"Familial Parkinson's Disease" – A Case-Control Study of Families

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ABSTRACT: ***Background:*** Parkinson's disease (PD) patients frequently report a family history of PD and this may provide etiological clues to PD. It has also been suggested that a report of a negative family history is reliable. We studied the prevalence of PD in relatives of PD patients to assess the reliability of family history and to evaluate possible explanations of "familial PD"(fPD). ***Methods:*** 81 of 650 (12.5%) PD probands (all PD patients seen at clinic in 4 years) reported a positive family history of PD. Each fPD proband was matched with non-familial PD (nfPD) proband by gender and year of birth. Screening and follow-up questionnaires were mailed to relatives to obtain information concerning pedigree and presence of neurodegenerative disease. Available family members (regardless of disease status) were examined. ***Results:*** On examination, 8 persons, said to be "normal" by probands, relatives and themselves, had definite or possible PD (5 fPD, 3 nfPD). The prevalence rate of PD among first and second degree living relatives of probands varied significantly between fPD and nfPD groups (6269/100 000 versus 1190/100 000; $p < 0.001$). The weighted prevalence (taking into account the proportions of fPD and nfPD within the clinic) was 1822/100 000, a value more than 5 times higher than reported prevalence rates of PD in the general population ($p < 0.001$). The prevalence rate was greater in first degree relatives than second degree. ***Conclusions:*** "Familial parkinsonism" cannot be explained merely by size of or advanced age within families. Significant numbers of previously unrecognized PD patients may be identified despite a "negative" family history. That is, the patient's report of an absence of familial parkinsonism is frequently inaccurate. The prevalence rate in relatives of PD patients appears to be higher than the general population – regardless of the family history reported by a PD patient. We believe our study suggests that genetic influences or early life environmental exposures are likely to be of etiological importance in PD.

RÉSUMÉ: "Maladie de Parkinson familiale" – Une étude familiale cas-témoins. ***Introduction:*** Les patients atteints de la maladie de Parkinson (MP) rapportent souvent une histoire familiale de MP, ce qui pourrait fournir des indices étiologiques sur la MP. Il a également été suggéré qu'on peut se fier à une histoire familiale négative fournie par le patient. Nous avons étudié la prévalence de la MP chez les apparentés de patients atteints de la MP pour évaluer la fiabilité de l'histoire familiale et identifier des explications possibles dans la "MP familiale". ***Méthodes:*** 81 des 650 (12.5%) des propositi (tous les patients examinés à la clinique en 4 ans) ont rapporté une histoire familiale positive de MP. Chaque cas familial de MP (fMP) a été apparié pour le sexe et l'année de naissance à un cas non familial (nfMP). Des questionnaires de dépistage et de suivi ont été postés aux apparentés pour obtenir de l'information concernant l'arbre généalogique et la présence de maladies neurodégénératives. Les membres des familles qui étaient disponibles (sans égard à la présence ou à l'absence rapportée de MP chez eux) ont été examinés. ***Résultats:*** À l'examen, 8 personnes rapportées comme normales par le propositus, par les apparentés et par la personne elle-même, avaient une MP certaine ou possible (5 fMP, 3 nfMP). Le taux de prévalence de la MP parmi les apparentés au 1er et au 2^{ième} degré qui étaient vivants variait significativement entre les groupes fMP et nfMP (6269/100 000 versus 1190/100 000; $p < 0.001$). La prévalence pondérée (en tenant compte de la proportion de fMP et de nfMP dans la clinique) était de 1822/100 000, une valeur plus de 5 fois supérieure à la prévalence de la MP rapportée dans la population en général ($p < 0.001$). La prévalence était plus élevée chez les apparentés au 1er degré qu'au 2^{ième} degré. ***Conclusions:*** Le "parkinsonisme familial" ne peut pas être expliqué simplement par la taille des familles ou par un âge avancé des individus dans les familles. Un nombre significatif de patients atteints de la MP, chez qui le diagnostic n'avait pas encore été posé, peuvent être identifiés malgré une histoire familiale "négative", i.e., l'absence de parkinsonisme familial rapportée par le patient est souvent inexacte. Le taux de prévalence chez les apparentés des patients atteints de la MP semble être plus élevé que dans la population en général, sans égard à l'histoire familiale rapportée par ces patients. Notre étude suggère que des influences génétiques ou une exposition environnementale tôt au cours de la vie ont probablement une importance étiologique dans la MP.

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The etiology of Parkinson's disease (PD or idiopathic parkinsonism) is unknown. Environmental and hereditary factors may play a role in the development of PD. There are clinicopathological reports of families of patients with apparently typical idiopathic parkinsonism where more than one family member has PD, "familial" PD (fPD).[1-4] Evaluation of such fPD pedigrees has led to speculation that PD is inherited as an autosomal dominant trait with reduced penetrance.[2,3] One might hypothesize that affected members in fPD pedigrees developed the condition majoritively because of a significant hereditable influence while those PD patients without a family history of PD ("non-familial" PD, nfPD) developed the disorder more as a consequence of acquired factors. We studied

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families of PD probands to identify 1) whether families in which probands report multiple members with PD (fPD) actually *do* have more affected members than those who do not report a positive PD history (nfPD families), 2) whether multiple instances of PD occur more frequently in some pedigrees merely on the basis of family members' age and size of family, 3) the accuracy of a negative PD family history, and 4) whether differences exist in terms of early life residence (urban vs. rural, shared vs. non-shared) between the fPD and nfPD families. A case-control study approach was employed, studying relatives of fPD and nfPD patients.

Patients and Methods

We identified all PD patients seen between 1990-1993 at the University of British Columbia movement disorder clinic who reported a positive family history of PD (fPD) by reviewing all out-patient records from this time period (family history was consistently documented in all records by DBC). Only idiopathic PD patients were included in this study. Each of the fPD probands were subsequently matched with an nfPD proband from the same clinic by sex and date of birth. (These matched probands reported a negative family history.) A questionnaire was mailed to each proband (both fPD and nfPD), requesting further information regarding the proband's family pedigree, the health of relatives with respect to neurodegenerative disease (specifically, PD, essential tremor, Alzheimer's disease, motor neuron disease and the "lay symptoms" of each of these conditions), the age, sex, and status (alive/dead) of relatives, and permission to contact relatives for questionnaire and direct interview. With receipt of the proband's questionnaire, another questionnaire was sent to family members identified by the proband, serving to corroborate the information received from the proband (others were similarly contacted by telephone when phone numbers were "listed"). Family members (from fPD and nfPD families) living in the region were asked to come to the clinic for direct interview, permitting pedigrees to be assessed with them for accuracy and completeness (collecting information on their relatives' sex, age, and neurological health status, including whether any had features of slowness, memory troubles, or weakness, to the best of their knowledge). Such individuals were also examined by one or more of the authors. Videotapes were made and authors who had not seen the patient in person viewed these "blindly" for diagnosis. When family members did not know the health status of a relative, or had no recent information about the relative (within the past two years for living persons and at the time of death for deceased), that relative was not recorded within the family pedigree. Persons said to have PD were identified and classified according to whether the diagnosis was made by a neurologist, a general physician, or merely according to the interviewee. When examined in person, patients were classified as having "definite PD" when they had two of the three cardinal features of PD (resting tremor, bradykinesia, and rigidity) and as "possible PD" when they had one. Family pedigrees were constructed using the information provided by questionnaire and interviews. Pedigrees were restricted to three generations, i.e., including the proband's and generations immediately prior to and after the proband's. Additionally, information concerning early life residence (i.e., urban vs. rural residence during the first two decades of life) and shared environmental exposure with the proband (i.e., shared residence at any time during life for more than two months) were collected, as possible, for all family members.

Descriptive statistical summaries were tabulated concerning the diagnosis, age, sex, number of living, residence, and shared environmental characteristics in fPD and nfPD families, with statistical comparisons being made between the two in regard to these features. Kaplan-Meier survival analyses were performed, in which the age of diagnosis of PD was the end-point and relatives who did not develop end-point were entered as censored, at their current age or age at death. Hence, these were comparisons of the distributions of age of PD diagnosis among various groups of relatives. Further comparisons were performed with previously published data concerning door-to-door surveys regarding the prevalence of PD in the general population.[5]

Results

Eighty-one fPD (12.5%) and 569 nfPD probands were retrieved from 650 out-patient PD records; the 81 fPD probands were matched successfully by sex and within one year of birthdate to nfPD probands. One hundred of 162 (62%) questionnaires were returned by probands (49 fPD and 51 nfPD). Twelve probands were found to be deceased (9 fPD, 3 nfPD) at the time of the initial questionnaire mailing. Fifty could no longer be reached at their previous address (nor could they be located through telephone directory assistance). One hundred and fifty-four family members were subsequently contacted: 53 questionnaires were mailed to proband family members whose addresses had been indicated by probands (31 to fPD and 22 to nfPD) and 30 of these were subsequently returned by mail (12 by fPD and 18 by nfPD); 124 family members (whose telephone numbers had been listed by probands) were contacted by telephone (66 fPD and 58 nfPD). In summary, data concerning pedigree and PD were collected in 93 familes (48 fPD and 45 nfPD families). Information concerning the presence of neurodegenerative disease and other demographic data was obtained in 2264 individuals via questionnaire and in 122 from interview and examination, forming the database in this study (see Tables 1 & 2).

Table 1: PD Family Information.

	fPD total/alive	nfPD total/alive
Pedigrees (probands)	48/48	45/43
Family members	1394/768	992/574
Family size range (persons)	5-63/1-49	5-56/1-51
Mean family size	29.5/16.0	22.0/13.3
Sex, M:F	460:464/214:229	428:311/202:174

(total = dead and alive; considering all first and second degree relatives in which information was available; alive = alive at the initiation of the study)

Four persons (two from fPD and two from nfPD families) who were said to be "normal" by probands, relatives, and who themselves thought they were normal, were examined by the authors and found to have definite PD; similarly four persons (three from fPD and one from nfPD families) were found to have possible PD. Videotapes of these individuals were reviewed by a co-author in a "blinded" fashion with the same diagnostic conclusions being made.

Table 2: Diagnostic Classification in Pedigrees.

Diagnosis	fPD total(alive)	nfPD total(alive)
definite PD – examined by authors	59 (59)	47 (47)
possible PD – examined by authors	3 (3)	1 (1)
PD – examined by a neurologist	13 (5)	2 (0)
PD – examined by another physician	19 (6)	2 (0)
PD – by relative's account	16 (5)	5 (4)
"shaking, slow" by relative's account	5 (1)	1 (1)
possible PD, by questionnaire	3 (3)	0 (0)
normal by relative's account	1260 (675)	888 (483)
normal (-ve), by questionnaire	4 (5)	14 (14)
-ve – examined by authors	7 (7)	5 (5)
no information	5 (0)	27 (16)
TOTAL	1394 (769)	992 (571)

The "diagnosis rate" (considering the entire pedigree – alive and dead) of PD among first (parents, siblings, and children) and second (grandparents and uncles/aunts) degree relatives of probands varied significantly ($p < 0.001$) between fPD and nfPD groups. The diagnosis rate of PD in relatives of fPD probands was greater than in nfPD probands, with a weighted prevalence of 1244/100 000 (considering the UBC movement disorder clinic as a whole: 12.5% fPD and 87.5% nfPD). If newly identified "definite" and "possible" PD patients were included, the weighted diagnosis rate was 1789/100 000 (see Table 3).

Table 3: Epidemiological Rates for Parkinson's Disease in Relatives of Probands.

	fPD	nfPD	weighted MDC^	general population[5]
diagnosis rate /100 000^^				
"definite"	4828*	734	1244	
+ "possible"	5337*	1284	1789	
prevalence rate /100 000				
"definite"	6269*,**	1190**	1822**	347
+ "possible"	6769*	1587	2225	

^ calculated to take into account true proportion of fPD and nfPD pedigrees within the UBC movement disorder clinic

^^ for PD in whole pedigree (living and dead) over age 40 years; diagnosis rate includes all persons ever carrying the diagnosis divided by the total number of persons within the pedigree; in contrast, prevalence rates indicate the rate among all those living at a single point in time.

*$p < 0.001$, vs. nfPD

**$p < 0.001$, vs. general population

When prevalence rates were calculated (considering only living persons aged 40 years or older), the rate was significantly greater in fPD relatives than in nfPD families; with a weighted prevalence rate of 1822/100 000. The relative risk of PD for first and second degree relatives of fPD probands was 5.27 times higher than in nfPD relatives and 18.1 times higher than the general population (aged 40 years or older); the relative risk for relatives of nfPD probands was 3.4 times higher than the general population (347/100 000[5])(see Table 3).

First degree relatives of probands (both fPD and nfPD) were more likely to develop PD than second degree relatives ($p < 0.00001$). The survival probability of not developing PD by age 80 was 52% (std. error 8%) in first degree relatives compared to 86% (std. error 6%) in second degree relatives.

No significant differences were observed between fPD and nfPD families in the prevalence of Alzheimer's disease or amyotrophic lateral sclerosis in first and second degree relatives (the total number of pedigrees with a history of dementia was 9 and motor neuron dysfunction 1; no significant differences between frequency in fPD and nfPD pedigrees were found).

There was no significant difference in family size between fPD and nfPD pedigrees (Mann-Whitney U test). Pedigrees from fPD were significantly older in age distribution ($p < 0.001$) than nfPD families. When considering all family members or only those living, the two groups of pedigrees showed similar numbers of siblings (same generation) and aunts/uncles (older generation) (Table 4). Similar proportions of fPD and nfPD pedigrees were living. When the prevalence rates in the two populations were compared up to age 65 years, the fPD families had a higher rate of PD than the nfPD families (7.5% vs. 3.2%, $p = 0.03$). However, when the same groups were compared, including the age group 65-80 years, the corresponding prevalence rates were not statistically significantly different (29.2% vs. 27%, $p = 0.88$). The fPD pedigrees were more likely to report rural residence during the first two decades of life ($p < 0.001$) and less likely ($p < 0.001$) to report shared residence with the proband (at any time during life) than nfPD pedigrees (see Table 5).

Table 4: Family Relationship to Proband.

	fPD total (alive)	nfPD total (alive)
Siblings (Brothers/Sisters)	186 (126)	154 (94)
Mean number of Siblings	3.38 (2.63)	3.42 (2.19)
Children	71 (69)	118 (115)
Mean number of Children/proband	1.48** (1.44**)	2.62/2.67
Half siblings	6 (3)	4 (4)
Uncles/Aunts	276 (57)	214 (66)
Mean number of Uncles+Aunts/proband	5.75 (1.19)	4.76 (1.53)

** $p < 0.001$

Table 5: Residence^ and Shared Environment^^.

	fPD total (alive)	nfPD total (alive)
Residence		
Urban	69 (59)	75 (46)
Rural	106** (80**)	72 (26)
Mixed	55 (37)	61 (41)
Unknown	1164	804
Shared Environment		
Yes	365 (230)	586** (229**)
No	181 (152)	43 (38)
Unknown	848 (386)	363 (397)

^ = residence during first two decades of life

^^ = shared residence (for more than two months at any time during life)

** = $p < 0.001$

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There was no significant difference between fPD and nfPD pedigrees in terms of the age of onset of PD symptoms in affected family members (mean age at onset of symptoms in fPD = 61 ± 13 yrs, nfPD = 59 ± 11, including probands and affected family members). In both groups of pedigrees, there was significant correlation between the age at onset of PD symptoms in the probands and secondary cases ($p < 0.01$) (Person's correlation coefficient = 0.686). There was no significant correlation between the year of onset of PD symptoms in probands and other affected members within the pedigree.

A significant difference in the age at end-point in the Kaplan-Meier analysis (in which the age of diagnosis of PD was the end-point, those not developing end-point being censored at the current age or age at death) among first degree relatives was identified; those of fPD probands had a mean age at diagnosis of 77.9 years, those of nfPD probands 79.6 ($p = 0.04$, 282 and 263 observations respectively); the mean among second degree relatives was 84.3 and 79.6 ($p = 0.02$, 650 fPD and 377 nfPD observations). When fPD and nfPD were combined, and first and second degree relatives were compared across patients, the first degree mean age was 79.0 years and second degree 85.0 years ($p < 0.0001$, 536 and 1025 observations). When first and second degree relatives were combined, and fPD and nfPD compared, the mean age in both groups was 82.4 years (NS, 924 and 637 observations). When first and second degree, and fPD and nfPD were combined, i.e., all patients and relatives, and compared shared environment vs. non-shared, no significant differences were found (shared: mean age = 78.4, non-shared = 71.1; $p = 0.77$, 475 and 181 observations). Sub-group analysis (first degree only, second degree only, fPD only, nfPD only, etc.,) also showed no significant differences between shared and non-shared. Comparisons of urban vs. rural also showed no significant difference when patients were pooled (urban: 72.2 years, rural 72.6; $p = 0.7$). In short, the only significant findings were in first vs. second degree relatives (fPD and nfPD pooled, $p < 0.0001$) and in fPD and nfPD (first degree alone and second degree alone).

Discussion

This study reviewed the prevalence of parkinsonism in family members of PD patients seen at a large clinic. Comparison of the prevalence in relatives from the group as a whole and the expected prevalence, based on prevalence rates in the general population, allowed determination of the relative risk of PD in the patient's families. By studying sub-groups – those *with* and *without* a reported positive family history, an attempt was made to identify whether there were simple explanations for the perceived frequency of parkinsonism within certain families (i.e., adjusting for family size/age). We also wished to ascertain whether there were other determinants (apart from genetic factors) for increased risk (such as shared residence) in "familial" parkinsonism. We hypothesized that a possible explanation for some instances of "familial" parkinsonism merely stemmed from family size and age distribution. PD being a fairly common condition, one would expect that patients from larger families (and those with more elderly individuals) would be more likely to have other affected relatives. We also hypothesized that shared residence might be as important a factor as genetic similarities in determining risk for PD. Finally, we attempted to examine as many family members as possible to help establish the accuracy of the family history reported by the proband.

Studies evaluating prevalence of PD are necessarily complicated by the fact that the likelihood of manifesting disease increases with age. Consequently, prevalence studies must account for not only the number of persons at risk but also their ages. Family studies must consider these issues when comparing risk within families to that of the general population, as different levels of scrutiny may be operating during the process of data collection and patient selection bias. Finally, information from pedigrees must be compared directly with similarly derived pedigree information. Otherwise, pedigree studies may give the false impression of an inordinately high risk for a disorder merely because pedigrees typically outline multiple generations, thereby increasing the probability of finding multiple instances of a disorder.

No study of PD prevalence has ever been reported in which data were obtained by a neurologist evaluating persons "door-to-door" in a community. The study from Copiah County, MS, reported by Schoenberg et al.[5] represents the best attempt at obtaining a true estimate of PD prevalence. In their study an initial door-to-door survey, employing questionnaires applied by "medically unsophisticated interviewers," was used to screen for persons who were later to be examined by a neurologist. Three per cent of households did not participate in the initial questionnaire process and a further 15% of individuals, who were identified as requiring an examination, refused to be evaluated. Consequently, the vast majority of persons in this study were never examined by a neurologist. Nevertheless, using such an approach, the prevalence of PD (age 40+) was calculated to be 347/100 000, with over 40% of identified cases being newly diagnosed. These values closely correspond to other prevalence data, based on medically serviced patients, when one takes into account the newly identified (and previously unserviced) contribution to overall prevalence.[6] Consequently, the Schoenberg study value of 347/100 000 represents the highest prevalence rate reported in the general population. Prevalence rates from any sample (regardless of their source, i.e., relatives of fPD or nfPD or neighbors of PD probands, etc.) that are higher than this value would have to be interpreted as being from a sample with higher risk for PD than the general population. Our study actually employed a process somewhat comparable to the Schoenberg study in that *in person* examinations (of both reportedly affected and unaffected relatives) followed a screening questionnaire whenever possible. Hence, prevalence comparisons in our study should be made with the highest prevalence rates reported. Despite comparison with these high prevalence rates, we found the weighted prevalence value of PD in our patients' relatives (not counting probands) to be significantly greater than the figure derived from the Copiah County, MS data. Our weighted prevalence figure of 1822/100 000 (taking into account both pedigrees and considering persons who were living and 40 years or older) is 5.3 times higher ($p < 0.001$) than that reported by Schoenberg et al.[5] We found that the prevalence rates in relatives from both subgroups demonstrated a significant disparity between first and second degree relatives. First degree relatives were significantly more at risk for PD than second degree relatives. Furthermore, the magnitude of the difference in prevalence was consistent with that predicted on a Mendelian basis, assuming shared genetic makeup as the sole reason for

The study presented is far from ideal. Ideally, all historic information (concerning residence, etc.) would be available and all pedigree members examined. However, the ideal study, including multiple generations spread across the world, will never be accomplished. Our study of PD family subgroups, those *with* and *without* a reported family history of parkinsonism, does however suggest several points. First, given the fact that at least four new PD patients (and another four with "possible" PD) were identified, who had all been reported as unaffected by probands, relatives and themselves, our experience indicates the importance of neurological examination in establishing the presence or absence of PD. It is certainly possible that those family members who chose to agree to be examined in person already had some inkling of their disorder. However, they denied such in mailed questionnaire and in-person questioning (understandably, as most had only mild signs of PD). In any event, our study suggests that the false-negative rate of historically asymptomatic individuals is not necessarily zero, in contrast to other reports.[2,3] Significant numbers of unrecognized PD patients may be identified despite a "negative" family history. This finding alone calls into question any conclusions based solely on reported family history within pedigrees. Furthermore, while we did not "reverse" a diagnosis of PD, it is certainly plausible that this may also occur fairly frequently. Consequently, it is imperative that every attempt be made to examine all members of pedigrees if genetic studies are being carried out. Having said this, and thereby recognizing the potential folly of our subsequent conclusions, we believe that "familial parkinsonism" cannot be explained merely by family size or age. When taking into account numbers and ages of relatives, fPD families continued to demonstrate a higher prevalence than nfPD families. This finding is not particularly surprising as we defined the two groups presumably upon this basis. Third, in our clinic, relatives of probands *with* and *without* a reported positive family history of parkinsonism are both at higher risk of developing parkinsonism than persons in the general population. This finding is in agreement with previous clinic-based studies (based on family history accounts of patients).[2,7,8] Fourth, the magnitude of increasing risk of PD mirrors that expected on the basis of shared genetic makeup with the proband, that is, first degree relatives have a greater risk than second degree relatives by approximately eight-fold. However, this finding must be considered carefully as other explanations, such as a possible case ascertainment bias favoring first degree relatives, may be important in explaining the disparity in prevalence between first and second degree relatives.

The study did not identify any differences in frequency of dementia or motor neuron disease between nfPD and fPD pedigrees. However, only a small number of pedigrees were identified with such individuals suggesting that the recognition and reporting of these disorders was likely even worse than for parkinsonism.

Other studies have also reported increased risk for development of PD in first-degree relatives of PD patients.[2,9] Payami et al.'s report (using data from questionnaires and some medical records without any examination of relatives by the authors) compared risk for patients' families and unrelated, unaffected persons' families.[9] Our results were similar to their findings of an age-adjusted odds ratio of 3.5, that is, both studies suggest that the risk of PD is increased over threefold for the parents and siblings of PD patients. However, the higher prevalence of parkinsonism in these families does not necessarily merely indicate genetic etiological influences.[10] Family members typically share common environmental exposures and first degree relatives share environment more commonly than second degree. While it was not possible to delineate the relative contributions of shared heredity and environment in our families, our data do suggest that if environmental factors are important in causing PD in these families, these may be particularly shared within the rural setting and during early life (i.e., the first two decades of life – when siblings and parents/children share residence). We found that early life rural residency was more common in fPD pedigrees, the group with the highest risk for developing PD. This would appear to support the initial report[11,12] concerning this factor that has been confirmed by others,[13,14] albeit not consistently.[15] This issue is far from definitively addressed in the present study, as we found relatives in the higher risk fPD pedigree group to have shared residence with probands significantly less often than their lower risk nfPD counterparts. We also frequently could not determine shared residence status. Another confounding factor is that increasing age itself (the fPD pedigrees were older) is also associated with prior rural residence.[16,17] However, given the fact that relatives of fPD and nfPD probands were at significantly greater risk than a general population with greater genetic diversity who all shared residence (at least for a short time during adult life within Copiah County), we suspect that the genetic risk factor may be significant in predisposing for PD. Furthermore, we suggest that if environmental influences are influential in the pathogenesis of PD, those operative during early life (when young parents and siblings typically share residence and environmental exposures) are likely to be the most important. To address this complicated issue fully, a study would have to be performed in which probands were matched with persons of similar early life exposure, age, and gender, etc., with all family members examined.

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