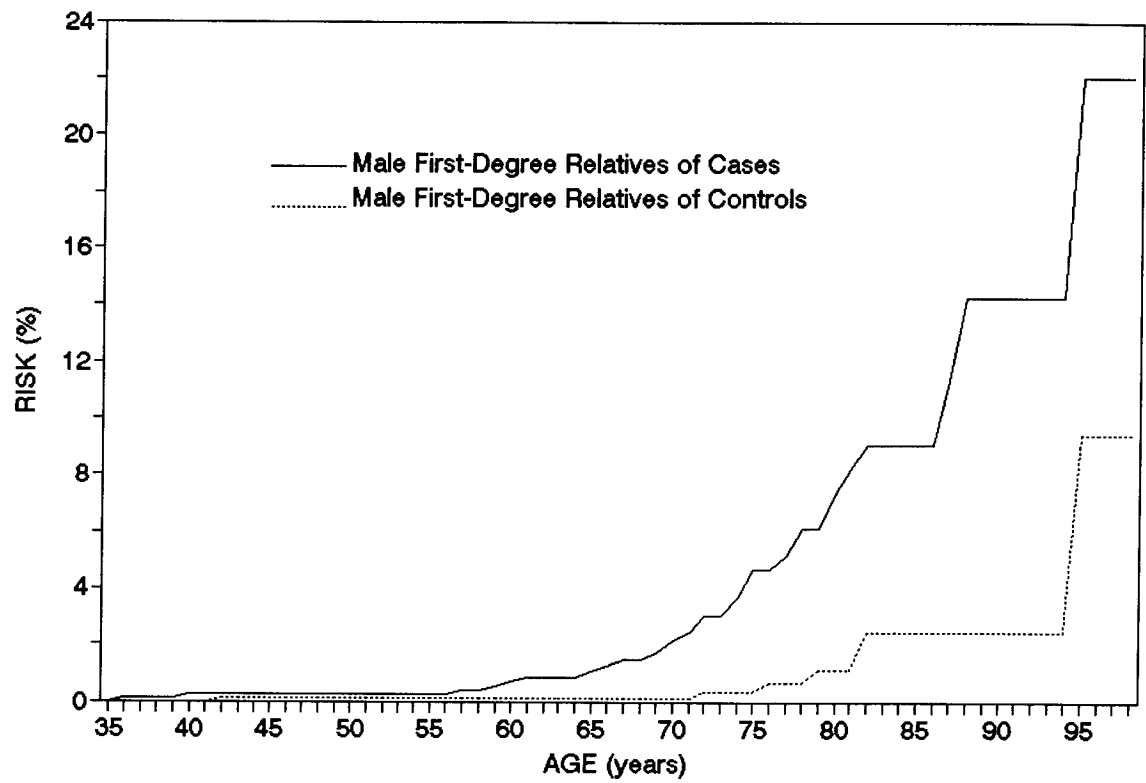
male relatives of cases begins at an earlier age than the risk to first-degree male relatives of controls and remains significantly higher (Log Rank Chi-Square = 19.61, df = 1, p < .001).

### 3.43 Risk Estimates for Female and Male First-Degree Relatives of Cases

Female and male first-degree relatives of cases show equal cumulative lifetime risks (28.97 ± 3.60%, 22.03 ± 8.29%, z = .78, p > .42). Figure 3.5 plots the risks to specific ages for both subgroups. The risk to female first-degree relatives of cases and male first-degree relatives of cases begins at approximately the same age, however the risk to female first-degree relatives increases much more rapidly than the risk to male first-degree relatives. The risk to female first-degree relatives then levels off at an earlier age, yielding a significantly different lifetime risk curve (Log Rank Chi-Square = 16.23, df = 1, p < 001).

### 3.44 Risk Estimates for Female and Male First-Degree Relatives of Controls

The cumulative lifetime risk to female and male first degree relatives of controls does not differ significantly (6.14 ± 1.78%, 9.43 ± 6.79%, z = .47, p > .62). The lifetime risk curves show similar increases in risk with age as well (Log Rank Chi-Square = 1.07, df = 1, p > .22). Figure 3.6 plots the lifetime risk curves for the two subgroups. While the risk to first-degree male relatives of controls begins at an earlier age, this risk is extremely low, and remains comparatively low until approximately age 70 when both subgroups begin to show a steady increase in risk.

Figure 3.5: Risk to Female and Male
First-Degree Relatives of Cases
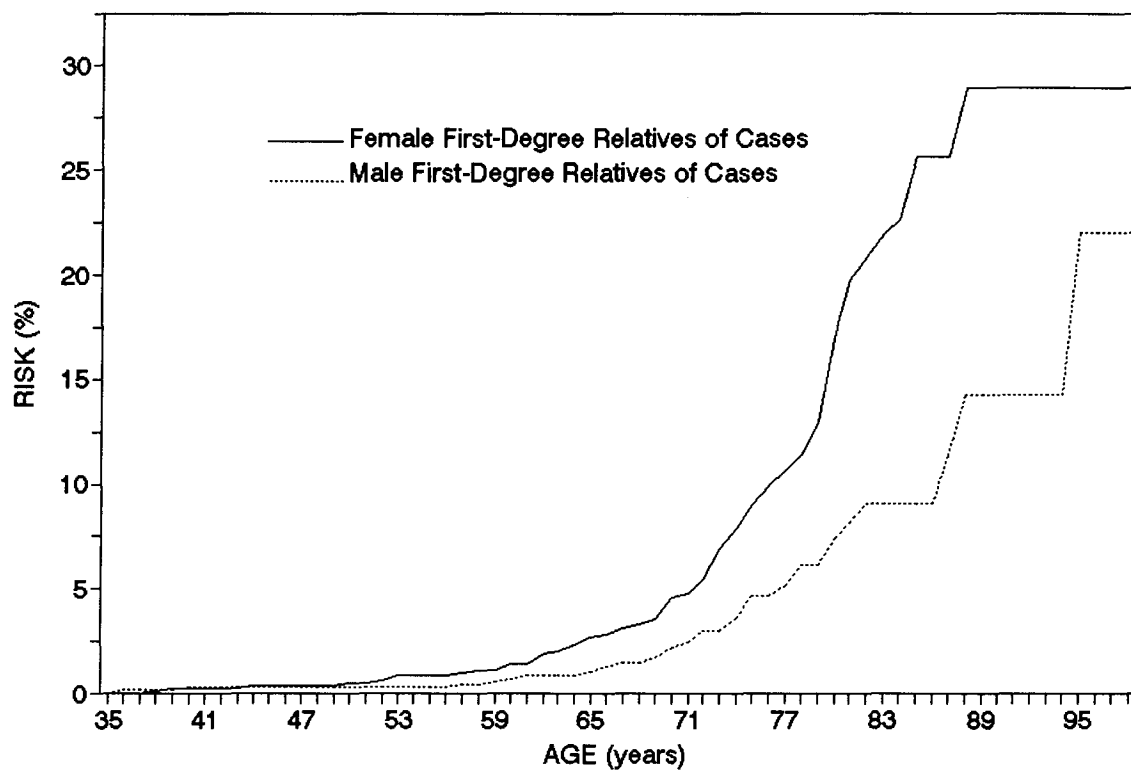
Figure 3.6: Risk to Female and Male
First-Degree Relatives of Controls

——— Female First-Degree Relatives of Controls

·············· Male First-Degree Relatives of Controls

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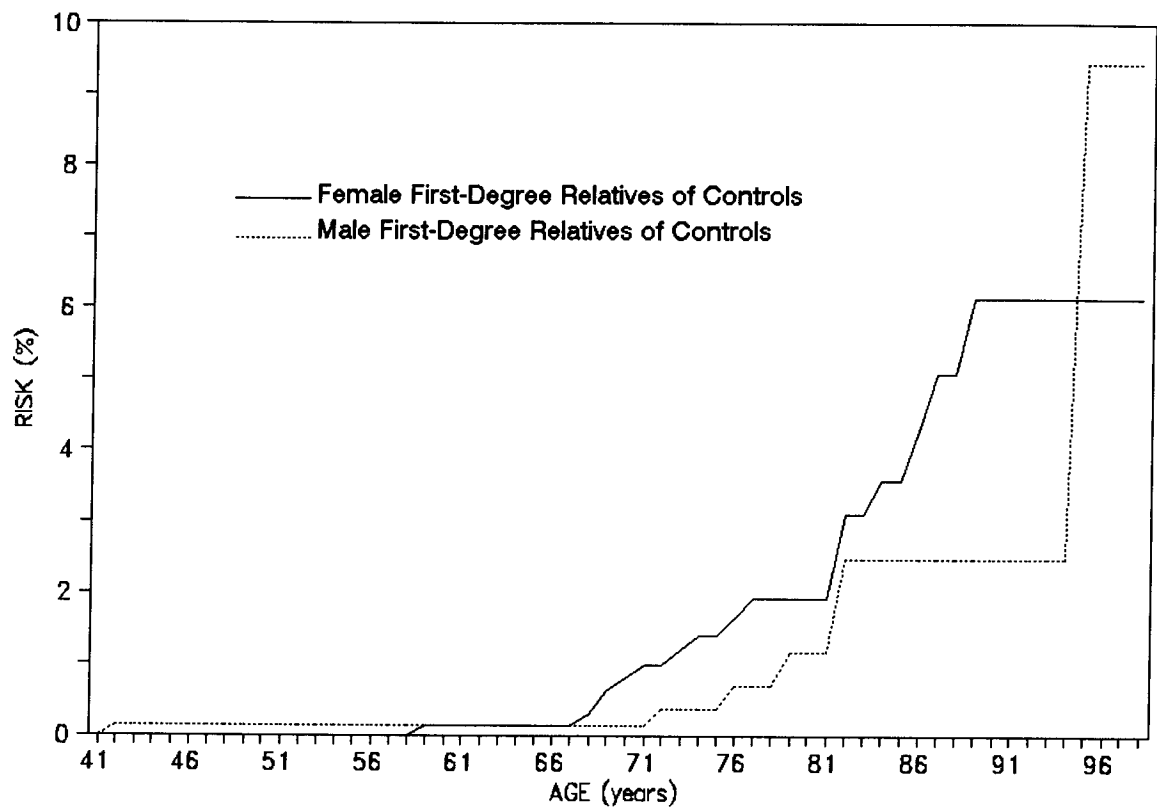
The small number of affected male first-degree relatives of controls as well as the use of the previously described procedure to deal with unknown age-of-onsets reduces the power of the tests comparing both cumulative lifetime risk, and lifetime risk curves.

### 3.5 Risk Estimates for Parents and Sibs of Cases and Controls

### 3.51 Risk Estimates for Parents of Cases and Controls

The age specific risks for parents of cases and controls are given in Table 3.9. The risk to both subgroups of parents increases with age. Parents of cases show a significantly higher cumulative lifetime risk than parents of controls ($27.67 \pm 4.50\%$, $6.86 \pm 2.92\%$, $z=3.91$ $p<.001$). The lifetime risk curves for the two subgroups of parents are plotted in Figure 3.7, demonstrating the risk to parents of cases begins to rise at an earlier age, and increases more rapidly than the lifetime risk to parents of controls (Log Rank Chi-Square$=60.09$, df$=1$, $p<.001$).

### 3.52 Risk Estimates for Sibs of Cases and Controls

Table 3.10 gives the age specific risks for sibs of cases and controls. The risk to both subgroups shows an increase with age as expected. The cumulative lifetime risk for sibs of cases is significantly higher than that to sibs of controls ($28.87 \pm 8.92\%$, $7.44 \pm 3.51\%$, $z=2.23$, $p<.03$). Figure 3.8 plots the lifetime risk curves for sibs of cases and controls. The risk to sibs of cases begins at an earlier age and rises much more rapidly than does the risk to sibs of controls (Log Rank Chi-Square$=27.16$, df$=1$, $p<.001$).

70

**Table 3.9: Age Specific Risks for Parents of Cases and Controls**

| Age | Cases Risk (%) | S.E. | Controls Risk (%) | S.E. |
|-----|------|------|------|------|
| 35 | 0.00 | 0.00 | 0.00 | 0.00 |
| 36 | 0.16 | 0.16 | 0.00 | 0.00 |
| 37 | 0.16 | 0.16 | 0.00 | 0.00 |
| 38 | 0.16 | 0.16 | 0.00 | 0.00 |
| 39 | 0.16 | 0.16 | 0.00 | 0.00 |
| 40 | 0.16 | 0.16 | 0.00 | 0.00 |
| 41 | 0.16 | 0.16 | 0.00 | 0.00 |
| 42 | 0.16 | 0.16 | 0.00 | 0.00 |
| 43 | 0.16 | 0.16 | 0.00 | 0.00 |
| 44 | 0.16 | 0.16 | 0.00 | 0.00 |
| 45 | 0.16 | 0.16 | 0.00 | 0.00 |
| 46 | 0.16 | 0.16 | 0.00 | 0.00 |
| 47 | 0.16 | 0.16 | 0.00 | 0.00 |
| 48 | 0.16 | 0.16 | 0.00 | 0.00 |
| 49 | 0.16 | 0.16 | 0.00 | 0.00 |
| 50 | 0.34 | 0.24 | 0.00 | 0.00 |
| 51 | 0.34 | 0.24 | 0.00 | 0.00 |
| 52 | 0.52 | 0.30 | 0.00 | 0.00 |
| 53 | 0.89 | 0.40 | 0.00 | 0.00 |
| 54 | 0.89 | 0.40 | 0.00 | 0.00 |
| 55 | 0.89 | 0.40 | 0.00 | 0.00 |
| 56 | 0.89 | 0.40 | 0.00 | 0.00 |
| 57 | 1.08 | 0.44 | 0.00 | 0.00 |
| 58 | 1.08 | 0.44 | 0.00 | 0.00 |
| 59 | 1.27 | 0.48 | 0.00 | 0.00 |
| 60 | 1.66 | 0.55 | 0.00 | 0.00 |
| 61 | 1.85 | 0.58 | 0.00 | 0.00 |
| 62 | 2.25 | 0.64 | 0.00 | 0.00 |

continued

|      | Cases      |      | Controls   |      |
|------|------------|------|------------|------|
| Age  | Risk (%)   | S.E. | Risk (%)   | S.E. |
| 63   | 2.45       | 0.67 | 0.00       | 0.00 |
| 64   | 2.66       | 0.67 | 0.00       | 0.00 |
| 65   | 3.27       | 0.78 | 0.00       | 0.00 |
| 66   | 3.71       | 0.84 | 0.00       | 0.00 |
| 67   | 3.71       | 0.84 | 0.00       | 0.00 |
| 68   | 3.71       | 0.84 | 0.00       | 0.00 |
| 69   | 3.94       | 0.87 | 0.00       | 0.00 |
| 70   | 4.67       | 0.96 | 0.21       | 0.21 |
| 71   | 4.92       | 0.99 | 0.43       | 0.30 |
| 72   | 5.43       | 1.05 | 0.43       | 0.30 |
| 73   | 5.98       | 1.11 | 0.66       | 0.38 |
| 74   | 7.37       | 1.26 | 0.66       | 0.38 |
| 75   | 8.80       | 1.39 | 0.66       | 0.38 |
| 76   | 9.12       | 1.42 | 1.19       | 0.53 |
| 77   | 9.80       | 1.49 | 1.46       | 0.60 |
| 78   | 11.21      | 1.62 | 1.46       | 0.60 |
| 79   | 12.71      | 1.76 | 1.46       | 0.60 |
| 80   | 16.61      | 2.07 | 1.46       | 0.60 |
| 81   | 17.49      | 2.14 | 1.46       | 0.60 |
| 82   | 18.87      | 2.25 | 3.36       | 1.02 |
| 83   | 19.88      | 2.33 | 3.36       | 1.02 |
| 84   | 20.44      | 2.38 | 3.36       | 1.02 |
| 85   | 21.75      | 2.51 | 3.36       | 1.02 |
| 86   | 21.75      | 2.51 | 3.36       | 1.02 |
| 87   | 22.81      | 2.69 | 3.36       | 1.02 |
| 88   | 24.05      | 2.92 | 3.36       | 1.02 |
| 89   | 24.05      | 2.92 | 4.20       | 1.31 |
| 90   | 24.05      | 2.92 | 4.20       | 1.31 |
| 91   | 24.05      | 2.92 | 4.20       | 1.31 |

| | Cases | | Controls | |
|---|---|---|---|---|
| Age | Risk (%) | S.E. | Risk (%) | S.E. |
| 92 | 24.05 | 2.92 | 4.20 | 1.31 |
| 93 | 24.05 | 2.92 | 4.20 | 1.31 |
| 94 | 24.05 | 2.92 | 4.20 | 1.31 |
| 95 | 27.67 | 4.50 | 6.86 | 2.92 |

## Table 3.10: Age Specific Risks for Sibs of Cases and Controls

| Age | Cases Risk (%) | S.E. | Controls Risk (%) | S.E. |
|-----|------|------|------|------|
| 37 | 0.00 | 0.00 | 0.00 | 0.00 |
| 38 | 0.10 | 0.10 | 0.00 | 0.00 |
| 39 | 0.29 | 0.17 | 0.00 | 0.00 |
| 40 | 0.29 | 0.17 | 0.00 | 0.00 |
| 41 | 0.29 | 0.17 | 0.00 | 0.00 |
| 42 | 0.29 | 0.17 | 0.10 | 0.10 |
| 43 | 0.29 | 0.17 | 0.10 | 0.10 |
| 44 | 0.39 | 0.19 | 0.10 | 0.10 |
| 45 | 0.39 | 0.19 | 0.10 | 0.10 |
| 46 | 0.39 | 0.19 | 0.10 | 0.10 |
| 47 | 0.39 | 0.19 | 0.10 | 0.10 |
| 48 | 0.39 | 0.19 | 0.10 | 0.10 |
| 49 | 0.39 | 0.19 | 0.10 | 0.10 |
| 50 | 0.39 | 0.19 | 0.10 | 0.10 |
| 51 | 0.39 | 0.19 | 0.10 | 0.10 |
| 52 | 0.39 | 0.19 | 0.10 | 0.10 |
| 53 | 0.39 | 0.19 | 0.10 | 0.10 |
| 54 | 0.39 | 0.19 | 0.10 | 0.10 |
| 55 | 0.39 | 0.19 | 0.10 | 0.10 |
| 56 | 0.39 | 0.19 | 0.10 | 0.10 |
| 57 | 0.50 | 0.22 | 0.10 | 0.10 |
| 58 | 0.61 | 0.25 | 0.10 | 0.10 |
| 59 | 0.61 | 0.25 | 0.21 | 0.15 |
| 60 | 0.74 | 0.28 | 0.21 | 0.15 |
| 61 | 0.74 | 0.28 | 0.21 | 0.15 |
| 62 | 0.87 | 0.31 | 0.21 | 0.15 |
| 63 | 0.87 | 0.31 | 0.21 | 0.15 |
| 64 | 1.00 | 0.34 | 0.21 | 0.15 |

continued

| | Cases | | Controls | |
|---|---|---|---|---|
| Age | Risk (%) | S.E. | Risk (%) | S.E. |
| 65 | 1.00 | 0.34 | 0.21 | 0.15 |
| 66 | 1.00 | 0.34 | 0.21 | 0.15 |
| 67 | 1.50 | 0.44 | 0.21 | 0.15 |
| 68 | 1.68 | 0.47 | 0.37 | 0.22 |
| 69 | 1.87 | 0.51 | 0.70 | 0.32 |
| 70 | 2.67 | 0.64 | 0.70 | 0.32 |
| 71 | 2.90 | 0.68 | 0.70 | 0.32 |
| 72 | 3.63 | 0.80 | 0.90 | 0.36 |
| 73 | 4.68 | 0.95 | 0.90 | 0.36 |
| 74 | 4.98 | 0.99 | 1.15 | 0.45 |
| 75 | 5.62 | 1.08 | 1.15 | 0.45 |
| 76 | 6.42 | 1.21 | 1.15 | 0.45 |
| 77 | 6.89 | 1.29 | 1.15 | 0.45 |
| 78 | 6.89 | 1.29 | 1.15 | 0.45 |
| 79 | 6.89 | 1.29 | 1.61 | 0.64 |
| 80 | 8.34 | 1.63 | 1.61 | 0.64 |
| 81 | 12.20 | 2.45 | 1.61 | 0.64 |
| 82 | 12.20 | 2.45 | 1.61 | 0.64 |
| 83 | 12.20 | 2.45 | 1.61 | 0.64 |
| 84 | 12.20 | 2.45 | 2.68 | 1.24 |
| 85 | 15.93 | 3.49 | 2.68 | 1.24 |
| 86 | 15.93 | 3.49 | 4.79 | 2.42 |
| 87 | 15.93 | 3.49 | 7.44 | 3.51 |
| 88 | 28.87 | 8.92 | 7.44 | 3.51 |

Figure 3.7: Risk to Parents
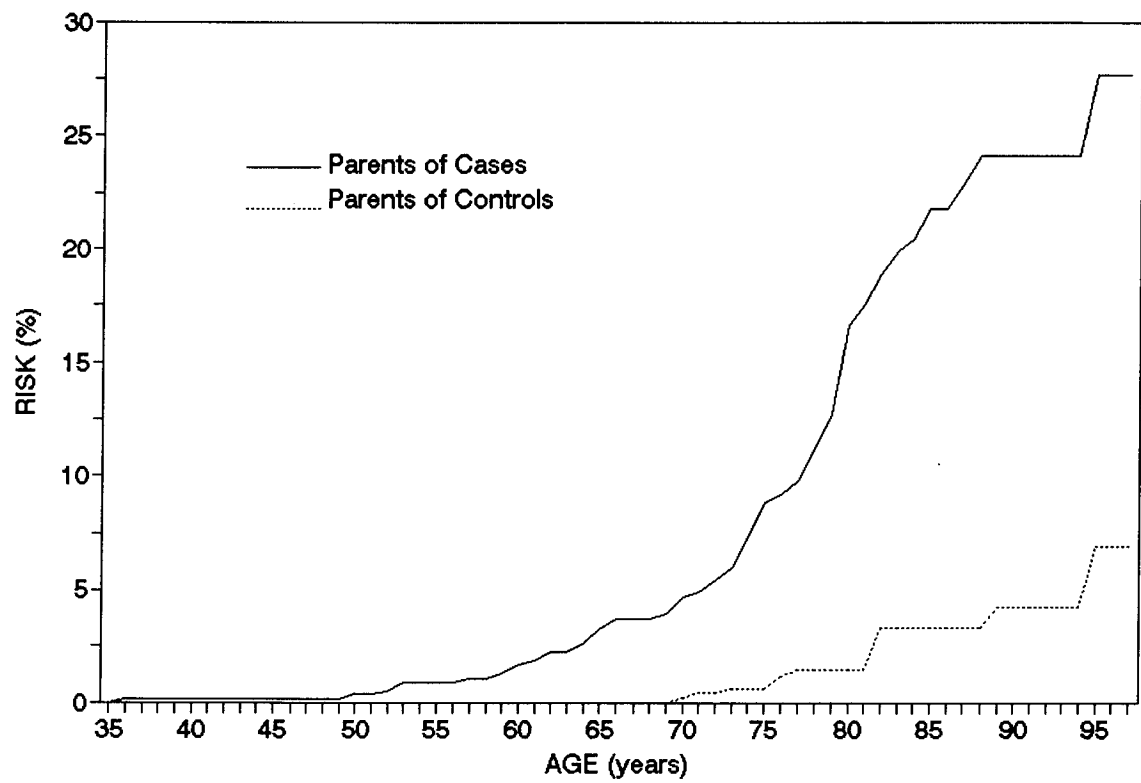of Cases and Controls
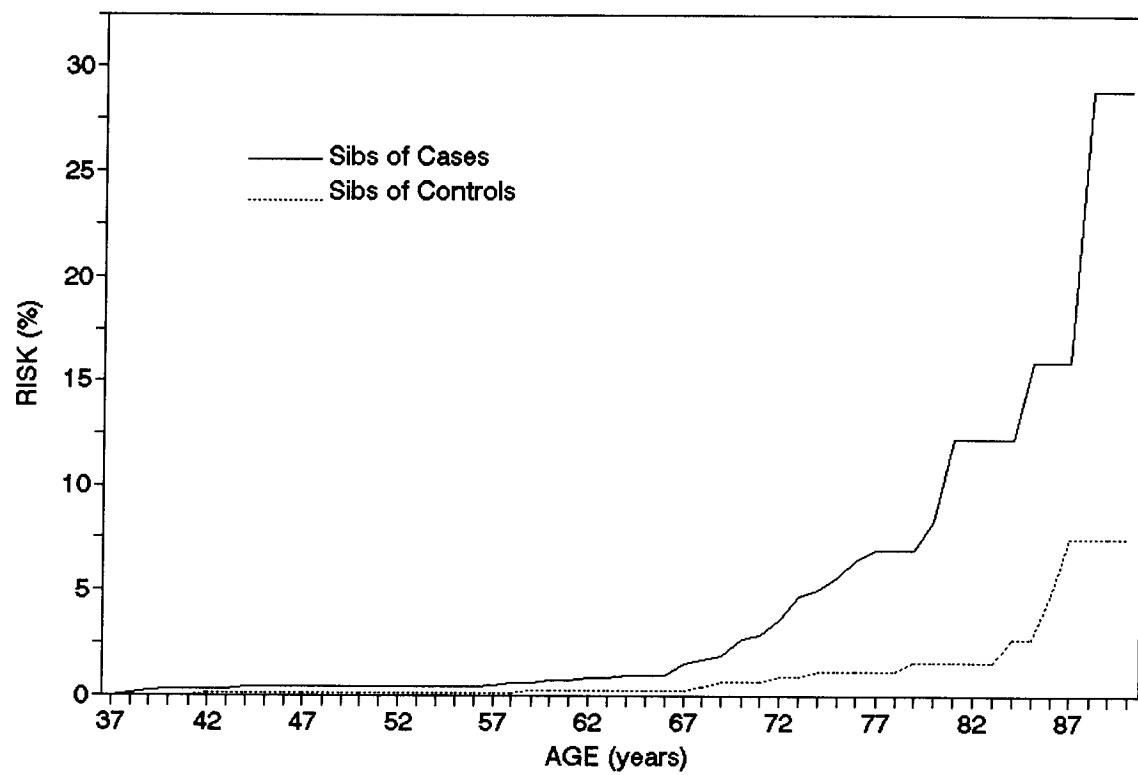
Figure 3.8: Risk to Sibs
of Cases and Controls

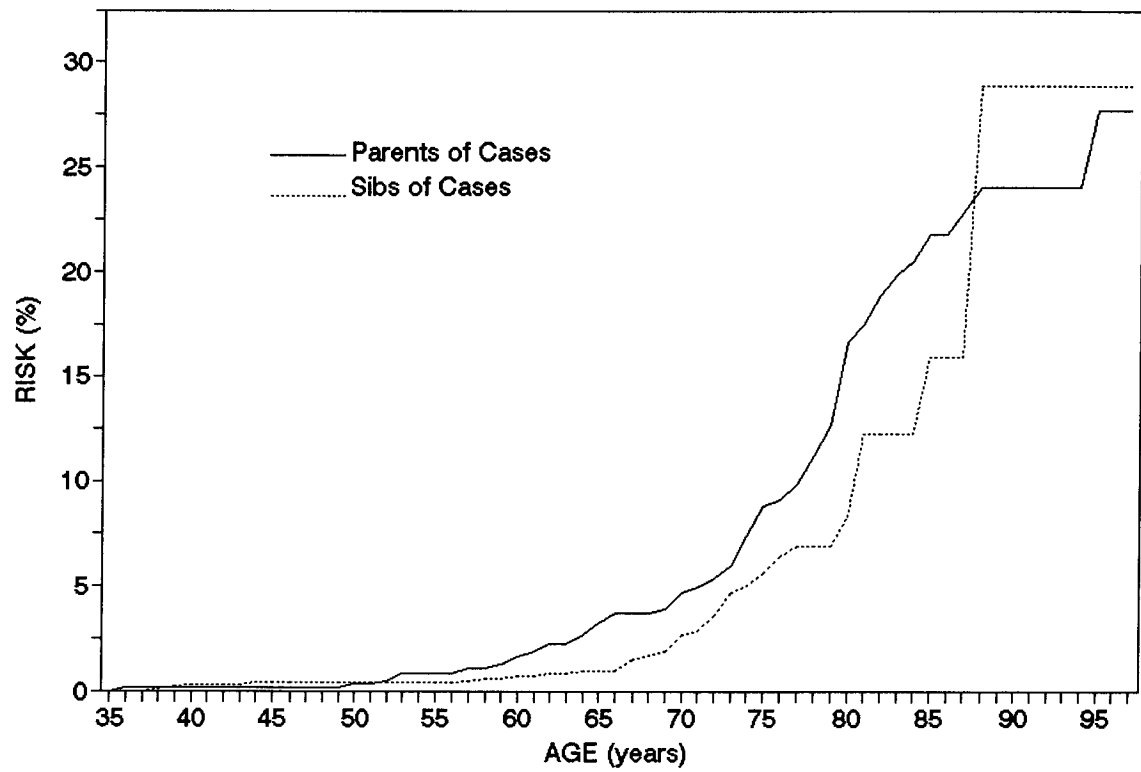Figure 3.9: Risk to Parents
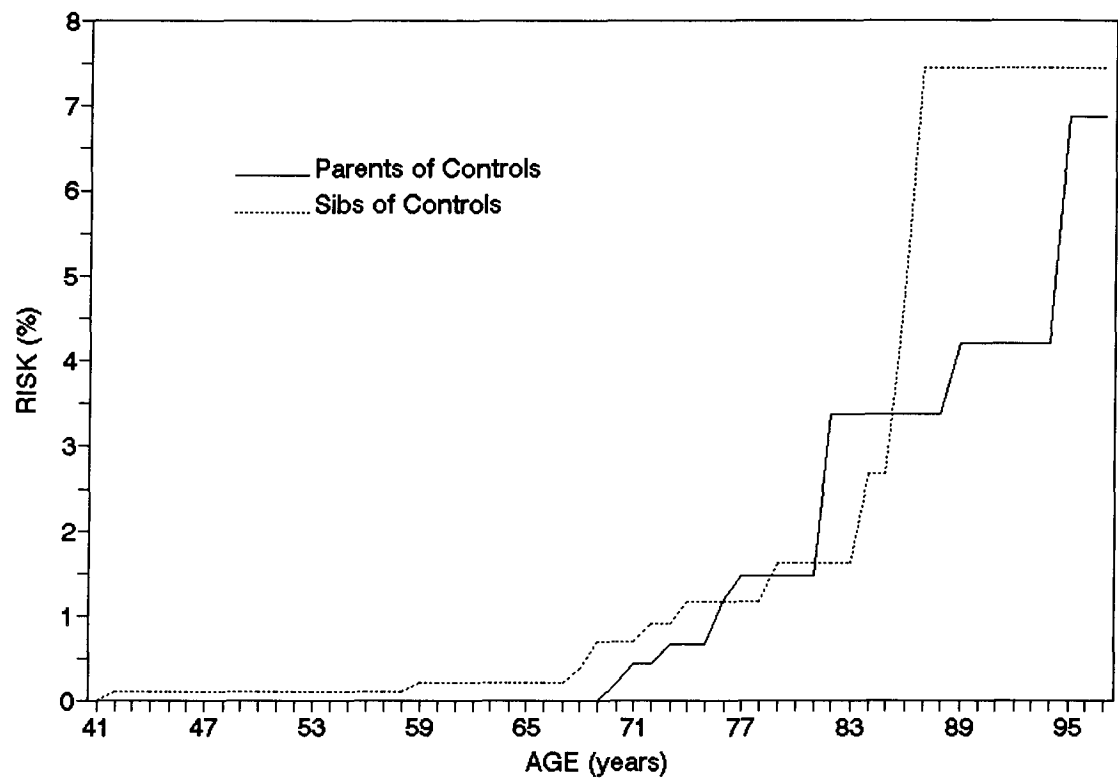and Sibs of Cases

Figure 3.10: Risk to Parents
and Sibs of Controls

Parents of Controls
Sibs of Controls

### 3.53 Risk Estimates for Parents and Sibs of Cases

The cumulative lifetime risk for parents and sibs of cases do not differ significantly ($z=.11$, $p>.90$). However, the lifetime risk curve for parents of cases does differ significantly from that for sibs of cases (Log Rank Chi-Square$=4.83$, df$=1$, $p<.03$). Figure 3.9 demonstrates that the risk to both parents and sibs of cases begin at approximately the same age. The risk to parents remains higher at every age until the very late ages of life where it levels off. The risk to sibs then continues to increases at a much more rapid rate until the risk to both parents and sibs become approximately equal.

### 3.54 Risk Estimates for Parents and Sibs of Controls

The lifetime risk curves for parents and sibs of controls are plotted in Figure 3.10. There is no significant difference between the two risk curves (Log Rank Chi-Square$=.24$, df$=1$, $p>.63$). The risk to sibs begins at an earlier age but remains extremely low until the later ages of life at which both risk curves show approximately equivalent increases until equal cumulative lifetime risks are reached ($z=.13$, $p>.84$).

### 3.6 Risk to First-Degree Relatives of Early-Onset and Late-Onset Cases

The age specific risks for first-degree relatives of early-onset cases (onset before age 65) and for first-degree relatives of late-onset cases (onset at or after age 65) are given in Table 3.11. Both subgroups show the expected increase in risk with age. Cumulative lifetime risk for the two groups are approximately equal when evaluated

**Table 3.11: Age Specific Risks for First-Degree**
**Relatives of Early-Onset and Late-Onset Cases**

| Age | Early-Onset Cases | | Late-Onset Cases | |
|-----|---------|------|---------|------|
|     | Risk (%) | S.E. | Risk (%) | S.E. |
| 35 | 0.00 | 0.00 | 0.00 | 0.00 |
| 36 | 0.17 | 0.17 | 0.00 | 0.00 |
| 37 | 0.17 | 0.17 | 0.00 | 0.00 |
| 38 | 0.34 | 0.24 | 0.00 | 0.00 |
| 39 | 0.51 | 0.30 | 0.00 | 0.00 |
| 40 | 0.68 | 0.34 | 0.00 | 0.00 |
| 41 | 0.68 | 0.34 | 0.00 | 0.00 |
| 42 | 0.68 | 0.34 | 0.00 | 0.00 |
| 43 | 0.68 | 0.34 | 0.00 | 0.00 |
| 44 | 0.86 | 0.38 | 0.00 | 0.00 |
| 45 | 0.86 | 0.38 | 0.00 | 0.00 |
| 46 | 0.86 | 0.38 | 0.00 | 0.00 |
| 47 | 0.86 | 0.38 | 0.00 | 0.00 |
| 48 | 0.86 | 0.38 | 0.00 | 0.00 |
| 49 | 0.86 | 0.38 | 0.00 | 0.00 |
| 50 | 1.05 | 0.43 | 0.00 | 0.00 |
| 51 | 1.05 | 0.43 | 0.00 | 0.00 |
| 52 | 1.24 | 0.47 | 0.00 | 0.00 |
| 53 | 1.44 | 0.51 | 0.10 | 0.10 |
| 54 | 1.44 | 0.51 | 0.10 | 0.10 |
| 55 | 1.44 | 0.51 | 0.10 | 0.10 |
| 56 | 1.44 | 0.51 | 0.10 | 0.10 |
| 57 | 1.87 | 0.59 | 0.10 | 0.10 |
| 58 | 1.87 | 0.59 | 0.21 | 0.15 |
| 59 | 2.10 | 0.63 | 0.21 | 0.15 |
| 60 | 2.34 | 0.67 | 0.42 | 0.21 |
| 61 | 2.60 | 0.72 | 0.42 | 0.21 |

continued

| Age | Early-Onset Cases | | Late-Onset Cases | |
|-----|-----------|------|-----------|------|
|     | Risk (%)  | S.E. | Risk (%)  | S.E. |
| 62 | 3.13 | 0.81 | 0.53 | 0.24 |
| 63 | 3.13 | 0.81 | 0.53 | 0.26 |
| 64 | 3.42 | 0.86 | 0.76 | 0.31 |
| 65 | 4.03 | 0.95 | 0.88 | 0.36 |
| 66 | 4.03 | 0.95 | 1.14 | 0.42 |
| 67 | 4.03 | 0.95 | 1.53 | 0.44 |
| 68 | 4.03 | 0.95 | 1.66 | 0.49 |
| 69 | 4.03 | 0.95 | 1.95 | 0.60 |
| 70 | 4.45 | 1.04 | 2.83 | 0.62 |
| 71 | 4.92 | 1.13 | 3.00 | 0.72 |
| 72 | 4.92 | 1.13 | 3.83 | 0.84 |
| 73 | 4.92 | 1.13 | 4.92 | 0.95 |
| 74 | 4.92 | 1.13 | 6.08 | 1.06 |
| 75 | 5.51 | 1.27 | 7.30 | 1.14 |
| 76 | 5.51 | 1.27 | 8.04 | 1.22 |
| 77 | 5.51 | 1.27 | 8.85 | 1.28 |
| 78 | 7.04 | 1.65 | 9.44 | 1.35 |
| 79 | 8.85 | 2.05 | 10.10 | 1.69 |
| 80 | 10.77 | 2.42 | 13.58 | 1.85 |
| 81 | 13.03 | 2.83 | 15.26 | 1.90 |
| 82 | 15.35 | 3.20 | 15.73 | 2.02 |
| 83 | 15.35 | 3.20 | 16.77 | 2.08 |
| 84 | 15.35 | 3.20 | 17.34 | 2.25 |
| 85 | 19.11 | 4.01 | 18.68 | 2.25 |
| 86 | 19.11 | 4.01 | 18.68 | 2.54 |
| 87 | 19.11 | 4.01 | 19.93 | 3.30 |
| 88 | 22.34 | 4.99 | 23.14 | 3.30 |
| 89 | 22.34 | 4.99 | 23.14 | 3.30 |
| 90 | 22.34 | 4.99 | 23.14 | 3.30 |

continued

| Age | Early-Onset Cases | | Late-Onset Cases | |
| --- | --- | --- | --- | --- |
| | Risk (%) | S.E. | Risk (%) | S.E. |
| 91 | 22.34 | 4.99 | 23.14 | 3.30 |
| 92 | 22.34 | 4.99 | 23.14 | 3.30 |
| 93 | 22.34 | 4.99 | 23.14 | 3.30 |
| 94 | 22.34 | 4.99 | 23.14 | 3.30 |
| 95 | 22.34 | 4.99 | 28.26 | 5.53 |

Figure 3.11: Risk to First-Degree
Relatives of Early and Late-Onset Cases
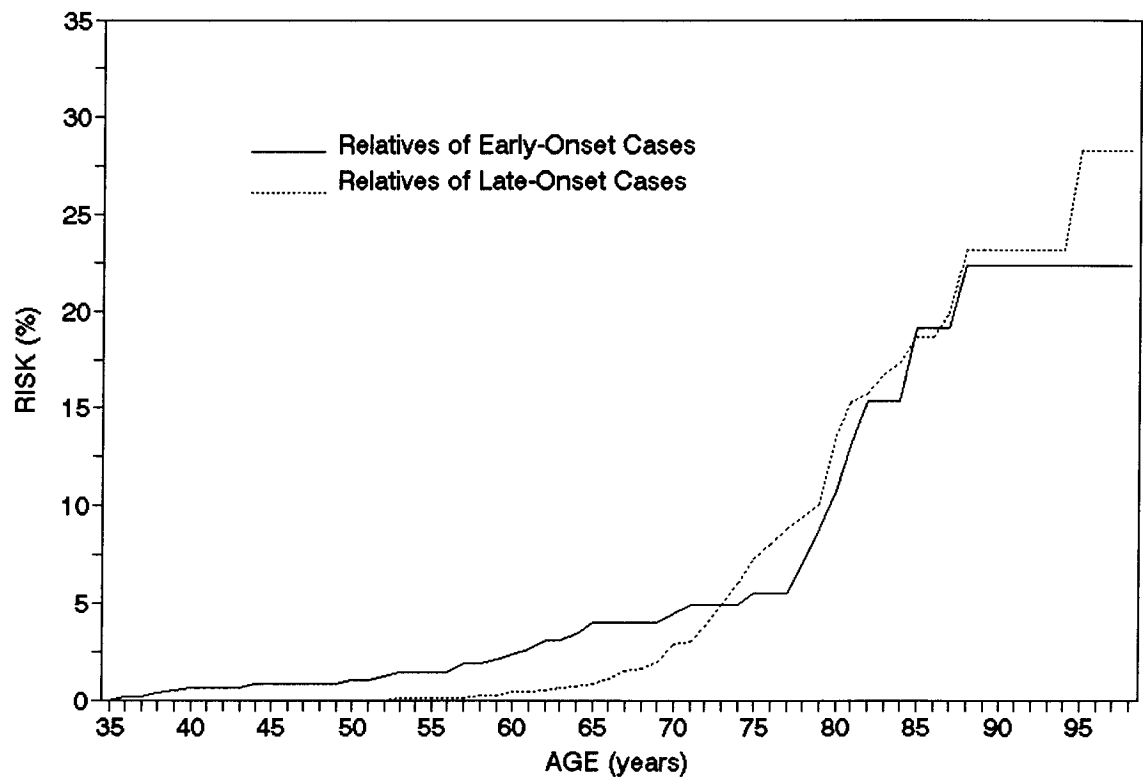
with a difference of proportions test (22.34 ± 4.98%, 28.26 ± 5.83%, z=.75, p>.42). The lifetime risk curves for the two subgroups of case relatives are plotted in Figure 3.11. The risk to first-degree relatives of early-onset cases shows a non-significant but notable tendency to develop at an earlier age after which both subgroups show an equal increase of risk with time (Log Rank Chi-Square=.21, df=1, p>.65).

## 3.7 Comparison of Previous and Present Samples

The earlier study on the predecessor of this sample ("original" sample) examined the risks to develop AD to 840 first-degree relatives of 151 AD cases (Sadovnick et al., 1989) and, using the Kaplan-Meier method, found a cumulative lifetime risk of 22.0 ± 3.6% by age 88. The risk to the consecutively and similarly ascertained group ("replication" sample) of 1043 first-degree relatives of 195 cases (8 cases from the "original" sample were rediagnosed) found a cumulative lifetime risk of 22.58 ± 3.77% by age 88 and 28.53 ± 6.70% by age 95. No significant differences in lifetime risk between the "original" and "replication" studies were found (z=0.86, p>.37; Log Rank Chi-Square=1.32, df=1, p>.25). The total sample reported here ("combined" sample) represents a 2.2 fold increase in size over the "original" sample. Figure 3.12 plots the lifetime risk for all first-degree relatives from the "original" and "replication" samples.

## 3.8 Effect of Using Missing Ages-of-Onset

The use of an affected relatives' last known age when definitely affected as their

Figure 3.12: Comparison of
Previous and Present Samples
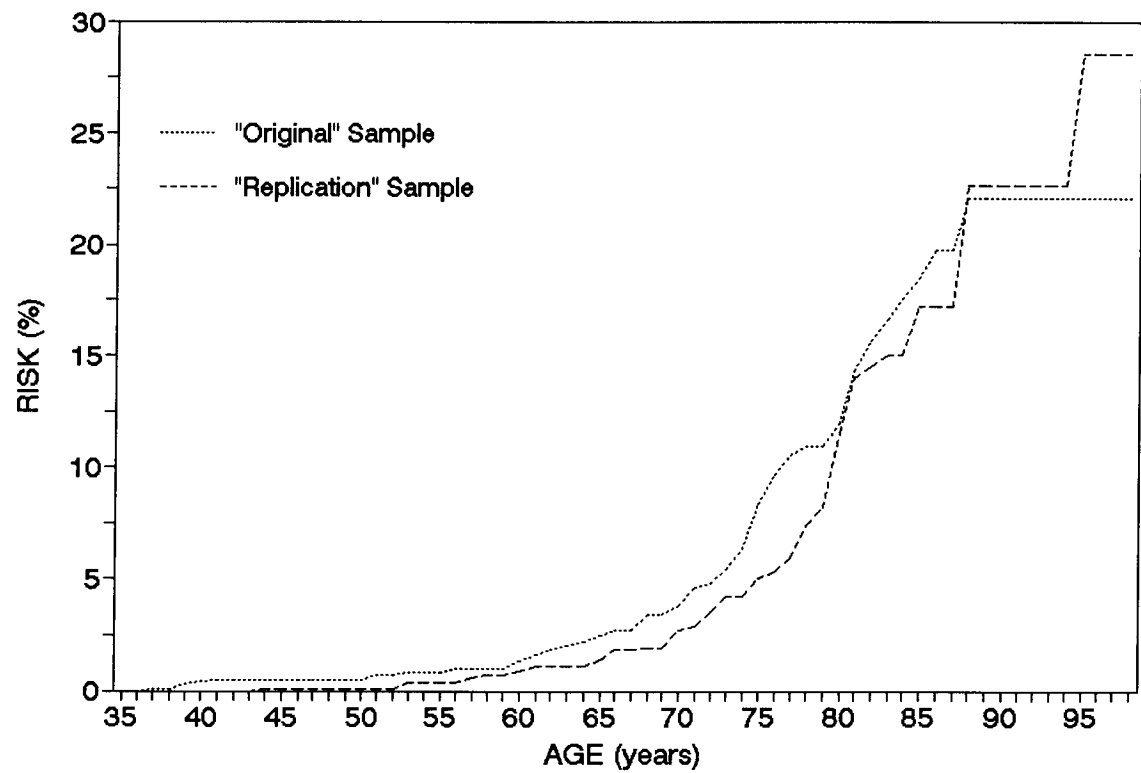
true age-of-onset in the instance of an unknown age-of-onset is a conservative approach previously used (Sadovnick et al., 1989) to treat data influenced by the imperfect recall of a family member giving the family history. The precise effect of this transformation remains unknown as the true age-of-onset for some individuals can never be known. However, several different estimates used in place of an unknown age-of-onset suggest that overall, no statistically significant differences in the lifetime risk curves will result from utilizing this procedure.

An illustrative example of the effect of using a different estimate in place of an affected relative's unknown age-of-onset is to use the average age-of-onset for the entire sample. This was calculated as 70.13 (maximum value = 85, minimum value = 32, standard deviation = 10.50). This estimate obviously has limitations; the most prominent being the wide range of values and the fact that using this estimate will definitely result in some relatives being considered affected long before their true age-of-onset, while others will not be considered affected long after their true age-of-onset. Nevertheless, this procedure was used only to illustrate the possible implications of the procedure described in section 2.51. The resulting Kaplan-Meier risk estimates are shown in Figure 3.13. A comparison of the lifetime risk curve calculated using the average age-of-onset in place of an unknown age-of-onset does not differ significantly from the risk curve calculated using the last known age when alive for an unknown age-at-onset using a log-rank test (Log Rank Chi-Square = .022, df = 1, p > .88). The lifetime cumulative risk does differ significantly (z = 2.15, p < .04), but, as will be discussed later in this section, does not have a significant effect on

testing the hypothesis of an autosomal dominant model of transmission. It is noted that these comparisons are not performed on strictly independent samples, but were completed only to illustrate the effect of the age-of-onset estimation.

Another comparison can be done using a "worst case" and "best case" scenario. This is accomplished by considering an affected relative with unknown age-of-onset to be affected at the earliest ("worst-case") or latest ("best-case") recorded onset ages documented in the sample (age 36 and 85). Using the "best case" scenario results in some relatives having onset ages after their recorded age at death, but the analysis was completed as if the relative lived at least to the onset age of 86. Using these estimates, as with the one previously described results in the improbable situation of a large group of relatives becoming affected at exactly the same age, therefore resulting in a large increase in risk at that particular age. These results are also shown in Figure 3.13, and as in the previous comparison, the lifetime risk curves show no statistically significant differences using the log-rank test (for age 36: Log Rank Chi-Square=.06, df=1, p>.81; for age 85: Log Rank Chi-Square=.11, df=1, p>.74). The cumulative lifetime risk estimate using age 36 differs significantly from the estimate used in section 3.2 (z=2.56, p<.012), while using age 85 does not result in a significantly different lifetime cumulative risk (z=.22, p>.84).

Using the procedure described in section 2.51 will result in a slight overestimation of the true cumulative lifetime risk due to the fact that some affected relatives will be considered to have an age-of-onset after their true age-of-onset. However, this method is considered reasonable as all affected relatives will definitely

suffer from AD at the time they are considered affected. The highest possible risk estimate calculated using an improbable age-of-onset approximation ("best case" scenario), results in a cumulative lifetime risk far below the 50% risk which would be consistent with an autosomal dominant model of transmission. This result shows that the method used will have no significant effect on hypothesis testing, and will not result in any statistically significant changes in lifetime risk curves.

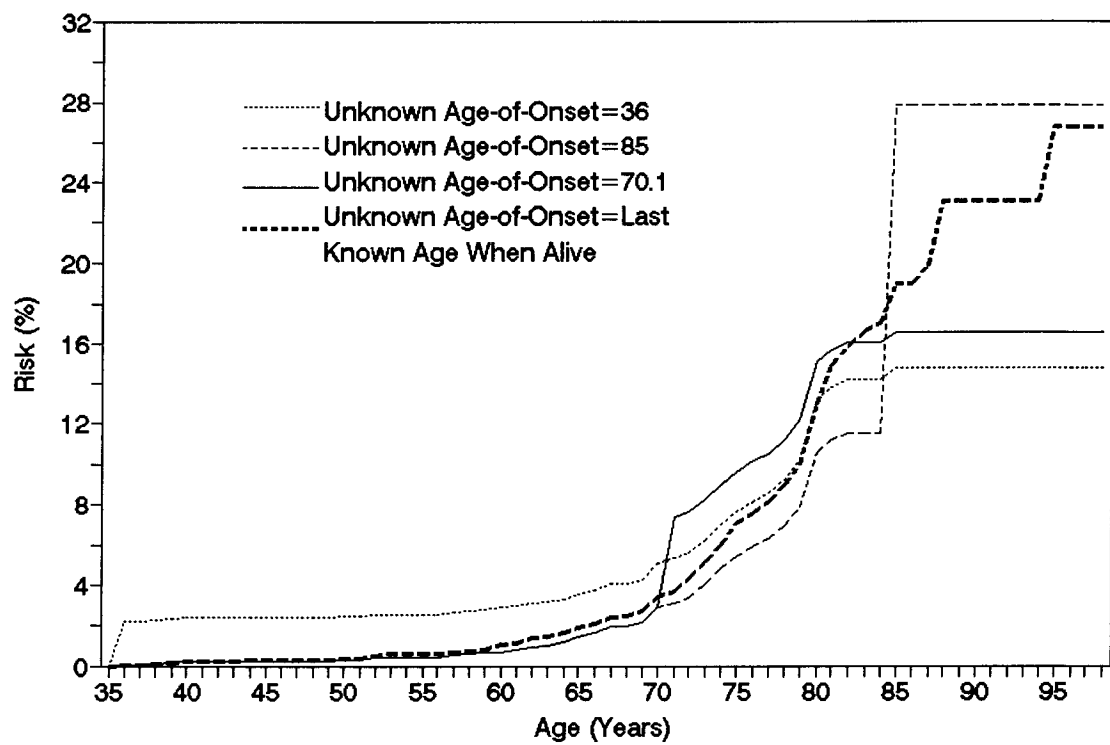Figure 3.13: Effect of Using
Unknown Ages-of-Onset

**Table 3.12: Summary of Results**

| Subgroup | Cumulative Lifetime Risk Estimate (%) | |
|---|---|---|
| | Cases | Controls |
| All First-Degree Relatives | 26.73 ± 4.42 | 7.26 ± 2.74 |
| Female First-Degree Relatives | 28.97 ± 3.60 | 6.14 ± 1.79 |
| Male-First Degree Relatives | 22.03 ± 8.29 | 9.44 ± 6.79 |
| Parents | 27.67 ± 4.50 | 6.86 ± 2.92 |
| Sibs | 28.87 ± 8.92 | 7.44 ± 3.51 |
| First-Degree Relatives of Early-Onset Cases | 22.34 ± 4.99 | N/A |
| First-Degree Relatives of Late-Onset Cases | 28.26 ± 5.53 | N/A |

| Subgroup Comparison | Difference of Proportions p Value | Log Rank p Value |
|---|---|---|
| First-Degree Relatives of Cases vs Controls | $<.001$ | $<.001$ |
| Female First-Degree Relatives of Cases vs Controls | $<.001$ | $<.001$ |
| Male First-Degree Relatives of Cases vs Controls | .23 | $<.001$ |
| Female vs Male First-Degree Relatives of Cases | .42 | $<.001$ |
| Female vs Male First-Degree Relatives of Controls | .62 | .22 |
| Parents of Cases vs Controls | $<.001$ | $<.001$ |
| Sibs of Cases vs Controls | .03 | $<.001$ |
| Parents vs Sibs of Cases | .90 | .03 |
| Parents vs Sibs of Controls | .63 | .83 |
| First-Degree Relatives of Early vs Late-Onset Cases | .42 | .65 |

# 4 DISCUSSION

## 4.1 First-Degree Relatives of Cases and Controls

This study group is the largest of its kind reported to date, and represents an increase of up to 15 fold in the number of cases compared to other studies in the literature (see Table 1.3). The number of cases and the resultant number of "at-risk" first-degree relatives is an important factor in studies of late onset diseases where there is a rapid decrease in the number of first-degree relatives surviving to the eighth or ninth decades of life. Table 4.1 shows the numbers of relatives "at-risk" to various ages for this study compared with other studies for which these numbers as well as the standard errors assumed by each age-specific risk estimate were available. The standard errors assumed by some previously reported risk estimates become rather large as the numbers of individuals "at-risk" decrease in the last decades of life (see Table 1.3, Table 4.1).

The risk estimates calculated for this sample represent important data for risk counselling of first-degree relatives of AD patients. As media reports on risk factors for AD increase, these relatives are more concerned about their own risks to develop AD.

The significantly higher lifetime risk curve and 3.7 fold higher lifetime cumulative risk to first-degree relatives of cases compared to first-degree relatives of controls agree with the results of other studies. However, the estimated cumulative lifetime risk for first-degree relatives of both cases and controls is substantially lower

**Table 4.1: Cumulative Risk Calculations and Numbers of
First-Degree Relatives "at-Risk" : A Literature Review[*]**

| References | Age | No. Relatives At Risk | Cumulative Incidence (%) |
|---|---|---|---|
| Mohs et al., 1987 | 60 | 173.5 | .58 ± .58 |
| | 65 | 139.5 | 2.71 ± 1.34 |
| | 70 | 91 | 7.71 ± 2.53 |
| | 75 | 53 | 14.62 ± 3.80 |
| | 80 | 26.5 | 24.06 ± 5.68 |
| | 86 | 8.5 | 45.87 ± 9.82 |
| Breitner et al., 1988 | 60 | 255 | 1.03 ± .60 |
| | 65 | 200 | 2.93 ± 1.11 |
| | 70 | 135.5 | 4.94 ± 1.58 |
| | 75 | 88 | 11.07 ± 2.68 |
| | 80 | 49 | 19.48 ± 4.13 |
| | 85 | 21 | 36.54 ± 6.41 |
| | 87 | 12 | 49.33 ± 8.38 |
| Martin et al., 1988 | 65 | 71 | 1.39 ± 1.38 |
| | 70 | 50 | 9.74 ± 3.81 |
| | 74 | 33 | 16.93 ± 5.31 |
| | 81 | 14 | 35.44 ± 8.60 |
| | 83 | 11 | 40.82 ± 9.42 |
| Present Study | 65 | 1158 | 1.89 ± .37 |
| | 70 | 889 | 3.34 ± .54 |
| | 75 | 622 | 7.03 ± .87 |
| | 80 | 352 | 13.03 ± 1.41 |
| | 85 | 167 | 18.99 ± 1.97 |
| | 90 | 55 | 23.07 ± 2.74 |
| | 95 | 20 | 26.73 ± 4.42 |

[*]Numbers of first-degree relatives at specific ages are shown for studies which gave
this information. For total number of cases used in previous studies see Table 1.3

than that estimated by most other studies (Breitner and Folstein, 1984; Breitner et al.,1988; Huff et al., 1988; Martin et al., 1988; Mayeux et al., 1991; Mohs et al., 1987). Notable exceptions are Farrer et al. (1989) and Sadovnick et al. (1989).

Previously published cumulative lifetime risk estimates for AD to first-degree relatives of non-demented controls range widely from 8.1 ± 6.0% to 29 ± 7%. All estimates assume extremely large standard error (Table 1.3). The estimated lifetime cumulative risk to first-degree relatives of controls found for this sample is not widely disparate from those estimates in the lower range of previously reported risks, but obviously differ greatly from the estimates in the higher range. The cumulative lifetime risk calculation for first-degree relatives of controls should approximate the lifetime risk of the general population, and it will be of interest to compare these results to those of the CSHA once it is completed. A study investigating AD in a Canadian population (Gautrin et al., 1990) used data from two Finnish studies (Molsa et al., 1982; Sulkava et al., 1985) to infer prevalence rates in the general population. The projected rates seem to agree with the results from this study considering the standard error of the risk estimates. Gautrin et al. (1990) projected prevalence rates of 1% for 65-74 year olds compared with .94 ± .30% to age 74 for this study; 4% for 75-84 year olds compared with 3.10 ± .76% to age 84 for this study; and 10.5% to those 85 years and over compared with 7.26 ± 2.74% to age 95 for this study. The data on which Gautrin et al. (1990) base their estimates vary widely with prevalence rates for 85 years old and above ranging from 6.30% (Molsa

et al., 1982) to 14.80% (Sulkava et al., 1985). This wide variation in estimates should be taken into account when considering the final overall prevalence estimates.

Although the cumulative lifetime risk to first-degree relatives of AD cases calculated for this study ("combined" sample), is much lower than that calculated for most other studies (Table 1.3), it agrees well with the cumulative lifetime risk estimate calculated for the predecessor of this sample ("original" sample). Since cumulative lifetime risks and lifetime risk curves between the "original" sample and the consecutively and similarly ascertained sample ("replication" sample) of 195 cases and 1043 of their first degree relatives are also in agreement it is unlikely that results represent sampling error. The results of analyses on the "replication" sample are slightly (though non-significantly) higher than the "original" sample. This can be explained by the fact that the "replication" sample contains a very long-lived individual with an unknown age-of-onset who is considered to become affected at the last possible age (age 95). Since this individual probably had a true age-of-onset at an earlier age, the cumulative lifetime risk estimate could presumably be slightly lower (see explanation in section 3.32). The similar results between the "original" and "replication" samples further suggests that the structure of the sample has remained relatively constant throughout the seven years of data collection.

One previous study (Farrer et al., 1989) estimated a lifetime risk for AD to first-degree relatives of AD cases of 24% by age 93. This estimate is much lower than that calculated by the majority of other studies, and similar to the one calculated for this study. Although Farrer et al. (1989) used the Kaplan-Meier method to

generate their risk estimate, this risk may not be directly comparable to other studies as it used an original weighting method to estimate the likelihood of a correct diagnosis in affected relatives.

There are several possible factors which may influence the lower risk estimate calculated for this, as well as the "original" sample. One reason may be the attempt to be as rigorous and conservative as possible in labelling a relative "affected". Care was taken to rule out dementia due to other causes whenever possible (see Table 1.1). This results in a sample relatively "clean" of confounding factors which may account for a relative being misclassified as "affected". In a prevalence of dementia study, Bachman et al. (1992) reported that only 55.6% of all cases of dementia were diagnosed as "probable" AD. The effect of including all reportedly senile or demented relatives as "affected" would be to artificially increase the lifetime risk estimates.

Secondly, the definition for onset may also impact the risk calculations. Onset is defined in this study as "the first detectable symptoms of cognitive embarrassment" rather than using the stricter definitions of "the first definite symptoms of dementia" or "evidence of progressive dementia" (Breitner et al., 1989). Although evidence of progressive and irreversible loss of cognitive function is one criteria used to consider an individual affected, the age-of-onset is considered to occur when these deficits first become apparent. Using "caseness" instead of "onset" as the definition for age-of-onset would result in relatives considered to become affected at a later age. Since a lower number of total relatives "at-risk" survive to each successive onset age, this

decreased number of "at-risk" relatives would result in an increase to risk estimates. Breitner et al. (1989) found that using the definition of "onset" rather than "caseness" may result in an estimate only 60% of that calculated for the latter.

A third factor which could explain the difference in risk estimates is the composition of the study sample. This sample is from a population to which universal health care is available, unlike the situation for studies from United States. Although the information is not available, the ethnic mix and education level of samples may differ as well.

The method in which cases for this study were ascertained should limit bias of the sample toward a population which was identified through a positive family history. The cumulative risk to families meeting the FAD criteria shows that the over-representation of these FAD aggregates in a sample would result in an upward shift in the lifetime risk curve as well as an increase in cumulative lifetime risk closer to 50%. Mayeux et al. (1991) found that in certain studies, possible selection and information biases may result in an increase in the risk of dementia to first-degree relatives of AD patients that is not specific, and may exist in first-degree relatives of patients suffering from other neurological disorders as well.

A lifetime cumulative risk approaching 50% would be consistent with an autosomal dominant model of inheritance as supported by several previous studies. However, this risk estimate would not be proof that a single autosomal dominant gene is responsible for all cases, a point which is further supported by molecular genetic studies suggesting etiologic heterogeneity. The cumulative lifetime risk

calculated for this sample supports the previous finding of Sadovnick et al. (1989) and

suggests that an autosomal dominant model of inheritance with full penetrance by the

end of the human lifespan is not responsible for all cases of AD. Nevertheless, the

elevated risk in first-degree relatives of AD index cases offers further evidence that

familial factors do have a role in AD etiology (Amaducci et al., 1986; Chandra et al.,

1987; Heyman et al., 1984; Shalat et al., 1986). The evidence presented by

epidemiological studies suggesting a wide range of possible environmental risk factors

combined with the molecular genetic studies seem to suggest etiological

heterogeneity. Although a polygenic model cannot be ruled out, it seems likely that

both genetic and environmental factors may combine to play a significant role in AD

etiology. An interesting repercussion of such a hypothesized interaction between

genetic and environmental factors in at least a proportion of AD cases is that

interventions delaying the onset of AD in a genetically susceptible individual for only

a few years, past the age-of-death, could greatly decrease the incidence of the disease.

The cumulative lifetime risk estimate for FAD in first-degree relatives of cases

from such families confirms that using the criteria outlined in the section 2.62

identifies families which show transmission of AD conforming to an autosomal

dominant model of transmission. If etiologic heterogeneity exists then a proportion

of cases in FAD families would be expected to be due to causes other than an

autosomal dominant gene(s). The results permit a slight increase over the expected

50% estimate (55.12 ± 7.93%) which would allow for such non-genetic cases

(phenocopies) to occur within FAD families. Using the criteria outlined in section

2.62, only approximately 5.36% of all Alzheimer Clinic cases of AD represent FAD. The true proportion of FAD cases may be higher, but the criteria used in this study were designed to identify an extremely rigorously defined group of FAD families on whom linkage analysis studies could be performed.

## 4.2 Gender-Specific Risks

The results show male and female first-degree relatives of AD cases both display a higher lifetime risk when compared to their analogous control subgroups. Although the difference in cumulative lifetime risk between male subgroups in this sample was found to be significant only at a level of $p < .25$, the risk to male first-degree relatives of controls could be, credibly, much lower (see section 3.42). The low number of male first-degree relatives surviving until the eighth decade of life is reflected in the large standard error reported for the cumulative lifetime risk estimates reported for males (Table 1.3). Farrer et al. (1989) found very few males in their sample surviving to the late ages of life, which presenting a greater problem since their total sample size was approximately half of this sample. Nevertheless, an elevated risk, regardless of gender, in first-degree relatives of AD cases lends further support to the contribution of genetic factors to AD etiology.

A female preponderance in the prevalence and incidence of AD compared with males has been reported (Åkesson 1969; Bachman et al, 1992; Broe et al., 1976; Hagnell et al., 1991; Schoenberg et al., 1985; Sturt, 1986; Sulkava et al., 1985; Treves et al., 1986). Since estimated prevalence rates of a disease are influenced by both its

duration and incidence, it has been suggested that increased prevalence of AD among females could result from of an increased duration among females which has been previously reported (Breitner et al., 1988; Gruenberg, 1978).

The findings suggesting female first-degree relatives of AD cases show a statistically greater increase in their cumulative risk at an earlier age, but a similar cumulative lifetime risk when compared to male first-degree relatives of AD cases affirms those results reported by Breitner et al. (1988). They reported a non-significant, but "notable" higher risk curve among female first-degree relatives of AD index cases. The present results also support the suggestion by Breitner et al. (1988) that the sex specific differences presented by the earlier epidemiologic studies mirror the differential age-specific expression of an identical propensity in both female and male first-degree relatives of AD cases. These findings are by no means universal, as others have asserted that no difference in risk exists and the increased incidence in females is due to an earlier censoring age in males (Farrer et al., 1989). These results also discount an X-linked gene(s) playing a significant role in AD etiology.

The differential age-specific expression found in this study would seem to be particular to female and male first-degree relatives of AD cases as female and male first-degree relatives of controls show an equal increase in cumulative risk as well as equal cumulative lifetime risks. The results seem to suggest that individuals in whom familial recurrence risk is high (first-degree relatives of AD cases) show a greater sex-specific expression, while individuals in whom this risk is lower (first-degree relatives of controls) are not as sensitive to this sex-specific difference.

A potential mechanism for this difference in the sex-specific expression of AD among genetically susceptible individuals is the difference in the expression of female and male hormones. The details of these differences are discussed in Section 1.31.5. Possible interaction of environmental and genetic factors affecting AD expression have been proposed previously, but to date, no suggestion of the effect such an interaction might have on the sex-specific expression of AD has been made.

## 4.3 Generational-Specific Risks

The increased risk to parents and sibs of AD cases compared to their respective control subgroups confirms that the increased familial risk among first-degree relatives of cases is not restricted to any particular subgroup. These results lend further support the supposition of a genetic contribution to the etiology of the disease.

The results of the comparison of risk to parents and sibs of cases is more difficult to interpret. Parents of cases appear to have a higher risk compared to sibs of cases throughout most of their lifetime. In the extremely late ages of life however, the cumulative lifetime risks appear to become equal, much as female first-degree relatives of cases show a higher lifetime risk compared to male first-degree relatives of cases throughout most of their lifetimes until the very late ages.

Previous studies present varied results. An earlier study done on a smaller but comparable sample found a higher, but non-significant, cumulative lifetime risk in sibs (Breitner et al., 1984). It was felt that poor or incomplete information on long

dead parents accounted for this difference. In a later study, the poor-quality information on the parental generation was discarded from analyses, resulting in similar risk calculations for both parents and sibs (Breitner et al., 1988). This result is also supported by another investigation which found a much lower but statistically similar lifetime risk among parents and sibs (Farrer et al., 1989). Other studies discount these findings and report a lower lifetime risk among sibs. These results may not be directly comparable however, as the first (Heyman et al., 1983) reports risk to only age 75, and the second (Heston et al., 1981) used only index cases diagnosed by examination of histopathologic material without benefit of a clinical history. It is important to note that the information regarding sibs may be more reliable than that for parents. Since sibs are contemporaries of cases, current knowledge is available when assessing medical histories. This is not the case for most of the parental generation who will have been deceased for at least 25 or 30 years at the time the family histories were collected making it more likely that some information will be forgotten or lost.

The results presented by this study support the majority of evidence and suggest that lifetime cumulative risk for parents and sibs are equal, thus providing evidence against an autosomal recessive gene(s) playing a part in the etiology of the majority of AD cases. Results show equal cumulative lifetime risks, but significantly different age-specific risk curves between parents and sibs of AD cases and an identical risk among parents and sibs of controls. Taken together, this evidence might suggest that

the differential age-specific expression in parents and sibs of cases is due to the effect of non-genetic factors on individuals with an identical genetic predisposition.

A recent investigation provides an example of the magnitude of an environmental agent's effect changing through time. A study on the epidemiology of asthma found the incidence rate of the disease was doubling and tripling among children and adolescents during the period from 1964 to 1983, whereas the incidence rates for adults and infants had remained constant (Yunginger et al., 1992). The authors suggested this increase in incident rates could be partly due to "unidentified environmental factors that preferentially exert their effects upon the lower airways of growing children...". They further suggest that the changes in the air exchange rates of newer, more energy efficient homes built in the last twenty years has resulted in increased levels of indoor allergens; the predominant cause of asthma. One might propose an analogous environmental factor exerting a greater impact on the parental generation resulting in the differential age-specific expression in identical genetically susceptible individuals, while having a diminished effect on the age-specific expression in less genetically susceptible individuals.

A recent workshop examining the role of environmental factors in the etiology of neurodegenerative disorders came to the consensus that a wide variety of agents including food additives, natural food contaminants, and atmospheric contaminants play a role in the etiology of some of these disorders (Henneberry and Spatz, 1990). Epidemiological studies examining exposure to all known environmental risk factors including aluminum, viruses and organic solvents may help to elucidate a possible

cause for the observed difference in risk. As previously suggested, if a multifactorial etiology plays a major role in AD, altering a susceptible individuals exposure to environmental risk factors could result in the delayed expression of the disease, past the age-of-death, a possible means of decreasing the incidence of AD exists.

## 4.4  First-Degree Relatives of Early-Onset and Late-Onset Cases

The partioning of the first-degree relatives of AD cases into early-onset and late-onset subgroups based on the age-of-onset of the proband, ($<65, \geq 65$), while somewhat arbitrary, follows the convention of several previously published reports (Huff et al, 1987; Selzer and Sherwin, 1983). It should be noted that the division of families based solely on the proband's onset age may not necessarily reflect the overall age-of-onset pattern within a family. It has been suggested that division of families based on the age-of-onset of proband is a method by which this heterogeneous disorder could be successfully partioned. It was further suggested that early-onset cases contained a greater familial component than late-onset cases (reviewed by Nalbantoglu et al., 1990).

The lifetime cumulative risks and lifetime risk curves to first-degree relatives of early-onset and late-onset cases appear to be similar. Although the lifetime risk curves are shown to be homogeneous overall by a log-rank test, risk to first-degree relatives of early-onset cases is elevated at an earlier age. Two previous studies (Farrer et al., 1989; Huff et al., 1988) present results which suggest that while no difference in cumulative lifetime risk exists between the two relative subgroups, a

difference in lifetime risk curves does exist. Similar age-of-onsets within families have been previously reported (Heston et al., 1981; Larsson et al., 1963; Powell and Folstein, 1984) leading one group to theorize the possible existence of an allelic, or tightly linked modifier gene of an AD gene (Huff et al., 1988). The results presented here, as well as those of several other studies (Breitner et al., 1988; Heyman et al., 1983; Heston et al., 1981) do not find any evidence of a modifier gene having a significant effect in the majority of cases, and do not support the proposal that individuals with an affected first-degree relative suffering from an early-onset form of the disease have a greater lifetime risk to develop AD.

A study on kindreds suffering from FAD by Farrer et al. (1990) found a higher risk in first-degree relatives of late-onset FAD families (86%) compared to first-degree relatives of early-onset FAD families. This suggests that two or more mechanisms may be involved in the disease etiology, with the possibility of both genetic and non-genetic cases (phenocopies) being expressed within the same family.

Taking into account these results, as well as the studies linking a late-onset FAD subset of individuals to chromosome 21 as well as chromosome 19, suggests that etiological heterogeneity exists, and partioning families by age-of-onset of the proband is not necessarily a way of increasing the chances of identifying FAD families.

## 4.5 Methodology Caveats

Although this is the largest study of its kind to date, and rigorous methods were used to document reportedly affected relatives, investigations of this type do have limitations, many of which are unavoidable. The most obvious drawback is the greatly diminished number of individuals surviving to the later ages of life. The decreasing numbers of individuals surviving into the eighth and ninth decades of life are reflected in the standard error of the risk estimates to these ages. In the present study this effect is most conspicuously evident in the risk calculations to male first-degree relatives of both cases and controls. This restriction will decrease somewhat as clinics continues to document family histories and the samples increase to a size to which minimal standard errors will be assumed by the cumulative lifetime risk estimates.

Since both the case and control samples were population based, ascertainment bias was minimal. Both samples are representative of the entire population of B.C.. Although the literature does not provide evidence of significant differences in the overall prevalence rates of AD within different ethnic groups, the infrequent occurrence of FAD clustering within certain ethnic groups has been documented (Bird et al., 1988; Goudsmit et al., 1981). Since FAD cases represent only approximately 5% of cases diagnosed with AD at the "Alzheimer Clinic" and since no overt "clustering" of ethnic groups has been noted for patients attending the "Alzheimer Clinic", any effect that the differing ethnicity of the case sample may have on results should be minimal. A detailed examination of the ethnicity of the elderly

B.C. population in comparison to the ethnicity of patients diagnosed with AD at the "Alzheimer Clinic" would be one way to conclusively rule out any ethnic differences between case and control samples.

An issue which is harder to address is that of collecting controls. Although the mean age of the control sample is at the age where most cases of AD should be evident, obviously this group may contain "at-risk" individuals who have not yet reached their age-of-onset. At present there is no method to determine which of these controls is susceptible. Even the use of family histories collected from non-demented, cognitively unimpaired elderly deceased individuals would not solve this problem as the age-of-death could occur before the age-of-onset in some individuals. The result of this dilemma may be the dilution of the homogeneity of the control proband sample. However, due to the advanced age of the sample used in this study this problem may be minimal.

The clinical diagnosis of cases gives approximately 90% accuracy in assigning diagnosis (Tierney et al., 1988) which, though excellent, will still result in the dilution of the homogeneity of the case proband sample. This problem can be minimized as the number of "autopsy-confirmed", definite AD, case probands which have been diagnosed based on clinical and neuropathological examinations also increases as clinics continue to collect data.

Another issue which is difficult to address is the form of the data, and the method of analyses. The data on individual first-degree relatives does not represent a collection of independent observations, but rather "clusters" of non-random

observations (ie. family histories). To date, no adequate means of taking this "clustering" into account has been used in studies of this type. The resolution of this quandary can only be accomplished by the future development of suitable analytical methods by statisticians.

Finally, the difficulty in determining the unknown age-of-onset for a long dead relative will remain intrinsic in studies utilizing the "family-history" method. One solution is the use of a recently developed maximum-likelihood method utilizing the EM algorithm (Cupples et al., 1991). This method uses a maximum-likelihood technique to estimate the age of onset distribution among relatives with both known and unknown ages-of-onset. This method was not used for the present study due to the authors having some reservations as to the application of the program in its' current form to the problem of lifetime risk estimation (personal communication). However, with further refinements, the use of this method should facilitate more accurate risk estimate calculations in data sets containing some missing information.

## 4.6 AD Models

Evidence to date suggests that the etiology of AD is complicated, and the prospect of discovering a single cause for the disease now seem nonexistent. An early model proposed by Bird et al. (1989) which draws analogies to the complex etiology of atherosclerosis is one possibility that seems to encompasses the body of evidence to date. Atherosclerosis, like AD, is a very common disease with a complex multifaceted etiology. Atherosclerosis has a final common pathway with arterial fatty

plaque deposits and coronary artery disease. The factors leading to this pathway are many and varied, with evidence pointing at environmental factors (including serum lipids as influenced by diet, blood pressure and smoking) several different monogenic factors, and multifactorial combinations of genetic and environmental factors. A definite familial risk has been recognized and numerous mutations have been identified in several genes including the LDL receptor as well as applipoproteins A-I, C-III, A-IV, and A-II (reviewed by Breslow et al., 1989). This model would appear to have parallels to the presumed cascade of events leading to AD. Whether genetic and environmental influences interact on a common pathway, or act separately to influence the disease outcome remains unknown and continuing studies are needed to clarify these interactions. However, this model provides a useful framework for further research into the etiology of AD.

Several recent proposals would seem to fit into this general model framework. Hardy and Higgins (1992) hypothesize that any number of causes can initially trigger the final cascade of ß-amyloid protein. Their hypothesis further proposes that the deposition of ß-amyloid protein is the final pathway leading to the pathologic changes characteristic of AD. Potter (1991) offered a hypothesis that can also be placed in the framework of this general model. One of the "triggers" proposed by Hardy and Higgins (1992) could be the accumulation of trisomy 21 cells developed through abnormal segregation during mitosis, which leads to AD through the same mechanism by which trisomy 21 DS patients develop the disease (Potter, 1991). The model also proposes this abnormal segregation could be caused by an inherited

genetic mutation near or at the centromere of chromosome 21, as well as through exposure to environmental agents like aluminum. Another model which fits into this overall framework is that of Tanzi and Bradley (1991) who hypothesize that mutations in the APP gene disrupt a translational regulatory stem-loop structure in the APP messenger RNA. The regulatory loop contains a consensus sequence characteristic of the "iron responsive elements", which would allow for both genetic and environmental factors to effect APP production, and eventually lead to the abnormal deposition of ß-amyloid protein. More recently Spurr et al. (1992) found that the frequency of mutations in cytochrome P450's and glutathione S-transferase, genes having a central role in the metabolism and detoxification of drugs as well as environmental and endogenous chemicals, occur more frequently in AD cases when compared to controls. This evidence lead the researchers to conclude that "genetic susceptibility to the environment may explain the majority of disease occurrence".

Placed into the context of this general model, the results presented by this study show that the less than 50% increased risk to all first-degree relatives of cases over first-degree relatives of controls is evidence of etiologic heterogeneity. A small proportion of these cases follow a model of transmission compatible with autosomal dominant inheritance, however the cumulative lifetime risk to all first-degree relatives of AD cases suggests that an autosomal dominant gene(s) is not responsible for all cases of AD, and that multifactorial inheritance may play a major role in the disease etiology. Although a polygenic model cannot be ruled out, given the preponderance of evidence from epidemiological studies, it seems likely that environmental agents

may play a part in the disease etiology. These same non-genetic agents may also play a part in the differential age specific expression seen between females and males as well as between parents and sibs.

# 5 CONCLUSION

The results presented in this study add to a growing body of evidence that suggest that AD is a etiologically heterogeneous disorder. The early hypothesis advocating all cases of AD are due to a fully penetrant autosomal dominant gene(s) are no longer supported by this investigation.

The elevated risk to all first-degree relatives of AD cases over all first-degree relatives of controls as well as the results of risk analysis to "FAD only" first-degree relatives are evidence that a genetic component to the etiology of AD exists. The lower lifetime risk estimates presented in this investigation agree with those reported for the "original" sample (Sadovnick et al., 1989), and probably reflect the stringent criteria used in accepting a relative as "affected", as well as the minimal ascertainment bias in identifying cases. Confidence in results is increased due to the relatively large size of the sample investigated and the agreement in results between the "original" sample and "replication" samples.

The increased risk to all subgroups of first-degree relatives of cases compared to the analogous subgroups of first-degree relatives of controls suggests that the genetic contribution to the etiology of AD is not generational or gender specific. However, although an equal cumulative lifetime risk for female and male first-degree relatives of cases exists, female first-degree relatives seem to be at a higher risk throughout most of their lifetime suggesting a differential age-specific expression of an analogous genetic predisposition exists. A similar age-specific differential expression appears to

exist between parents and sibs of cases with parents showing a higher risk throughout most of their lifetime. Possibly, differences in hormonal or environmental exposure may account for the differences in the expression of AD. If exposure to such an environmental risk factor plays a major role in the age-specific expression of AD, the possibility of delaying the onset past the age-of-death as a means of decreasing the overall incidence of the disease exists. The identification of possible risk factors is therefore vitally important, and the continued conduct of large case-control studies is of major import.

The separation of families into early-onset and late-onset aggregates based only on the age-of-onset of the proband as a means of identifying a larger proportion of families which exhibit an autosomal dominant model of disease transmission seems unfounded based on the results of this investigation. Further, the molecular genetic studies identifying a subset of late-onset families with an autosomal dominantly segregating FAD gene discounts the supposition that families exhibiting an early-onset are a means by which to identify FAD families.

An important step in the process of unravelling the complex etiology of AD is to collect and document those families meeting a strict criteria for FAD. As previous investigations have shown, using these families in linkage analysis studies allows the identification of purely genetic etiologies of AD. A clinical marker making a simple definitive diagnosis of AD is another necessary step in improving studies of this type, hopefully leading to the final goal of finding therapies to extend the age-of-onset past the age-of-death, or ultimately finding a cure.

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# Appendix A

Family History Questionnaire

**MEMORY**

Did (does) the
subject have any
problems with:

| | YES | NO | Don't Know | Date |
|---|---|---|---|---|
| **1)** memory? | — | — | — | ———— |
| **2)** remembering peoples names? | — | — | — | ———— |
| **3)** recognizing familiar faces? | — | — | — | ———— |
| **4)** finding way about indoors? | — | — | — | ———— |
| **5)** finding way on familiar streets? | — | — | — | ———— |
| **6)** remembering a short list of items? | — | — | — | ———— |

**7)** did trouble with memory begin suddenly __ or slowly __?

**8)** has the course of the memory problems been a steady downhill progression __ or have there been abrupt declines __?

**9)** Ever see a doctor for memory problems?   —   —   —   ————

**10)** If yes, what was the cause given _____

**EXPRESSION**

**11)** Ever have trouble finding the right word or expressing self?

   —        —        —        ———

**12)** talking become less over time?

   —        —        —        ———

**13)** tendency to dwell in the past?

   —        —        —        ———

**DAILY FUNCTIONING**

**14)** Trouble with household tasks?

   —        —        —        ———

**15)** Handling money?

   —        —        —        ———

**16)** Grasping situations or explanations?

   —        —        —        ———

**17)** Difficulty at work? (N/A __)

   —        —        —        ———

**18)** Trouble dressing or caring for self?

   —        —        —        ———

**19)** Trouble feeding self?

   —        —        —        ———

**20)** controlling
bladder and bowels?    —      —      —      ——

**21)** agitation and
nervousness?    —      —      —      ——

**OTHER PROBLEMS**

**22)** High blood
pressure?    —      —      —      ——

**23)** Stroke?    —      —      —      ——

**24)** More than 1
stroke?    —      —      —      ——

**25)** Is one side of
body weaker than
other side?    —      —      —      ——

**26)** Parkinson's
disease? (tremors,
shuffling gait,
rigidity of limbs)    —      —      —      ——

**27)** Injury to the
head resulting in a
loss of consciousness
for more than a
second or two?    —      —      —      ——

**28)** Seizure or fits?    —      —      —      ——

**29)** Syphilis?   —      —      —      _____

**30)** Diabetes?   —      —      —      _____

**31)** Drinking problem? (if alcoholism suspected explore further SADS Sxs)   —      —      —      _____

**32)** Did memory problems coincide with drinking?   —      —      —      _____

**33)** Ever depressed or sad for two weeks or more? (if depression suspected explore further SADS Sxs)   —      —      —      _____

**34)** If yes, ever seek treatment?   —      —      —      _____

**35)** Ever very high, euphoric, top of the world?   —      —      —      _____

**36)** If yes, ever seek treatment?   —      —      —      _____

**37)** Ever seek psychiatric or psychological help for any reason?   —      —      —      _____

**38)** If yes, ever
hospitalized for
psychiatric illness?          __            __            __            ____


**39)** Down's
syndrome?                     __            __            __            ____


**40)** Other medical
problems we have
not talked about?             __            __            __            ____


## MEDICAL CONTACTS

**42)** Name and address of first doctor seen for problems _____

_____

_____


**43)** Ever receive
medications?                  __            __            __            ____


**44)** Ever receive a
neurological or
psychiatric exam?             __            __            __            ____


**45)** Ever receive a
CAT scan?                     __            __            __            ____


**46)** Ever in an
institution?
(name _____)             __            __            __            ____

**47)** What was the diagnosis given for the problem? _____

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## RECOGNITION

**48)** Who was the first person to notice something wrong?_____

**49)** What was noticed?_____

**50)** When was the last time (the subject) seemed to be really well, or his old self?_____