

Depression in the elderly community: I. Prevalence by different diagnostic criteria and clinical profile

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ABSTRACT – Background and Objectives: Depression is one of the most intriguing disorders in the elderly. We conjecture that prevalence of depression in the community vary according to the diagnostic criteria used. Furthermore, we anticipate that important proportions of depression go untreated or inadequately treated in a Southern European city.

Methodology: This report is part of the Zaragoza Study (or ZARADEMP 0), an epidemiological project to document psychiatric morbidity in a representative sample of the elderly. A two - phase design was completed in a sample of n= 1080 elderly (65+ years). Standardized instruments were used, and the Geriatric Mental State (GMS) was the main instrument. Cases of depression were diagnosed with three different sets of diagnostic criteria: AGE-CAT syndrome, AGE-CAT diagnosis and DSM - IV criteria. Descriptive statistics were used.

Results: In support of the working hypothesis, the prevalence of depression tended to be lower when stringent diagnostic criteria were used. It was 7.0 % with AGE-CAT syndrome, 5.7% with AGE-CAT diagnosis among the cases, 4.8% with DSM - IV criteria. Anxiety, co - morbid syndromes were frequent among the cases (45.5%) and 18.2% of

them had co - morbid AGECAT organic syndromes. Differential psychopathological profiles are observed between cases of major and minor depression. Undertreatment or inadequate treatment was very frequent, and only 54.5% of major depression cases were on antidepressants.

Conclusions: The prevalence of depression in the elderly varies according to diagnostic criteria used, and does not increase with age. Co-morbid anxiety and "organic" syndromes are common, and only half the major depressive cases were on antidepressants.

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Introduction

Elderly depression is one of the commonest psychiatric conditions in this age group¹. It is usually underdiagnosed and undertreated² and has negative implications, including disability^{3,4} and high use of medical services^{5,6}. Furthermore, it may complicate the outcome of other conditions⁷ and has been associated with high mortality rates⁸.

We have previously reported that the prevalence of depression in Zaragoza is 4.8% when using DSM - IV criteria⁹. Now, it would be relevant to report the differences when using different diagnostic criteria in the same sample. We have also reported comparative studies between Liverpool and Zaragoza^{10,11} and cross-national differences during the EURODEP investigation in several European countries^{12,13}. Zaragoza was one of the cities with lowest prevalence rates of depression. In both these studies the same instruments and methods were used, but results were limited to the use of screening and assessment instruments administered by lay interviewers. Therefore, it would now be important to report data from the assessment completed by experienced, standardized clinicians.

The aims of this paper are: (1) To try to confirm the hypothesis that differences in the prevalence of depression in the elderly will be observed when different diagnostic criteria are used (2) To report differences by age and sex. It is expected to find higher rates of depression in women, but not an increase in the prevalence of depression by age (3) To report descriptive, psychopathological profiles of depression (4) To describe clinical and treatment characteristics in relation to type of depression. It is hypothesized that a considerable proportion of the elderly depressed will be either untreated or inadequately treated.

Methods

Study population

The site of the study was Zaragoza, the fifth city by size in the country, located in the North - Eastern part of Spain. Presently, it has approximately 600,000 inhabitants. A representative sample was collected, and the general methods of the study have been described elsewhere⁹.

Diagnostic and Screening Instruments

The following international instruments, previously standardized in Spain by the same research group were used:

*Examen Cognoscitivo Mini-Mental (MMSE)*¹⁴, the Spanish version of the Mini-Mental Status Examination (MMSE), a widely used, reliable and valid indicator of cognitive disturbance¹⁵.

*Geriatric Mental State (GMS)*¹⁶, a semi-structured, standardized clinical interview for assessing the mental state of elderly persons. Lay interviewers are able to administer this instrument. For the purposes of the study, we used the shortened community version. This interview is also a syndrome case finding instrument: the GMS "threshold global score" discriminates between "non - cases" (scores 0, 1) and "cases". The latter are graded by severity into "mild cases" (score 2) and "moderate/severe cases" (score 3), that we use as a "severity index". In the final step of the GMS administration, subjects receive a diagnosis of probable "dementia", "depression" or "others". The reliability and validity of the Spanish version of the GMS has been found to be adequate in hospital samples, when it is administered by both lay interviewers and psychiatrists¹⁷.

AGECAT^{18,19} (Automated Geriatric Examination for Computer Assisted Taxonomy) is a set of computer programs which analyze GMS data. The AGECAT groups the items of the GMS into components, which are gathered under eight diagnostic "clusters" (or "syndromes"), including "organic" and depressive syndromes. Experience with the GMS - AGECAT package includes community studies^{20,21} and international comparisons^{22,23}. The validity of the Spanish version has also been reported elsewhere²⁴.

History and Aetiology Schedule (HAS), a standardized method of collecting history and aetiology data from an informant to accompany the data obtained from the respondent with the GMS. It is crucial to complete the GMS and facilitate a diagnostic process such as the one done in the present study with the DSM system^{20,25}.

Sampling and Case - Finding Procedures

The study sample of the elderly (65+ years) was proportionately stratified by sex and age (5 - year age categories). Sampling size error was fixed at 2.5% and confidence level at 95%, for a 25% probability of having a mental disturbance in some age groups. The sample was randomly selected from the municipal census list and included 1,134 elderly, 449 males and 685 females living in the city.

A two - phase epidemiological screening design was used in this study. In phase 1, lay interviewers previously standardized in the methods^{17,24,26}, administered the Spanish versions of the GMS and the MMSE to the elderly. The individuals were nominated as "probable cases" on the basis of GMS threshold "global" score and/or MMSE cut - off point (23/24), which we previously reported to have good validity coefficients^{9,14}. Some prevalence results based on the data in phase 1 have been reported in previous papers^{10,12}.

All the "probable cases" and a similar number of "probable normal" randomly selected were examined in phase 2, two months later and blind to the results of phase 1, by research psychiatrists standardized in the methods. They used the GMS and MMSE as well as the HAS. Outside informants were interviewed when the selected

elderly was considered to be unreliable. Medical reports, which are commonly kept at home by Spanish patients and may include laboratory data, were used in some cases to help in the diagnostic process.

At the end of phase 2, the psychiatrists diagnosed the identified “cases” according to DSM - IV criteria²⁷. The instruments used in this study generate enough information to diagnose according to these criteria the main nosological categories found in the elderly community. The research psychiatrists were previously considered to be reliable in the diagnoses of the main DSM categories in hospital samples¹⁷.

For the purpose of reporting co - morbid-ity in the study we consider cases of depression according to the DSM-IV criteria which present also either organic level of cognitive disturbances in AGE-CAT or anxiety levels in the same instrument.

Quality control and ethics

Systematic checks on the reliability of the assessments were implemented to prevent the “reliability - drift”. Standard ethical principles were maintained throughout the study. Participants were given a standard information sheet, written consent was obtained, and privacy, confidentiality and

security were maintained, according to Spanish Law 5/1992.

Statistical Analysis

The prevalence (and 95% Confidence Interval) of depression and subtypes of depression were estimated from the stratified sample of the elderly responders included in the clinical evaluation. χ^2 analyses were used to test the independence of prevalence rates. Nass’s correction factor²⁸ was applied when low frequencies appeared in some of the boxes. When sample size was small and/or the frequency of the characteristic being compared was low, Fisher’s exact test was used²⁹. Throughout, the $p = 0.05$ level was adopted as a reference point for considering results to be statistically significant.

Results

One thousand and eighty individuals completed phase 1 of the study. The distribution and characteristics of the samples are shown in a previous paper⁹. Three hundred and twenty four individuals completed phase 2 of the study (Table I). The majority of individuals interviewed in phase 2 had

Table I
Distribution of the sample by age and sex

Age	Men		Women		Total	
	n	%	n	%	n	%
65 - 69	28	8.6	37	11.4	65	20.1
70 - 74	37	11.4	49	15.1	86	26.5
75 - 79	39	12.0	44	13.6	83	25.6
80 - 84	20	6.2	36	11.1	56	17.3
85+	10	3.1	24	7.4	34	10.5
Total	134	41.4	190	58.6	324	100.0

been born in rural areas outside the city of Zaragoza, particularly in the major depression diagnostic group, but the differences with other groups were non significant ($\chi^2 = 2.43$; $p = 0.291$) (Table II). An important proportion of the sample was widowed, particularly in the adjustment depression group, but the differences with other groups were non - significant. A considerable proportion of the patients in this sample had limited educational level, and the proportion was significantly higher in the depressed elderly as compared to the “non - cases”.

The prevalence of depression differed depending on the diagnostic criteria used (Table III), the proportion being lower if the diagnostic criteria were stringent: seven percent of the sample had AGECAT depressive syndromes, but only 5.7% had an AGECAT diagnosis of depression and 4.8% fulfilled DSM-IV criteria. In all diagnostic groups, depression was more prevalent in women with respect to men, and the differences were close to statistical significance when the diagnostic criteria were either AGECAT

syndrome ($\chi^2 = 3.04$; $p = 0.081$) or DSM - IV criteria ($\chi^2 = 3.41$; $p = 0.064$).

Figure 1 shows the prevalence distribution of depression by different diagnostic criteria, by age groups. We observed differences in relation to the age groups, being the prevalence higher in the 65 to 69 and in the 80 to 84 years sub - groups. The differences of prevalence were statistically significant by any of the three diagnostic criteria used. Differences were maximal between the 65 - 69 group years and 75 - 79 years group. Figure 1 also shows that the prevalence does not increase after the age of 80 years, the exception being AGECAT syndromic case. In fact, depression decreases when DSM -IV, stringent criteria are used.

Depression was severe (GMS criteria) in an important proportion of DSM-IV cases, particularly in the major depression group (81.8%) but only in 14.2% of the dysthymic group. It is remarkable that 44.4% of the adjustment disorder group according to DSM-IV had a severe level of depression.

Table II
Sociodemographic characteristics by depression subtypes (DSM - IV criteria)

Characteristic	Non cases (n = 196)		Major depression (n = 11)		Dysthymic disorder (n = 14)		Asjurement disorder, depressed (n = 27)		p
	n	%	n	%	n	%	n	%	
Place of birth									
Urban	65	33.2	2	18.2	6	42.9	11	40.7	0.5075
Rural	131	66.8	9	81.8	8	57.1	16	59.3	
Marital status									
Single	21	10.7	0	0.0	0	0.0	2	7.4	0.3612
Married	97	49.5	6	54.5	7	50.0	9	33.3	
Widowed	77	39.3	5	45.5	7	50.0	16	59.3	
Separated	1	0.5	0	0.0	0	0.0	0	0.0	
Educational level									
Primary incomplete	19	9.7	2	18.2	0	0.0	7	25.9	0.0291
Primary	146	74.5	9	81.8	14	100	18	66.7	
High school	15	7.6	0	0.0	0	0.0	2	7.4	
University	16	8.2	0	0.0	0	0.0	0	0.0	

Table III
Prevalence of depression by different diagnostic criteria, by sex

Diagnostic criteria	Men		Women		Total	
	%	(CI 95%)	%	(CI 95%)	%	(CI 95%)
AGECAT depressive syndrome						
1+2 levels (subcases)	5.5	(4.1 - 6.9)	7.0	(5.5 - 8.5)	6.4	(4.9 - 7.9)
3 + levels	5.5	(4.1 - 6.9)	7.9	(6.3 - 9.5)	7.0	(5.5 - 8.5)
AGECAT diagnosis						
"Minor" depression	2.8	(1.8 - 3.8)	4.5	(3.3 - 5.7)	3.8	(2.7 - 4.9)
"Major" depression	1.8	(1.0 - 2.6)	1.9	(1.1 - 2.7)	1.9	(1.1 - 2.7)
Total depression	4.6	(3.4 - 5.8)	6.4	(4.9 - 7.9)	5.7	(4.3 - 7.1)
DSM - IV diagnosis						
Major depression	0.7	(0.1 - 1.5)	1.2	(0.4 - 2.0)	1.0	(0.4 - 1.6)
Dysthymic disorder	1.4	(0.3 - 2.5)	1.2	(0.4 - 2.0)	1.3	(0.6 - 2.0)
Adjustment disorder	1.4	(0.3 - 2.5)	3.3	(1.9 - 4.7)	2.5	(1.6 - 3.4)
Total depression	3.4	(1.7 - 5.1)	5.7	(3.9 - 7.5)	4.8	(3.5 - 6.1)

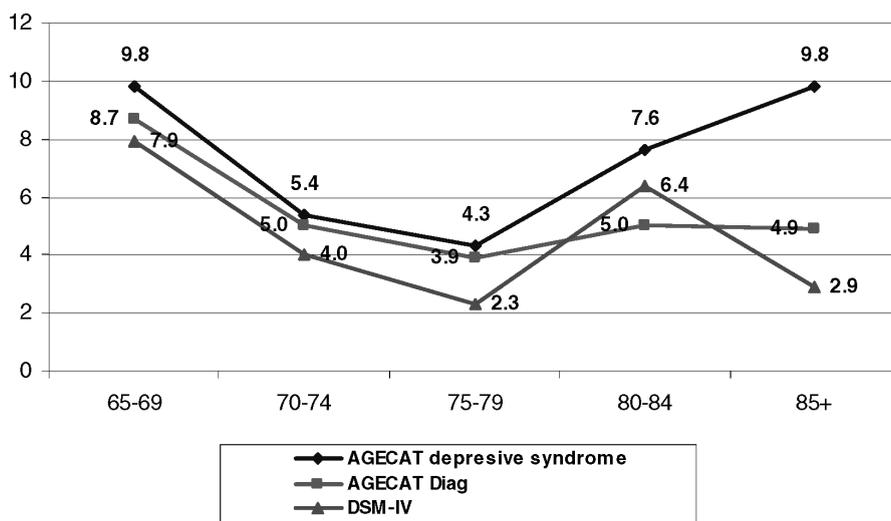


Figure 1. Prevalence of depression by different diagnostic criteria, by age groups*.
*Prevalence data are given in percent

The differences in the proportion of the severe cases between groups were statistically significant ($\chi^2 = 11.39$; $p = 0.003$).

In relation to co-morbidity in the depressed subjects diagnosed with DSM-IV criteria, we found that among major depression individuals, 18.2% had organic syndromes (case

level 3 according AGE-CAT criteria), and 45.5% of them had co-morbid anxiety, which was severe (AGECAT case level 4+) in 36.4%. In the dysthymic/adjustment disorder, compacted subgroup, only 7.3% had "organic" syndromes, and 36.6% had anxiety syndromes, which were severe in 14.6%.

For the purpose of describing clinical characteristics of depression observed in the general population of the elderly, only AGE-CAT diagnostic criteria will be used. Table IV shows the prevalence of selected GMS symptoms of depression in "cases" and also in "non - cases". Worries, anxiety, sleep disturbances, fatigue and lack of energy were frequent in the cases, but were also observed in "non - cases". As expected, the differences between "cases" and "non - cases" were statistically significant. In the minor depression sub - group, the following symptoms were frequent: pessimism, loss of interest, fatigue and reduced activity. Finally, in the major depression sub-group, anxiety, worse in the mornings, wished to be dead and suicidal plans, appetite diminished and loss of weight were the most remarkable symptoms. Sub-

jective memory complaints were important in both subtypes of depression.

Table V shows clinical characteristics of "cases" of depression (AGECAT criteria) in relation to items on the History and Aetiology Schedule. In the major depression sub - group two thirds of the sample had history of depression with onset before the age of 65. In the minor depression subgroup this was true in only 23.7% (the differences being statistically significant: $\chi^2 = 4.51$; $p = 0.034$). Both, life events related to depression and physical disability were more frequent in the minor depression subgroup compared to the major depression subgroup, but the differences were non - significant ($\chi^2 = 0.67$, $p = 0.412$, and $\chi^2 = 1.12$, $p = 0.29$, respectively).

Table IV

Prevalence of selected GMS symptoms of depression in "non cases" and "cases" (mD, MD*).

Items	Non cases N = 192		mD N = 41		MD N = 11	
	%	(95%CI)	%	(95%CI)	%	(95%CI)
Worries	41.9	(34.8 - 49.2)	63.4	(46.9 - 77.8)	60.0	(27.7 - 86.8)
Anxiety	24.5	(18.5 - 31.2)	66.6	(50.1 - 80.5)	91.0	(58.8 - 99.7)
Depressed mood	13.3	(8.8 - 18.9)	100	(91.4 - 100)	100	(71.5 - 100)
Cried	13.3	(8.8 - 18.9)	85.7	(71.2 - 94.6)	80.0	(46.3 - 97.0)
Depression longer than few hours	0.0	(0.0 - 1.9)	78.6	(63.0 - 89.8)	90.9	(58.7 - 99.7)
Worse in the mornings	0.5	(0.0 - 2.8)	14.3	(5.3 - 28.7)	36.4	(10.9 - 69.2)
Pessimism Suicide	1.5	(0.3 - 4.4)	71.4	(55.1 - 84.4)	18.2	(2.2 - 51.8)
Life not worth living	5.6	(2.8 - 9.8)	81.0	(65.7 - 91.5)	90.6	(58.3 - 99.7)
Wished to be dead	0.5	(0.0 - 2.8)	47.6	(31.8 - 63.7)	72.7	(39.0 - 93.9)
Suicidal plans or attempts	0.5	(0.0 - 2.8)	4.8	(0.5 - 16.4)	18.2	(2.2 - 51.8)
Guilt	1.6	(0.3 - 4.5)	5.0	(0.6 - 16.7)	10.0	(3.0 - 42.4)
Loss of interest	2.6	(0.8 - 5.9)	63.4	(46.9 - 77.8)	30.0	(7.3 - 63.5)
Looks depressed	3.1	(1.1 - 6.6)	92.7	(80.1 - 98.4)	90.0	(57.6 - 99.6)
Appetite diminished	6.2	(3.2 - 10.6)	26.2	(13.7 - 42.2)	64.3	(31.3 - 89.4)
Loss of weight	1.0	(0.1 - 3.6)	12.5	(4.2 - 26.5)	30.0	(7.3 - 63.5)
Sleep disturbance	47.4	(39.7 - 54.3)	81.0	(65.7 - 91.5)	90.9	(58.7 - 99.7)
Fatigue	20.1	(14.6 - 26.4)	60.8	(44.3 - 75.6)	45.5	(16.7 - 76.6)
Lack of energy	21.9	(16.2 - 28.4)	61.0	(44.5 - 75.8)	80.0	(46.3 - 97.0)
Reduced activity	9.4	(5.6 - 14.4)	39.0	(24.1 - 55.4)	10.0	(3.0 - 42.4)
Memory complaints	40.0	(33.0 - 47.3)	70.7	(54.4 - 83.8)	77.8	(44.0 - 96.2)

*mD= Minor depression; MD= Major depression.

Table V
Clinical and treatment characteristics (HAS*) of cases of depression (AGECAT criteria)

	mD**		MD**		p	Total depression	
	n/N	%	n/N	%		n/N	%
History of depression before age 65	9/38	23.7	7/11	63.6	0.03	16/49	32.7
Life events related to depression	20/36	55.6	1/3	33.3	0.89	23/45	51.5
Physical disability							
Home ridden last month	9/38	23.7	1/10	10.0	0.61	5/24	20.8
Physical illness							
Mild	5/39	12.8	1/11	9.1	0.85	1/10	12.0
Moderate/severe	7/39	17.9	0/11	0.0	0.31	7/50	14.0
On psychotropic medication	22/41	53.7	10/11	90.9	0.06	32/52	61.5
Antidepressants	0/41	0.0	6/11	54.5	<0.01	6/52	11.5
Anxiolytics	16/41	39.0	9/11	81.8	0.03	25/52	48.1
Hypnotics	9/41	22.0	3/11	27.3	0.98	12/52	23.1
Others	1/41	2.4	1/11	9.1	0.89	2/52	3.8
Consulted general practitioner because of depression	28/39	71.8	8/11	72.7	0.75	36/50	72.0
Consulted to psychiatrist because of depression	5/40	12.5	6/11	54.5	0.01	11/51	21.6

*HAS= History and Aetiology Schedule.

**mD = Minor depression; MD = Major depression.

Table V also shows some treatment characteristics in the depressive subjects according to data in the History and Aetiology Schedule. In the major depression subgroup, 90.9% were on psychotropic medication, but only half of them were on antidepressants. In the minor depression subgroup more than half were on psychotropic medication, but none were on antidepressant medication. Two thirds of the sample in both subgroups had consulted to the general practitioner because of the depression, but a very small proportion in the minor depression subgroup (12.5%) and a bit more than half the cases of major depression (54.5%) had consulted a psychiatrist for the same reason.

Discussion

The results of this study in a representative population of the elderly support the notion

that the prevalence of depression is considerable. If we use AGECAAT criteria, the prevalence observed (5.7%) is similar to the low range cities in the European study completed by the EURODEP consortium¹². However, to our knowledge, this is the first report in the international literature comparing three different kinds of diagnostic criteria. In support of the working hypothesis, differences are observed in dependence of the criteria used, the lowest frequency being observed when using the stringent, DSM - IV criteria²⁷. The proportion of major depression would be in the low range of epidemiological studies in the literature³⁰⁻³², with similar proportions reported in studies by authors such as Blazer³³ y Newman³⁴. The important point is that methods of assessment are indispensable to consider when reporting between - studies differences.

As expected, in relation to sex, our findings are consistent with most of epidemiological studies^{12,35,36}. Although statistical differences

have not been observed, the frequency of depression is considerably higher in women in relation to men, independently of the criteria used. Possible explanations for this have been discussed by several authors³⁷⁻³⁹.

In relation to age, rather different patterns are also observed in dependence of diagnostic criteria used. A decrement in prevalence of depression is observed between the ages of 65 - 69 and 75 - 79 years approximately, independent of diagnostic criteria used.

Possible reasons might be related to an increased prevalence around the retirement age of 65 - 69 years⁴⁰. However, other studies have not found an increased frequency of depression in relation to age of retirement⁴¹⁻⁴³.

In our study, the prevalence of depression syndromes tends to increase again after the age of 80 years, but not the prevalence of the other diagnostic groups. In particular, the frequency of DSM - IV depression tends to decrease in the oldest. This differential pattern of an increase of symptoms with age, but not of diagnostic groups have been reported previously⁴⁴. Copeland *et al.*¹² found no relevant differences in the prevalence of depression by age in the EURODEP, cross - national study. Increases in prevalence might be due to a somatic ill health in the elderly, since the differences by age tend to disappear in some studies when somatic conditions are controlled^{45,46}. Possible reasons for the tendency observed of a decreased prevalence in the oldest might be the expected increased mortality in the depressed⁴⁷; the increase of dementia in this age group⁴⁸ or the decrease emotional response in the oldest^{46,49}. Institutionalization of the elderly has been suggested in some studies to account for this decrement of depression in the oldest⁴⁹, but could not be argued in our study, since the institutionalized were also included in the sample. However, we have

also documented recently that somatic and psychiatric comorbidity tends to be stable in the oldest old. This finding is consistent with hypotheses related to vulnerability to illness, concentrated and clustered in a subgroup of individual, while other subgroup remains particularly healthy⁵⁰. A remarkable finding in this study relates to severity of illness in the depressed elderly. While the high proportion of severe illness was expected in the "major" depression subgroup, close to half the adjustment disorder subgroup (44.4%) scored in the moderate - severe level. Adjustment disorders are usually considered to be of mild severity. Since the assessment of patients was done by expert, standardized clinicians, the possibility that adjustment disorders in this age group may be severe has both, clinical and public health implications.

In relation to symptom profiles, we have found that subjective "depressed mood" and observed sadness ("looks depressed") were very frequent among the depression diagnostic subgroups. This is in contradiction with reports of masked or somatised depression among the elderly^{51,52}. Furthermore, this finding may direct attention when developing screening instruments, which may be limited to a small number of items⁵³. Contrary to reports of frequent self - reproach among the elderly depressed^{10,54}, we found this to be rather uncommon. This might be related to socio - cultural influences. On the contrary, pessimism was particularly frequent in our sample of "minor" depressions (71.4%). This was also observed during the Liverpool - Zaragoza study¹⁰; and, similarly, "lack of interest", "fatigue" and "reduced activity", all tended to be more frequent in this subgroup. In coincidence with previous authors⁵⁵, anxiety and particularly melancholic symptoms, tended to be more frequent in the "major" when compared to the "minor" depression subgroup.

An important finding to underline in this study, as in other previous studies⁵⁶ relates to psychiatric co-morbidity, which was very common here, particularly in the “major” depression category: close to half of them (45.5%) had co-morbid anxiety (AGECAT 3+) and 18.2% had cognitive disturbance. While co - morbidity was less frequent in the other subgroups of depression, it should not be minimized, since negative implications have been documented in previous studies⁵⁷⁻⁵⁹.

In fact, this co-morbidity could point to a more severe form of disorder⁵⁶. Furthermore, the anxiety could mask the depressive core psychopathologies⁶⁰ and lead to the inappropriate treatment in some cases, as suggested in this study. The cognitive co-morbidity should also be emphasized, since it may herald a future dementia⁶¹. In fact, the association and negative implications of psychiatric and somatic co-morbidity might also be expected in view of some findings reported also in Zaragoza⁵⁰.

This study suggests that “major” depression in the elderly community has an onset before the age of 65, and might be related to personal vulnerabilities. However, “minor” depression might be more related to both physical impairment and life - events, that tended to be more frequent in this subgroup. A rather important proportion of the elderly depressed were on psychotropic medication, but the suggestion is that treatment was insufficient (close to half the “minor” depression subgroup had no psychotropic prescription and to a good extent inadequate (for example, half the “major” depression subgroup was on antidepressants, but more than

80% were on anxiolytics; and only 54.5% of them had been seen by psychiatrists). The role of the G.P. must be emphasized, since close to three quarters of the depressed patients had consulted with them.

While this study follows contemporary requirements in epidemiological research in psychiatry, some limitations may be pointed out. We have previously argued in favour of the response rate and the general design of the study. However, we are aware of limitations in two - stage studies, since some false negative probable cases may escape assessment of depression. We place more emphasis on the “major” depression cases diagnosed with DSM - IV criteria. In fact, “minor” depression cases should not be minimized, because negative outcomes even in “subcases”, have been reported in the literature⁶²⁻⁶⁵; furthermore, the meaning of “minor” psychopathological disturbance, in particular subjective complaints, in the general population is not well known. Since this is a cross - sectional, descriptive study, we can not anticipate outcomes, and certainly we can not document causal associations. Follow-up, longitudinal studies are now underway in our research group, which might present new evidence about both, outcome and causal associations⁶⁶.

References and Acknowledgements

References and Acknowledgements for this article are included at the end of paper II.