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The Genetics of Depression

A Family Study of Unipolar and Neurotic-Reactive Depressed Patients*

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Abstract. Sixty unipolar (23 male and 37 female) patients and 67 patients (25 male and 42 female) suffering from a neurotic-reactive depressive disorder, consecutively admitted to the Department of Psychiatry of Umeå University have participated in a family study aimed at identifying morbidity risks for psychiatric illnesses among first degree relatives ($n=437$). Besides the classification of affective disorders used in Umeå for research purposes the patients have been classified, according to the ICD-9, DSM-III, age at onset (below or above 40 years), and the Winokur's classification of primary affective disorders. However, only the findings regarding the Umeå classification and the Winokur's classification are given in the present article. Of the patients 90% fulfilled Kendell's criteria for depression at the time of the investigation whereas the others were in a phase of remission when studied. The diagnosis of secondary cases were made without knowledge of the diagnoses of the probands. Among relatives of unipolar probands only two secondary cases of bipolar affective disorder were found—one among parents, and one among siblings (MR% 1.1 and 0.6 respectively). The overall morbidity risk for affective disorders (MR% 22.8 among parents and 15.5 among siblings) proved to be higher than in previous studies. In the families of neurotic-reactive patients the morbidity risk for bipolar affective disorders was also very low (MR% 1.0 among parents and 0.7 among siblings), whereas the overall MR% for affective disorders proved to be surprisingly high (12.1 among parents and 6.7 among siblings). No increased risk for schizophrenia or alcoholism was found among the relatives of either group. When the relatives were divided according to their sex no clear-cut difference in morbidity risk emerged when fathers and brothers were compared with mothers and sisters but alcoholisms occurred more frequently in male relatives. Preliminary findings in second degree relatives suggest that secondary cases of affective disorders might occur among second degree relatives of patients classified as suffering from "sporadic depression" according to Winokur's classification.

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Key words: Unipolar depression - Neurotic-reactive depression - Sporadic depression - Morbidity risk - Genetics

Zusammenfassung. Sechzig (23 Männer und 37 Frauen) monopolare Patienten und 67 (25 Männer und 42 Frauen) Patienten mit einer neurotisch-reaktiven Depression, fortlaufend in die Psychiatrische Klinik der Universität Umeå aufgenommen, nahmen an einer Familienstudie mit dem Ziel das Morbiditätsrisiko (MR) für psychiatrische Erkrankungen unter Verwandten 1. Grades ($n=437$) zu identifizieren, teil. Außer dem in Umeå zu Forschungszwecken angewandten Klassifikationssystems, wurden die Patienten auch gemäß dem ICD-9, DSM-III, Ausbruchsalter (unter bzw. über 40 Jahre alt) und der Winokurschen Klassifikation der primären affektiven Erkrankungen eingeteilt. In diesem Artikel sind jedoch nur die Ergebnisse hinsichtlich der Umeå- und der Winokurschen Klassifikation wiedergegeben.

Neunzig Prozent der Patienten erfüllten Kendells Kriteria für Depressionen zur Zeit der Untersuchung, wohingegen der Rest sich in der Besserungsphase befand. Die Diagnosen der Sekundärfälle wurden ohne Kenntnis der Diagnosen der Probanden gestellt. Unter den Verwandten der monopolaren Probanden wurden nur 2 sekundäre Fälle von bipolaren affektiven Erkrankungen gefunden - einer unter Eltern und einer unter Geschwistern (MR% 1,1 bzw. 0,6). Das Gesamtmorbiditätsrisiko für affektive Erkrankungen (MR% 22,8 unter Eltern und 15.5 unter Geschwistern) erwies sich höher als in früheren Untersuchungen. Auch in den Familien der neurotisch-reaktiven Patienten lag das Morbiditätsrisiko für manisch-depressive Erkrankungen sehr niedrig (MR% 1,0 unter Eltern und 0,7 unter Geschwistern), das Gesamtmorbiditätsrisiko für affektive Erkrankungen dagegen stellte sich als überraschend hoch (12,1% unter Eltern bzw. 6,7% unter Geschwistern) heraus. In keiner der beiden Gruppen zeigte sich ein erhöhtes Risiko für Schizophrenia oder Alkoholismus unter den Verwandten. Bei der Aufteilung der Verwandten nach dem Geschlecht ergab sich, außer für Alkoholismus, der häufiger unter männlichen Verwandten auftrat, kein eindeutiger Unterschied bezüglich des Morbiditätsrisikos, nachdem die Väter und Brüder mit den Müttern und Schwestern verglichen worden waren.

Vorläufige Ergebnisse unter Verwandten zweiten Grades deuten darauf hin, daß sekundäre Fälle von affektiven Erkrankungen unter Verwandten zweiten Grades von solchen Patienten auftreten, die gemäß der Winokurschen Klassifikation als an einer „sporadischen Depression" leidend, bezeichnet werden können.

Schlüsselwörter: Monopolare Depression - Neurotisch-reaktive Depression - Sporadische Depression - Morbiditätsrisiko - Genetik

Introduction

Since the middle of the sixties, studies of affective disorders have taken into account the distinction between bipolar (manic depressive) and unipolar types of

depression suggested by Leonhard (1957) and substantiated by the genetic findings of Angst (1966), Perris (1966) and Winokur and Clyton (1967). Such a distinction is now taken into account both in the International Classification of Disease (ICD-9) of the World Health Organization (WHO 1978) and in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) of the American Psychiatric Association (1980).

In his original work Perris (1966) maintained that the separation of bipolar from unipolar depression was an important step towards the identification of more homogeneous subgroups within the very comprehensive realm of the Kraepelinian manic depressive insanity. However, when analysing the mode of transmission of the two disorders in his original series of probands Perris (1968) suggested that the hypothesis of a possible heterogeneity of both the bipolar and the unipolar types of disorders should be taken into account. Eventually, support for the hypothesis of the heterogeneous nature of bipolar and unipolar depression emerged from the findings of several research workers, and different subdivisions have been proposed resulting in more detailed classifications (Mendlewicz 1974; Maas 1975; Winokur 1979; Carrol et al. 1980; Angst et al. 1981). However, the validity of most of these subdivisions is still uncertain.

In discussions concerning the concept of „unipolar depression" (Klerman 1973; Perris 1973; see also the discussion that followed those papers in the volume edited by Angst 1973) it clearly emerged that the term is used inconsistently by different research workers, both as concerns the severity of the disorder to which it is applied, and as concerns the number of episodes required by different authors before a patient is labelled "unipolar". Furthermore, just how the boundaries of unipolar "endogenous" and "neurotic-reactive" depression are drawn remains unclear.

Apparently, the classification of depressive disorders has followed a different course in Europe and in the USA. In Europe the concept of "unipolar depression" has been regarded as equivalent to that of "endogenous depression", and has been kept separate from that of "neurotic-reactive depression" (Kielholz 1973; Angst et al. 1981; Roth 1981) while in the USA attention has been focused upon a distinction between "primary" and "secondary" depression (Robins et al. 1972), and the concept of "neurotic-reactive depression" does not appear at all in Winokur's classification (Winokur 1979). In the DSM-III, "dysthymic disorder" is equated with "depressive neurosis" but its definition is unclear and mostly inconsistent. In fact, while it maintains that the disorder is expected to be "not of sufficient severity and *duration* to meet the criteria for a major depressive episode" it states in the next line that "in adults *2 years duration* is required". Since the definition also states that "normal periods" in the course of a dysthymic disorder "may last a few days to a few weeks" it seems to suggest more a habitual personality disturbance of the depressive type, than discrete episodes of a milder type appropriate to "major depression". It is also unclear whether a chronicized major depression would be misclassified under the heading "dysthymic disorder" if the definition were strictly followed. Probably, a large proportion of the European "neurotic-depressive" episodes would be classified in the DSM-III in the category of "atypical depression" together with some forms of depression secondary to schizophrenia, thus increasing the confusion.

Table 1. Different meanings of "endogenous depression"

1. Of internal origin. Independent of external events
2. Hereditary
3. A depressive syndrome characterized by diurnal rhythm (worse in the morning) early awakening, retardation, weight loss
4. The depressive phase of a bipolar affective disorder
5. A depressive syndrome in older patients
6. A depressive syndrome which responds favourably to E.C.T.
7. A depressive syndrome of unknown etiology (cryptogenetic)
8. A depressive syndrome occurring in subjects with a stable, non-neurotic premorbid personality
9. A combination of several of the above criteria

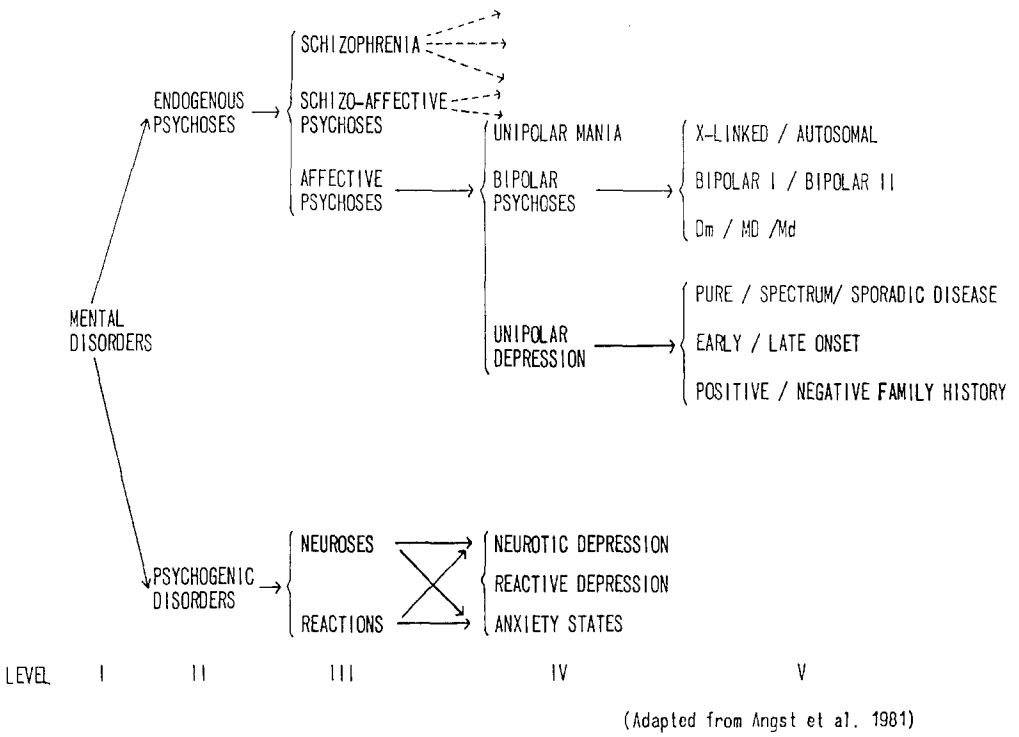

Fig. 1. The classification of depression proposed by Angst

A major source of inconsistency and confusion in studies of depression is found in the different interpretations of the term "endogenous" (Klerman 1973; Perris 1976) some of which are shown in Table 1. In fact, whereas for some authors (Roth 1981) the distinction is based mainly on symptomatology, personality characteristics, the absence of stressful life events and response to treatment, for others (Angst 1981) the main criterion is, apparently, aetiological (Fig. 1).

In the paper from which Fig. 1 has been adapted, Angst pointed out that the question of a continuum of unipolar, neurotic, and reactive depression is still open since we lack comparative genetic investigations for the validation of controversial hypotheses. The study that will be presented in this article is simply intended as a contribution to the solution of this major issue. In fact, we will report some preliminary comparative findings from a family study of depressed patients comprising both unipolar, and neurotic-reactive probands.

Patients and Methods

Depressed patients of any kind, consecutively admitted to the Department of Psychiatry of Umeå University in Umeå have, since 1977, participated in a comprehensive study of depression, which is on-going. Among the several variables taken into account is familial occurrence of mental disorders in first as well as second degree relatives. The patients are classified from their records and from the results of their rating for psychopathology according to different current classifications of affective disorders by two experienced psychiatrists, who are unaware of all the other results.

Definition of "Unipolar" Depressive Disorder

a) Unipolar "Certain". The occurrence of at least three separate episodes of depression of a psychotic severity (i.e. with impaired reality testing) is required.

b) Unipolar "Probable". The occurrence of at least two episodes of psychotic depression in a subject aged 45 years or more with a verified family history of recurrent depressive episodes among the first degree relatives.

c) Unipolar "Possible". The occurrence of at least three separate episodes of severe depression, with melancholic features, occurring apparently indepently from stressful life-events. Not all episodes need to be of a psychotic severity.

In no instances have episodes of mania (hypomania) occurred.

Definition of "Neurotic-Reactive" Depressive Disorder

Refers to the occurrence at any age of one or more episodes of depressive breakdown requiring medical attention but independently, severity of either:

a) Prevalently Neurotic. In subjects with a verified history of a neurotic personality disorder mainly of a depressive, asthenic, neurasthenic or passive-dependent type.

b) Prevalently Reactive. Occurring as an understandable reaction to the impact of a stressful life-event, also in subjects without a verified history of a neurotic personality disorder. To be taken into account, the disorder must be characterized by a dominant depressive symptomatology which affects the subject's feeling of well being and his/her social functioning.

c) Mixed Neurotic and Reactive. A combination of the above mentioned criteria.

Demographic information about the patients and their relatives is obtained from the Parish Registers, whereas information on the occurrence of mental disorders in the family is gathered from the probands and their relatives interviewed at the time of the patient's stay in the Department. Records concerning relatives who had been treated by a different doctor or in another hospital are obtained and a diagnosis of the secondary cases is made by the same psychiatrists, who are ignorant of the relationship between secondary cases and probands, and who applied the same diagnostic criteria to the secondary cases as to the probands. Since the series of probands is so far comprised of some 250 patients divided into several subgroups, and since the psychiatrists who classified their records and those of their relatives did not treat the

Table 2a. The series according to different systems of classification

Groups	*N*		Feighner's criteria					Kendell's criteria of depression			
	M	F	Total	Def prim aff dis	Prob prim aff dis	Def s aff dis	No depr acc to the crit	Yes		No[a]	
Unipolar depression	23	37	60	40	10	0	10	55	90.2%	5	9.8%
RND:	25	42	67	17	13	3	33	59	89.4%	7	10.6%

[a] Depending upon missing information the *n* in the different classifications are occasionally lower than in the Umeå classification

Table 2 b. The series: Diagnostic distribution according to different diagnostic systems

Umeå classification[a]	ICD-classification								
	296.1	296.3	296.4	296.5	296.6	296.9	298.0	300.4	309.0
Unipolar depression ($n=60$)	47 (78.3%)	–	–	–	3 (5.0%)	2 (3.3%)	–	8 (13.3%)	–
Reactive-neurotic depression ($n=67$)	–	–	–	–	3 (4.5%)	1 (1.5%)	–	49 (73.1%)	12 (20%)
Umeå classification[a]	DSM-III classification								
	296.2	296.3	296.5	296.8	300.4	309.0			
Unipolar depression ($n=60$)	2 (3.3%)	54 (88.5%)	–	4 (6.6%)	1 (1.6%)	–			
Reactive-neurotic depression ($n=65$)	8 (12.3%)	24 (37.0%)	–	15 (23.1%)	9 (13.8%)	9 (13.8%)			

[a] Depending upon missing information the n in the different classifications are occasionally lower than in the Umeå classification

Table 2 c. Distribution of the patients according to the Umeå and the Winokur's classification of depression

Umeå classification	Winokur's classification			Others[a]
	Pure depressive disease	Depression spectrum disease	Sporadic	
Unipolar depression ($n=60$)	26 (43.3%)	3 (5.0%)	23 (38.3%)	8 (13.3%)
Reactive-neurotic depression ($n=65$)	16 (24.6%)	12 (18.5%)	31 (47.7%)	6 (9.2%)

[a] Patients with first degree relatives suffering from other psychiatric disorders (for example, schizophrenia)

Table 3. Unipolar probands ($n=60$): overall morbidity among relatives

Diagnoses	Relatives								
	Parents ($n=119$)			Siblings ($n=301$)			Half-siblings ($n=17$)		
	At risk	Cases	MR %	At risk	Cases	MR %	At risk	Cases	MR %
All depr disorders certain + uncertain + suicide	87.5	19	21.7	148	22	14.8	7	–	–
Bipolar disorder	87.5	1	1.1	148	1	0.6	7	–	–
All affective disorders	87.5	20	22.8	148	23	15.5	7	–	–
Schizophrenia	109	1	0.9	216.5	5	2.3	8.5	–	–
Schizoaffective psychosis	109	–	–	216.5	1	0.4	8.5	–	–
Alcoholism	119	–	–	270	3	1.1	14	–	–
Anxiety + other neuroses	87.5	–	–	148	–	–	–	–	–
Other diagnoses	87.5	4	4.57	148	3	2.0	–	–	–
Unspecified disorders without medical care	87.5	14	16.0	148	7	4.7	–	–	–

Table 4. Reactive neurotic probands ($n=67$): overall morbidity among relatives

Diagnoses	Relatives								
	Parents ($n=133$)			Siblings ($n=257$)			Half-siblings ($n=21$)		
	At risk	Cases	MR%	At risk	Cases	MR%	At risk	Cases	MR%
All depr. disorders certain + uncertain + suicide	98.5	11	11.1	134	8	5.9	9	–	–
Bipolar disorders	98.5	1	1.0	134	1	0.7	9	–	–
All affective disorders	98.5	12	12.1	134	9	6.7	9	–	–
Schizophrenia	122	–	–	174	2	1.1	10.5	–	–
Schizoaffective psychosis	122	1	0.8	174	1	0.5	10.5	–	–
Alcoholism	133	5	3.7	233	3	1.2	17	–	–
Anxiety + other neuroses	98.5	–	–	134	3	2.2	–	–	–
Other diagnoses	98.5	2	2.0	134	7	5.2	–	–	–
Unspecified disorders without medical care	98.5	15	15.2	134	4	2.9	–	–	–

patients, we assume that the diagnoses of the secondary cases are not biased by any previous knowledge of the diagnoses of the proband. The fact that some family names are very common in Sweden and among our probands, and that most of the probands and their relatives have different family names because of marriage has also contributed to keeping the diagnostic decision blind. Here the results referring to probands classified as unipolar and neurotic-reactive will be given, and only the first degree relatives will be taken into account.

In classifying primary and secondary cases the following classification system have been used: a general classification of mental disorders, mainly related to the ICD-8 (WHO 1968) as used in Umeå except the affective disorders for which a more detailed classification has been used (see below for the present series), a classification according to the Multi-Aspects Classification Model for Mental Disorders (MACM) (Ottosson and Perris 1973; von Knorring et al. 1980), the ICD-9 (WHO 1978), and the DSM-III. For cases of affective disorders the Feighner et al. (1972) criteria, Winokur's classification (1979), and Kendell's criteria for depression (Brockington and Leff 1979) were also applied. Finally the patients and the sick relatives were also classified according to age at onset of the disorder (below or above 40 years).

The composition of the series used in this article is shown in Tables 2a-d, where the patients are classified according to different systems. For this family study the probands were divided fristly into unipolar and neurotic-reactive according to the Umeå classification, and secondly into the subgroups comprised in the Winokur classification. To the three subgroups proposed by Winokur a fourth has been added, comprising of probands who did not fit into Winokur's subgroups since there were other mental disorders besides affective disorders, alcoholism, and personality disorders among first degree relatives. Separate calculations have been made for female and male probands and for female and male relatives. Half-sibs have been divided according to the parental relationship.

For the calculation of the percentage morbidity risk (MR%), the population at risk has been corrected by using Weinberg's abridged method (Weinberg 1925). For affective disorders a risk period between the ages of 15 and 70 years was taken into account to enable comparison with the previous results of Perris (1966). For schizophrenia the risk period of 15 to 50 years was used, whereas for alcoholism all individuals above 15 years were included, and for old age psychoses all subjects aged over 50.

Results

Tables 3 and 4 show a general survey of the main results when the probands are divided into unipolar and neurotic-reactive. Since no secondary cases were found among the half-sibs, they were omitted in the Tables. In all, 29 unipolar probands and 20 neurotic-reactive patients had at least one relative suffering from an affective disorder. The difference is statistically significant (χ^2, Yates correction = 5.37, $P < 0.05$). The MR% for affective disorders is significantly higher among the relatives of unipolar than those of neurotic-reactive probands (χ^2, Yates correction: for parents = 4.49, $P < 0.05$, for siblings = 6.35, $P < 0.02$). The MR% for unipolar psychosis is very low among the relatives of both series of probands, and for the unipolar group is in agreement with previous results (Perris 1966). Also the risk for schizophrenia and for alcoholism does not seem to be increased.

In both series probands and relatives interviewed reported a high number of relatives with "unspecified mental disorders" for which no medical care had been received. Since most of the subjects who had suffered from "unspecified disorders" had already died at the time of the investigation, it was impossible to reach any closer clinical diagnosis. Very likely probably further cases of depressive disorders might be concealed under this unspecific heading.

As shown in Tables 5 and 6 the MR% for affective disorders is similar among male and female relatives of unipolar probands and only slightly higher among

Table 5. Neurotic-reactive probands ($n=67$)

	Relatives			Morbidity									
	n male (M) and female (F) probands		At risk	All depr disorders		Bipolar disorders		Alcoholism			Schizophrenia		
				n	MR%	n	MR%	n	At risk	MR%	n	At risk	MR%
Fathers + brothers	(M)	67	37	2		–		3	63		–	51	
	(F)	127	71.5	6		–		5	119		1	96.5	
Total		194	108.5	8	7.3	–	–	8	182	4.3	1	147.5	0.6
Mothers + sisters	(M)	69	35.5	6		2		–	63		–	46	
	(F)	128	75.5	6		–		1	122		3	103	
Total		197	111	12	10.8	2	1.8	1	185	0.5	3	149	2.0

Table 6. Unipolar probands ($n=60$)

	Relatives			Morbidity									
	n male (M) and female (F) probands		At risk	All depr disorders		Bipolar disorders		Alcoholism			Schizophrenia		
				n	MR%	n	MR%	n	At risk	MR%	n	At risk	MR%
Fathers + brothers	(M)	88	49.5	10		1		–	80		1	67	
	(F)	138	81.5	13		–		3	131		2	113	
Total		226	131	23	17.5	1	0.7	3	211	1.4	3	180	1.6
Mothers + sisters	(M)	71	38	7		–		–	63		3	52.5	
	(F)	123	66.5	11		1		–	115		1	95.5	
Total		194	104.5	18	17.2	1	0.9	–	178	–	4	145	2.7

Table 7. Winokur's classification. I. Pure depressive disease ($n=41$): overall morbidity among relatives

Diagnoses	Relatives								
	Parents ($n=81$)			Siblings ($n=167$)			Half-siblings ($n=5$)		
	At risk	Cases	MR%	At risk	Cases	MR%	At risk	Cases	MR%
All depr. disorders certain + uncertain + suicide	57	22	38.5	89	21	23.5	2.5	–	–
Bipolar disorder	57	1	1.7	89	2	2.2	2.5	–	–
All affective disorders	57	23	40.3	89	23	25.8	2.5	–	–
Schizophrenia	78	–	–	128	–	–	2.5	–	–
Schizoaffective psychosis	78	1	1.2	128	–	–	2.5	–	–
Alcoholism	81	–	–	161	–	–	5	–	–
Anxiety + other neuroses	57	–	–	89	2	2.2	2.5	–	–
Other diagnoses	57	3	5.2	89	1	1.1	2.5	–	–
Unspecified disorders without medical care	57	8	14.0	89	4	4.4	2.5	–	–

Table 8. Winokur's classification. II. Depression spectrum disease ($n=13$): overall morbidity among relatives

Diagnoses	Relatives								
	Parents ($n=26$)			Siblings ($n=49$)			Half-siblings ($n=3$)		
	At risk	Cases	MR%	At risk	Cases	MR%	At risk	Cases	MR%
All depr. disorders certain + uncertain + suicide	16.5	3	18.1	23.5	2	8.5	1.5	–	–
Bipolar disorder	16.5	–	–	23.5	–	–	1.5	–	–
All affective disorders	16.5	3	18.1	23.5	2	8.5	1.5	–	–
Schizophrenia	23	–	–	29	1	3.4	1.5	–	–
Schizoaffective psychosis	23	–	–	29	–	–	1.5	–	–
Alcoholism	26	4	15.3	42	5	11.9	3	–	–
Anxiety + other neuroses	23	–	–	23.5	–	–	1.5	–	–
Other diagnoses	23	2	8.6	23.5	–	–	1.5	–	–
Unspecified disorders without medical care	23	4	17.3	23.5	3	12.7	1.5	–	–

Table 9. Winokur's classification. III. Sporadic ($n=55$): overall morbidity among relatives

Diagnoses	Relatives								
	Parents ($n=108$)			Siblings ($n=227$)			Half-siblings ($n=6$)		
	At risk	Cases	MR%	At risk	Cases	MR%	At risk	Cases	MR%
All deopr. disorders certain + uncertain + suicide	75.5	2	2.6	110	4	3.6	2.5	–	–
Bipolar disorder	75.5	–	–	110	–	–	2.5	–	–
All affective disorders	75.5	2	2.6	110	4	3.6	2.5	–	–
Schizophrenia	98.5	–	–	163.5	–	–	4.5	–	–
Schizoaffective psychosis	98.5	–	–	163.5	–	–	4.5	–	–
Alcoholism	108	–	–	208	–	–	5	–	–
Anxiety + other neuroses	75.5	–	–	110	–	–	2.5	–	–
Other diagnoses	75.5	2	2.6	110	–	–	2.5	–	–
Unspecified disorders without medical care	75.5	12	15.8	110	1	0.9	2.5	–	–

Table 10. Winokur's classification. IV. Others ($n=15$): overall morbidity among relatives

Diagnoses	Relatives								
	Parents ($n=30$)			Siblings ($n=83$)			Half-siblings ($n=11$)		
	At risk	Cases	MR%	At risk	Cases	MR%	At risk	Cases	MR%
All depr. disorders certain + uncertain + suicide	25	6	24	37	5	13.5	4	—	—
Bipolar disorder	25	—	—	37	—	—	4	—	—
All affective disorders	25	6	24	37	5	13.5	4	—	—
Schizophrenia	28.5	1	3.5	52	4	7.6	5	—	—
Schizoaffective psychosis	28.5	—	—	52	2	3.8	5	—	—
Alcoholism	30	—	—	70	—	—	7	—	—
Anxiety + other neuroses	25	—	—	37	2	5.4	4	—	—
Other diagnoses	25	1	4	37	5	13.5	4	—	—
Unspecified disorders without medical care	25	3	12	37	1	2.7	4	—	—

Table 11. Morbidity risk (%) for affective disorders in 1st degree relatives of unipolar Probands

	Bipolar	Unipolar	Unspecified and suicide	Total
Angst (1966)	0.3	9.1	2.3	11.7
Perris (1966)	0.4	7.4	6.8	14.6
Winokur (1971)	–	–	–	15.4
Gershon (1974)	2.1	11.5	–	13.6
Trzebiatowska (1976)	–	7.5	5.0	12.5
Smeraldi (1977)	0.6	8.0	4.3	12.9
Total	0.8	8.7	4.6	13.4

the female relatives of neurotic-reactive probands. In Tables 7, 8, 9 and 10 the MR % among relatives of probands divided according to Winokur's classification are shown. As expected the highest MR % was found in the group of probands with Pure Depressive Disease, and most of the secondary cases of alcoholism in the group of probands with Depression Spectrum Disease. In fact in this last group there was also a lower MR % for affective disorders. Although alcoholism occurred mostly among male relatives we did not find the distribution of alcoholism among male, affective disorders occurring among female relatives as suggested by Winokur. In fact, alcoholism occurred in all in 14 families—in 8 of them there was no secondary case of affective disorder.

Although the investigation concerning second degree relatives is not yet completed, preliminary findings suggest that secondary cases of affective disorders occur among second degree relatives of probands with "sporadic depression".

Comparison with Earlier Studies

Before dicussing the results of the present investigation it is necessary to present a brief reminder of previous research work, which bears some relation to the present study. Table 11 shows a general survey of the results obtained in various studies of unipolar patients. It is evident that the findings of several authors, despite differences in risk period and in the definition of "unipolar", are fairly consistent, both as concerns the total morbidity risk for affective disorders among first degree relatives, and as concerns a clear prevalence of non-bipolar disorders among the secondary cases.

As to neurotic-reactive probands, the only study comparable with our own is that by Stenstedt (1966) who analysed retrospectively the disease expectancy among parents and siblings of two series of neurotic-reactive depressed patients collected on the occasion of earlier genetic studies of affective disorders. The main results of Stenstedt's investigation are summarized in Tables 12 and 13.

The total morbidity risk for affective disorders among the parents and siblings of the probands in Stenstedt's series was 4.7%. Stenstedt used a risk period of 20 to 59 years. When his result are recalculated using the risk period of 15 to 70 years

Table 12. Expectancy of mental disorders among parents and siblings of probands suffering from neurotic depression (constructed from the data by Stenstedt 1966)

	Corrected population	No. of cases	MR%	
Affective disorders				
1st series	358	12	3.4	4.7
2nd series	436	26	6.0	
Schizophrenia: parents	323	2	0.6	
Schizophrenia: siblings	594	8	1.3	
Alcoholism: only males	506	15	2.9	
Psychopathia	1138	24	2.1	

Table 13. Expectancy of affective disorders among male and female relatives of probands suffering from neurotic depression (adapted from Stenstedt 1966)

Relatives (parents and siblings)	Corrected population	No. of cases	MR%
Male	393	8	2.0
Female	401	30	7.5

as in the present study the morbidity risk rises to 5.4%, while the higher expectancy of affective disorders among female as opposed to male relatives remains unchanged. Stenstedt did not divide all his secondary cases into subgroups of affective disorders, only parents who were afflicted. Among them (corrected population 15 to 70 years, $n=258.5$) there were seven cases with manic-depressive (both bipolar and unipolar) psychosis (MR%=1.5). Stenstedt admitted, however, that his material may not be quite representative of neurotic depression, and that cases of manic-depressive disorder could have been wrongly diagnosed as cases of neurotic depression, especially in his second series.

Discussion

In line with earlier investigations, the results of the present study confirm that unipolar depression runs in families independently of bipolar psychosis. In fact, the total MR% for bipolar psychosis among relatives of unipolar probands (parents and siblings) is only 0.8 and corresponds to the average of the studies presented in Table 11. In the present series, the total MR% for affective disorders among relatives of unipolar probands is much higher than in all previous studies, and could have been higher if we had had the opportunity to interview all relatives in whom "unspecified mental disorders" had occurred. This result is probably due to the fact that our probands have been studied very intensively, and that an excellent collaboration was obtained from each of them. However, other factors may contribute, for example the occurrence of consanguineous

marriages among more remote ancestors of the probands. When the study of second degree relatives is completed, we will have additional information in that respect.

Also, the MR% for affective disorders among relatives of neurotic-reactive probands is very high, and of a magnitude corresponding to that found in previous studies of unipolar patients (Table 11). The MR% in the families of our patients is approximately twice as high as that found by Stenstedt in his two series (Table 12). However, Stenstedt admitted that his investigated could have had sources of error.

Of interest is the fact that the MR% for affective disorders is similar in male and female relatives of unipolar probands, and that the difference in MR% in relatives of the two sexes is not so pronounced in families of neurotic-reactive patients as it was in the study by Stenstedt. This finding challenges the current opinion that affective disorders of a depressive type are much more frequent in females than in males.

Although the morbidity for affective disorders is significantly higher among relatives of unipolar than of neurotic-reactive probands, the high MR% found among relatives of the latter suggests that a heredity factor is also important in the occurrence of neurotic-reactive depression.

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