# Original

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# Health Related Quality of Life in Major Depressive Disorder: evolution in time and factors associated

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#### ABSTRACT

Introduction. Major Depressive Disorder (MDD) is the most prevalent mental disorder. We aimed to analyze which factors were associated to their Health-Related Quality of Life (HRQoL) perception in patients diagnosed of MDD and how they evolved over six months.

Methods. We included 432 subjects with MDD (DSM-IV-TR) from hospital consultations, mental health centres and primary care centres in Basque Country, Madrid and Canary Islands. Patients were followed for 6 months. Clinical, sociodemographic and therapeutic variables were collected. HRQoL was measured by EQ-5D-5L, expressed as "utilities". Generalized Linear Models were constructed to meet the objectives.

**Results.** Women, older people, disadvantaged social groups and those with higher "physical comorbidity" expressed a worse HRQoL at inclusion. At 6 months, 305 subjects remained in follow-up. The average change in "utilities" was 0.033 (Cl95%: 0.008-0.059), and 0.132 (Cl95%: 0.093-0.171) in the 109 subjects (35.51%) who expressed improvement in their health status. "Physical comorbidity", the presence of eating disorders, older age, belonging to disadvantaged socioeconomic groups or the need for greater therapeutic effort were negatively associated with HRQoL evolution.

**Conclusion.** MDD is associated with a great impact on HRQoL, which partially reverts when the patients showed good clinical evolution. Older age, comorbidity and disadvantaged socioeconomic group are associated with a worse evolution of HRQOoL.

\*Autor de correspondencia: UDMAFyC Oeste. Calle Alonso Cano 8, 28933 Móstoles, Madrid jmfernandez@salud.madrid.org Keyword. Major Depressive Disorder; Health-Related Quality Of Life; Surveys and Questionnaires; Prognosis

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#### LA CALIDAD DE VIDA RELACIONADA CON LA SALUD EN EL TRASTORNO DEPRESIVO MAYOR: FACTORES ASOCIA-DOS CON SU EVOLUCIÓN

#### RESUMEN

Introducción. La Depresión Mayor (DM) es el trastorno de salud mental más prevalente. Se pretende analizar el peso de los factores asociados a la percepción de la Calidad de Vida Relacionada con la Salud (CVRS) en pacientes con diagnóstico de DM y su evolución durante seis meses.

Metodología. Se incluyeron 432 sujetos con DM (DSM-IV-TR) de consultas hospitalarias, centros de salud mental y centros de atención primaria en País Vasco, Madrid y Canarias. Se siguió a los pacientes durante 6 meses. Se recogieron variables clínicas, sociodemográficas y de abordaje terapéutico. La CVRS se midió mediante el EQ-5D-5L, expresado como "utilidades". Se construyeron Modelos Lineales Generalizados para responder los objetivos.

**Resultados.** Las mujeres, las personas de mayor edad, los grupos sociales menos favorecidos y aquellos con mayor comorbilidad "orgánica" expresaron una peor CVRS inicial. A los 6 meses permanecían en seguimiento 305 sujetos. El cambio medio en las "utilidades" fue de 0,033 (IC95%: 0,008-0,059), y de 0,132 (IC95%: 0,093-0,171) en los 109 sujetos (35,51%) que expresaron mejoría en su estado de salud. Se asociaron negativamente con la evolución de la CVRS la comorbilidad "orgánica", la presencia de trastornos de la conducta alimentaria, una mayor edad, el pertenecer a grupos socioeconómicos desfavorecidos o la necesidad de un mayor esfuerzo terapéutico.

**Conclusiones.** La DM se asocia con un gran impacto en la CVRS, que revierte parcialmente en el grupo con buena evolución clínica. La mayor edad, la comorbilidad y el grupo socioeconómico se asocian a una peor evolución de la CVRS.

Palabras clave. Depresión Mayor; Calidad De Vida Relacionada con la Salud; Encuestas y Cuestionarios; Pronóstico.

#### INTRODUCTION

Depression related disorders are the most prevalent type of mental health disorder. More commonly than not, they are associated with other mental, medical or social problems<sup>1</sup>. Major Depression Disorder (MDD) could affect more than 300 million people currently. In terms of health loss, consequences of MDD are huge. According to the WHO, it is the health condition that contributes the most to global disability (7.5% of the total of Years Lived with Dissability in 2015)<sup>2</sup>. This is due to its high prevalence, high impact in functioning and early onset. Prevalence of depression reaches 10% among subjects from the community who demand healthcare<sup>3</sup> and life long prevalence is believed to be 12.8% in European population<sup>4</sup>. Nowadays, total cost per MDD sufferer is very high, a recent review in Europe portrays almost 12,000 euros per patient per year in direct costs and 14,000 euros per patient per year in indirect costs<sup>5</sup>. In Spain, total economic impact of mental disorders equals 2.2% of GDP. Half of this cost, as well as the main reason for disability is MDD<sup>6</sup>. Despite the fact that research into disease burden offers heterogeneous results depending on the methodology employed, it seems clear that because of its tendency towards chronicity, depression might be one of the most devastating diseases in terms of social costs<sup>7</sup>, especially in cases of treatment resistance<sup>8</sup>.

The impact of depression is thus acknowledged both by those who suffer it and from society as a whole. It is therefore particularly necessary to study the patient's perspective with regards to its impact in their life. Health Related Quality of Life (HRQoL) is severely affected in MDD<sup>9,10</sup>, and it could even continue so after an apparent clinical "improvement"<sup>11</sup>. Some authors have suggested HRQoL as an outcome measure in MDD<sup>12,13</sup>. This highlights how important it is to examine factors associated with deterioration and worse courses in terms of HRQoL<sup>13</sup>.

HRQoL can be assessed by generic or specific questionnaires<sup>14</sup>. Although specific questionnaires are more commonly used in clinical settings, generic questionnaires

can give health status specific and standardised scores, named "utilities". These measurements, based in people's preferences, are needed to perform economic evaluations of health interventions, since they are used to construct the variable Quality Adjusted Life Year (QALY)<sup>15</sup>. The most commonly used generic questionnaire is the EQ-5D<sup>16</sup>. Based on preferences, it allows us to link an "utility" value to each of the described health status. In Spain it has been proposed that scores or "utilities" from the latest version of this tool (the EQ-5D-5L) may be used to perform economic evaluations of health technologies<sup>17</sup>.

HRQoL perception is mediated by social and cultural factors. It is therefore important to assess how they impact the health perceptions of a specific population in the presence of certain diseases. In Spain, HRQoL amongst MDD patients has been described<sup>9</sup>, but information regarding utility associated to the corresponding health status and its modification with time has only been reported in international cohorts<sup>18</sup>.

With this study we aim to analyse how sociodemographic, clinical and treatment related factors affect HRQoL and its progression in a six months period, by using the EQ-5D-5L in patients diagnosed with MDD.

# METHODOLOGY

# **Study population**

Patients were included by consecutive sampling in specialist mental health outpatient units within hospital settings, community mental health services and primary care, all belonging to the National Health Service in three different regions of Spain: Madrid, the Canary Islands and the Basque Country.

Included subjects were over 18, whose main diagnosis was MDD according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition, revised. (DSM-IV-TR)<sup>19</sup>. Those subjects diagnosed with bipolar disorder, psychotic disorders, distimia or postpartum depression were excluded; as well as those with cancerous diseases, organic or psychiatric disorders that could interfere with participation and those who could not read or understand Spanish. Data collection occurred between November 2014 and July 2016. All participants gave consent in written and the study was approved by ethical committees of the three regions.

#### Variables and measurements

For those who met inclusion criteria, sociodemographic data, clinical variables (diagnostic date and treatment),

psychiatric comorbidities (classified by DSM-IV), global morbidity (Charlson Index) and HRQoL (EQ-5D-5L questionnaire)<sup>20</sup>. Intensity of depressive symptoms was assessed by the Spanish version of the PHQ-9<sup>21</sup>.

Diagnosis, severity classification and study inclusion were assessed by the treating physician. She also collected data from the clinical records. Sociodemographic data and EQ-5D were collected by qualified research personnel.

EQ-5D-5L has 5 questions about health status: 1) mobility; 2) selfcare; 3) usual activities; 4) pain / discomfort and 5) anxiety/depression. There are five possible answers or levels, ranging from 1(no problems) to 5 (extreme problems). Combining these dimensions,  $5^5 =$ 3,125 theoretical health status can possibly be described by answering the 5 questions. The scoring function based on Spanish population preference was used to calculate the (weighed) utility index. It can vary between -0.4162 and 1, higher scoring corresponding to better results in HRQoL<sup>17</sup>. The questionnaire has also a visual analogue scale (EQ-VAS), in which individuals classify their own health during the interview, ranging from 0 (worst imaginable health) to 100 (best imaginable health). Psychometric properties of EQ-5D in patients with MDD have been recently evaluated<sup>22</sup>.

PHQ-9 consists of 9 items on depressive symptoms, selected according to DSM-IV-TR criteria. Each time scores 0 to 3 according to the intensity of the explored symptom. Total scoring then varies from 0 to 27, with higher results corresponding to higher severity of depressive symptoms. The following classification has been suggested: minimal depression (from 0 to 9), mild depression (from 10 to 14), moderate depression (from 15 to 19) and severe depression (from 20 to 27)<sup>23</sup>.

Collected clinical variables were: classification of depressive episode according to the DSM-IV-TR (MDD single episode, relapse after single episode, MDD recurrent, relapse after recurrent episodes), date of latest diagnosis, time since first diagnosis and three variables which aim was to estimate therapeutic effort. Two of these variables reflected whether the patient received either psychotherapy of benzodiazepines within the 6 months prior to assessment and the third one the number of pharmaceutical strategies used in said period. The strategies were classified in the following subgroups: tricyclic antidepressants, selective serotonin reuptake inhibitor (SSRI), new antidepressants non SSRI and other non benzodiazepines psychiatric drugs. Comorbidity was grouped by the Carlson Index, which relates comorbidity to expected survival<sup>24</sup>. Presence of anxiety, eating disorders, personality and substance misuse disorders was collected according to DSM-IV-TR criteria<sup>19</sup>.

In terms of socio-demographic variables, sex, age, civil status (with a partner, widow, single, divorced), household composition (one-person, with family or in an nursing home) and social group were assesed. The classification of social group was made according to that suggested by Domingo-Salvany et al.,<sup>25</sup>, taking into account the highest level among the household. During the analysis, the highest category was used as baseline and the rest were grouped into two.

Six months later, the same questionnaires were administered, together with transitional questions, whether to be filled during the clinical visit or sent back by post. Transitional questions were aimed at understanding how the patient perceived her own health status compared to the initial visit: a lot better, somehow better, the same, somehow worse, a lot worse. Therapeutic effort in the six previous months was assessed in the same way as in the first visit; together with information regarding hospital admissions in between the two study visits. The same methodology was followed during data collection.

# Data analysis

Quantitative data was represented by measures of central tendency and dispersion and qualitative data using frequency tables.

Two Generalized Linear Models (GLM) were built. For the first the utility index assigned by the subject was the dependent variable, for the second the change in the 6 months of duration of the study. In order to select the best model, its link function and its probability distribution, Akaike Information Criteria (AIC) and Bayes Information Criteria (BIC) were used. Standard errors (SE) were calculated by robust methods, taking into account data aggregation in the different regions<sup>15</sup>.

Model construction was made by "blocks": first, clinical variables but for treatment were included, followed by sociodemographic variables and finally those related to treatment. Models were compared according to the change in AIC (better adjustments correspond to lower AIC scores) and using the "Akaike weights", which show the probability that a new model may be better when compared to the rest<sup>26</sup>.

BIC improvement was also assessed, according to the interpretations suggested by Kass and Raftery, who consider evidence for favoring one model over another is "very strong" when the former's BIC is at least inferior in 10 units<sup>27</sup>. When studying utility change, all models were adjusted by initial health status to avoid regression towards the mean, this method is equivalent to the "regressor variable method"<sup>28</sup>. Statistical software STATA 14 <sup>®</sup> was used for the analysis.

# RESULTS

432 subjects were included, from which 305 completed the EQ-D5-L5 questionnaire 6 months later. Table 1 shows characteristics of the included participants.

Three quarters of the sample were women, more frequently between their fifties and seventies and from a low socioeconomic background. Severity of depressive symptoms was moderate or severe, according to the PHQ-9.

The group that completed follow up was slightly older when compared with the totality of the sample (approximately three years) and were less likely to have a substance misuse disorder. There was no other relevant difference from a clinical point of view. During follow up there were more losses in primary care when compared to hospital based care and they were more common in the Canary Islands and the Basque Country than in Madrid (Table 2). The initial average utility was 0.560 (Cl95%: 0.535- 0.586); 0.590 (Cl95%: 0.559- 0.621) at the end of the follow up period (Table 3).

Three possible models were designed to identify which variables were associated with HRQoL at the beginning of the study (Table 4). The first model includes clinical characteristics only, the second one clinical plus sociodemographic characteristics and the third one adds on, on top of the previous one, measurements of therapeutic effort. The third model was found to be more suitable, both according to AIC and BIC criteria (both values were lower for model 3 when comparing to the other two). Akaike weights showed there was a possibility close to 100% of number three being the best model. According to this model, there were worse HRQoL in subjects who had previous depressive episodes, had a longer time since onset, had more severe depressive symptoms and were being followed in Community Mental Health centres. Women, those of older age, low socioeconomic backgrounds and higher levels of physical comorbidity also show worse results in terms of HRQoL, measured as a utility. People from Madrid or the Canary Islands had an average worse situation than those recruited in the Basque Country. Therapeutic effort was not related to the utility measure, however, previous psychotherapy treatment was related to a worse heath status.

In those 305 subjects that could be followed up, change in utilities was calculated by subtracting the final score to the initial one, therefore a positive result implied improvement and viceversa. Average within subject change was 0.033 (Cl95%: 0.008- 0.059). For those who believed

Table 1	Pop bas	opulation characteristics at aseline						
QUALITATIVE VARIABLES		CATEGORIES	Ν	PERCENTAGE				
Sex (N=432)		woman	321	74.31				
		alone	69	16.12				
Living status (n=428)		with someone else	357	83.41				
		nursing home	1	0.23				
		others	1	0.23				
- Civil status (N=428)		single	51	11.92				
		married	263	61.45				
		divorced	75	17.52				
		widow	9.11					
		high	47	11.27				
Socio- economi	c level	medium-high	82	19.66				
(N=417)	_	medium-low	80	19.18				
	-	low	208	49.88				
Previous episode (N=432)	2	yes	282	65.28				
Admissions last (N=432)	5 years	no	387	89.58				
Anxiety disorder (N=432)	·	no	250	57.87				
(N=432) Personality disorder (N=432)		no 400		92.59				
Eating disorder (N=432)		no	412	95.37				
Substance use (I	Substance use (N=432)		no 422					
Psychiatric come (N=432)	orbidity	no	416	96.3				
(N=432) New generation antidepressants (N=430)		no	216	50.23				
SSRI (N=429)		no 238		55.48				
Tricyclic antidepressants (N=427)		no	371	86.89				
Benzodiazepines (N=430)	5	si	339	78.84				
Other psychopharmace (N=429)	ology	no	336	78.32				
Psychotherapy (N=430)		no 295		68.6				
NUMERIC VARIA	NUMERIC VARIABLES		MEDIAN	SD				
Age		54.22	55	13.06				
PHQ-9		16.49	17	6.12				
Charlson Index		0.45	0	0.92				
EQ-5D-5L (utilit	ies)	0.56	0.58	0.27				
EQ-5D-5L VAS (	0-100)	47.50	50	21.86				

SSRI: Selective Serotonin Reuptake Inhibitors VAS: Visual Analogue Scale

Table 2Comparison betweeand those lost to for	n subjects that comp llow up ("not include	leted study ("include d"[idem])	d" [in the prospective	analysis])	
	Categories	Included 305 (70.6%)	Not included 127 (29.4%)	P (Chi2)	
	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	22 (17.3%)			
Origen	CMHS	P (Chi2)	77 (60.6%)	0.001	
-	Hospital	30 (9.8%)	28 (22.0%)	-	
	Basque Country	121 (39.7%)	54 (42.5%)		
Region	Canary Islands	47 (15.4%)	59 (46.5%)	< 0.001	
-	Madrid	137 (44.9%)	14 (11.0%)		
	woman	229 (75.1%)	92 (72.4%)		
bex	man	76 (24.9%)	35 (27.6%)	- 0.567	
Anxiety disorder	no	169 (55.4%)	81 (63.8%)	0.108	
Personality disorder	no	285 (93.4%)	115 (90.6%)	0.296	
Eating disorder	no	294 (96.4%)	118 (92.9%)	0.117	
Substance use	no	302 (99.0%)	120 (94.5%)	0.004	
Other psychiatric comorbidity	no	296 (97.0%)	120 (94.5%)	0.199	
New generation AD	no	156 (51.1%)	60 (47.2%)	0.075	
SSRI	no	165 (54.1%)	73 (57.5%)	0.269	
Trievelic AD	no	259 (84.9%)	112 (88.2%)	0.012	
Benzodiazepines	Ves	247 (81.0%)	92 (72.4%)	0.050	
Other psychopharmacology	no	251 (82.3%)	85 (66.9%)	0.000	
	0	25 (8.2%)	17 (13.4%)		
-	1	191 (62.6%)	60 (47.2%)	-	
Number of psychopharmacologic drugs	2	72 (23.6%)	34 (26.8%)	0.005	
therapeutic effort) -	3	14 (4.6%)	10 (7.9%)		
-	4	2 (0.7%)	1 (0.8%)	-	
	single	35 (11.5%)	16 (12.6%)		
- Chuil status	married	195 (63.9%)	68 (53.5%)	- 0.021	
	divorced	44 (14.4%)	31 (24.4%)	0.021	
-	widow	30 (9.8%)	9 (7.1%)	-	
	high	35 (11.5%)	12 (9.4%)		
	medium high	58 (19.0%)	24 (18.9%)	-	
socio-economic level	medium low	55 (18.0%)	25 (19.7%)	- 0.304	
-	low	150 (49.2%)	58 (45.7%)		
/ariable		Mean (SD)	Rank	p (Wilcoxon rank-test)	
Ane	Included	55.02 (13.12)	19 - 88	- 0.010	
·yc	Not included 52.29 (12.78) 20 - 92		20 - 92	0.010	
harlson Index	Included	0.51 (0.98)	0 - 7	- 0.041	
	Not included	0.33 (0.75)	0 - 4	0.041	
240-9	Included		0 - 27	0 502	
11Q-J	Not included	16.76 (6.21)	0 - 27	0.502	
EQ ED EL (utilition)	Included	0.56 (0.27)	-0.384 - 1	0.070	
-u-ou-ou (utilities) -	Not included	0.57 (0.26)	-0.082 - 1	0.879	
	Included	46.04 (21.77)	0 - 100	0.110	
EU-5D-5E VAS (0-100)	Not included	48.90 (22.13)	0.1		

CMHS: Community Mental Health Services. AD: antidepressants. SSRI:Selective Serotonin Reuptake Inhibitors . VAS: Visual Analogue Scale. SD: Standard deviation

Table 3

Data at 6 months follow up

QUALITATIVE VARIABLES	CATEGORIES	Ν	PERCEN- TAGE
Hospital admissions (N=309)	no	296	95.79
New generation anti- depressants (N=308)	no	162	52.6
SSRI (N=309)	no	168	54.37
Tricyclic (N=309)	no	274	88.67
Benzodiazepines (N=309)	yes	225	72.82
Other psychophar- macology (N=310)	no	244	78.71
Psychotherapy (N=308)	no	247	80.19
	a lot worse	28	9.12
Health	somehow worse	79	25.73
(N=307)	the same	91	29.64
(11-307)	somehow better	78	25.41
	a lot better	31	10.1
NUMERICAL VARIA- BLES	MEAN	MEDIAN	SD
EQ-5D-5L (utilities)	0.590	0.630	0.270
EQ-5D-5L VAS (0-100)	52.01	54	19.18

that their health status had improved according to the transitional questions (109 subjects, 35.51%), average change in utility was 0.132 (Cl95%: 0.093- 0.171).

In Table 5, we can see the association between studied variables and change in utilities. Same as of basal score, model 1 includes clinical characteristics, model 2 adds sociodemographic variables and model 3 adds, on top of those, previous therapeutic effort. The third model had the best adjustment: both AIC and BIC were lower for model 3 than for any of the other two. By the Akaike weight, it was estimated that the probability of model number 3 being the best among the presented ones was almost 100%. All models were adjusted by basal status, which was the variable that predicted change best: worse initial health status was strongly associated with a bigger positive change in utility. Worse physical comorbidity and eating disorders were linked to worsening utilities and the same happened for time since onset, although the size of this association did not seem relevant. Older age and worse socioeconomic background was also associated with worse utility progression. Subjects who belonged to one of the regions with worse initial scores had better evolution in their utility scores, even after adjusting for baseline status. Need for a bigger therapeutic effort, expressed by the use of several groups of drugs was associated with worse evolution in HRQoL and the same happened with benzodiazepine use and psychotherapy.

Table 4

Explanatory model of HRQoL (utilities) variability at baseline

Link function: identity Distribution: gaussian		MODEL 1 (N=430)		MODEL 2 (N=416)		MODEL 3 (N=412)		
		Coef. (Cl95%)	р	Coef. (Cl95%)	р	Coef. (Cl95%)	р	
CLINICAL VARIABLES								
Origen	CMHS vs. PC	-0.019 (-0.124;0.086)	0.724	-0.09 (-0.145;-0.035)	0.001	-0.064 (-0.116;-0.012)	0.016	
	Hospital vs. PC	0.042 (-0.017;0.101)	0.165	0.006 (-0.168;0.179)	0.949	0.074 (-0.096;0.243)	0.396	
Previous depressive episodes (yes vs. no)		-0.075 (-0.113;-0.037)	<0.001	-0.068 (-0.105;-0.03)	<0.001	-0.058 (-0.108;-0.009)	0.021	
Episode duration (months)		-0.001 (-0.002;-0.001)	<0.001	-0.001 (-0.001;-0.001)	< 0.001	-0.001 (-0.001;-0.001)	< 0.001	
PHQ-9	Moderate vs. mild	-0.256(-0.303;-0.208)	<0.001	-0.274 (-0.343;-0.205)	<0.001	-0.252 (-0.325;-0.18)	<0.001	
	Severe vs. mild	-0.438 (-0.459;-0.418)	<0.001	-0.452 (-0.475;-0.43)	<0.001	-0.424 (-0.472;-0.376)	<0.001	
Charlson Index		-0.029 (-0.036;-0.021)	<0.001	-0.03 (-0.047;-0.014)	<0.001	-0.036 (-0.049;-0.022)	<0.001	
Comorbid eating	disorder	-0.105 (-0.182;-0.028)	0.008	-0.085 (-0.155;-0.015)	0.018	-0.053 (-0.125;0.02)	0.154	
SOCIODEMOGRAPHIC VARIABLES								
Age				-0.001 (-0.003; -0.000)	0.025	-0.001 (-0.002;-0.000)	0.013	
	Medium-high vs.			0.033 (0.001;0.066)	0.042	0.042 (0.026;0.057)	<0.001	
Socio-economic	high LoMedium-low			0 (-0.064;0.063)	0.988	0.007 (-0.059;0.072)	0.846	
level	vs. high Low vs. high			-0.021 (-0.034;-0.008)	0.001	-0.019 (-0.058;0.02)	0.332	
	Canary Islands vs. Basque Country			-0.127 (-0.189;-0.066)	<0.001	-0.13 (-0.195;-0.065)	<0.001	
Region	Madrid vs. Basque Country			-0.123 (-0.158;-0.087)	<0.001	-0.11 (-0.148;-0.072)	<0.001	
THERAPEUTIC EFFORT								
Therapeutic effort	1 drug group vs. 0					-0.002 (-0.128;0.124)	0.977	
	2 drug groups vs. 0					-0.106 (-0.238;0.026)	0.117	
	3 drug groups vs. 0					-0.008 (-0.046;0.029)	0.665	
	4 drug groups vs. 0					-0.064 (-0.489;0.362)	0.770	
Psychotherapy (yes vs. no)						-0.057 (-0.067;-0.046)	<0.001	
Benzodiazepines (yes vs. no)						-0.058 (-0.126;0.011)	0.099	
BIC		-16.54656		-43.88907		-67.76788		
AIC		-24.67413		-51.95044		-75.80993		

PC: Primary Care. CMHS: Community Mental Health Services. Cl95%: confidence interval at 95%.. BIC: Bayes Information Criteria. AIC: Akaike Information Criteria. Sex. civil status. DSM diagnosis. anxiety and personality disorder and substance use neither yielded statistical significance neither improved adjustment in any scenario.

#### Table 5

# Explanatory model of HRQoL (utilities) change over six month period

Link function: identity. Distri- bution: gaussian		MODEL 1 (N=305) MODEL 2 (N=297)			MODEL 3 (N=295)		
		Coef. (Cl95%)	р	Coef. (Cl95%)	р	Coef. (Cl95%)	р
CLINICAL VARIABLES							
Basal utility		-0.382 (-0.504;-0.259)	<0.001	-0.361 (-0.484;-0.238)	<0.001	-0.390 (-0.5;-0.281)	<0.001
Origen	CMHS vs. PC	-0.035 (-0.11;0.039)	0.356	-0.008 (-0.081;0.064)	0.821	0.020 (-0.063;0.102)	0.640
	Hospital vs. PC	-0.004 (-0.162;0.154)	0.963	0.046 (-0.09;0.182)	0.508	0.095 (-0.027;0.218)	0.126
Episode dura	tion in months	<0.001 (-0.001;<0.001)	0.054	<0.001 (-0.001;<0.001)	0.141	<0.001 (<0.001;<0.001)	0.026
Admissions during the previous 6 months (yes vs. no)		0.028 (-0.131;0.188)	0.729	0.053 (-0.12;0.226)	0.55	0.105 (-0.151;0.361)	0.420
Charlson ind	ex	-0.026 (-0.044;-0.007)	0.007	-0.018 (-0.031;-0.005)	0.009	-0.019 (-0.03;-0.007)	0.002
Comorbid ea vs. no)	ting disorder (yes	-0.112 (-0.15;-0.075)	<0.001	-0.143 (-0.181;-0.105)	<0.001	-0.142 (-0.199;-0.085)	<0.001
		SOCI	O-DEMOGRA	APHIC VARIABLES			
Age				-0.002 (-0.003;-0.001)	<0.001	-0.001 (-0.002;-0.001)	0.001
Civil status	Married vs. single			0.01 (-0.085;0.105)	0.832	-0.014 (-0.096;0.068)	0.735
	Divorced vs. single			-0.078 (-0.204;0.048)	0.225	-0.092 (-0.2;0.016)	0.094
	Widow vs. single			-0.008 (-0.108;0.092)	0.871	-0.019 (-0.134;0.095)	0.743
	Medium-high vs. high			-0.102 (-0.149;-0.056)	<0.001	-0.108 (-0.133;-0.082)	<0.001
Socio	Medium-low vs. high			-0.087 (-0.153;-0.022)	0.009	-0.096 (-0.151;-0.041)	0.001
level	Low vs. high			-0.071 (-0.098;-0.044)	<0.001	-0.079 (-0.098;-0.06)	<0.001
	Canary Islands vs. Basque Country			0.028 (-0.011;0.067)	0.164	0.045 (-0.006;0.097)	0.085
Region	Madrid vs. Basque Country			0.077 (0.033;0.121)	0.001	0.089 (0.047;0.132)	<0.001
THERAPEUTIC EFFORT							
	1 vs. 0 drug groups					-0.067 (-0.076;-0.058)	<0.001
Therapeutic effort	2 vs. 0 drug groups					-0.115 (-0.233;0.002)	0.055
	3 vs. 0 drug groups					-0.204 (-0.381;-0.028)	0.023
Benzodiazepines (yes vs. no)						-0.038 (-0.06;-0.016)	0.001
Psychotherapy (yes vs. no)						-0.054 (-0.107;-0.002)	0.044
BIC		-100.1538		-123.3864		-144.3972	
AIC		-107.5945		-130.7738		-151.7711	

APC: Primary Care. CMHS: Community Mental Health Services. CI95%: confidence interval at 95%.. BIC: Bayes Information Criteria. AIC: Akaike Information Criteria. Sex. civil status. anxiety and personality disorder and substance use neither yielded statistical significance neither improved adjustment in any scenario. Origin of recruitment and admission over the 6 previous months did not result significant in any scenario but did improve model adjustment significantly.

#### DISCUSSION AND CONCLUSIONS

This study shows how big an impact MDD has on HRQoL and also how this impact slackens, at least partially, when the subject improves clinically. It shows as well how gender, age, comorbidity and lower socioeconomic background keep their influence in utilities, even once adjusted for the effect of MDD on utility scores. On the other hand, those subjects that state an improvement in their health status also improve in their utility score twice as much as the threshold established for Minimally Important Difference (MID), which in Spain seems to be 0.061  $\pm$  0.008 for general population<sup>29</sup>. Also age, comorbidity and belonging to lower socioeconomic status are negatively associated with the change in HRQoL when measured by utilities.

Impact of depressive symptoms in HRQoL had already been described for non institutionalised population in our environment<sup>30</sup>. Raggi et al. described the role of depressive symptoms in explaining variability in HRQoL in general population<sup>31</sup>. It is pretty intuitive to understand that higher severity of depressive symptoms is related to worse perception of HRQoL as our results show and as it has been previously described. Kolovos et al. found a difference of 0.39 points in average utilities expressed by patients with severe depression when compared with those that were in remission<sup>10</sup>. It has also been seen that severity of depressive symptoms explains only half of the utility variation<sup>13</sup>. It was already known that in women, the impact of MDD on HRQoL was higher<sup>32</sup>. Older age, worse socioeconomic status<sup>13</sup> or belonging to a social minority<sup>33</sup> were also associated with worse HRQoL in patients with MDD. It is expected that people with comorbidities show worse HRQoL. Several reviews have shown that the association both of physical and mental comorbidities with MDD particularly affect HRQoL perception<sup>12,34</sup>. Moussavi et al. reported that having depression was associated with a worse health status perception than other chronic diseases. The association of these diseases with depression lowered health perception even more than the added effect of both<sup>34</sup>.

Once more, we can see that longer episode duration and existence of previous episodes are associated with worse perception in HRQoL, an idea already mentioned in the literature, as impact of MDD on HRQoL persists even after the depressive episode has remitted<sup>11,35</sup>. Ishak and cols described how between 30 and 60% of patients in remission from depression still reported deterioration in their HRQoL a year later<sup>11</sup>.

Presence of physical comorbidity has not only been associated with a worse perception in HRQoL but also with worse progression. In this case, coexistence of several diseases or psychiatric disorders, such as eating disorders, are linked to worse perception of HRQoL. This is consistent with the idea that the impact of depression on HRQoL adds on to the impact of these other disorders. Riihimäki K et al. showed that anxiety was related to a worse perception of HRQoL during long term follow up of patients with diagnosis of depression<sup>36</sup>. Hansson described the enormous effect of MDD on HRQoL on the long term, as well as the higher impact on HRQoL when other mental comorbidities were present<sup>37</sup>. Something similar happens with age and low socioeconomic background, which are related to worse evolution in the perception of HRQoL. Saragoussi et al. reported differences of about 0.10 points in utility scores measured with EQ-D5 in subjects with MDD that were older than 55 years old when compared to those under, both at the point of diagnosis and after a year of follow up18. López et al. reported worse HRQoL in patients with MDD that belonged to minorities at the time of diagnosis, but not during follow up<sup>33</sup>. Clear associations have been established between socioeconomic status and HRQoL perception, both in the general population<sup>30</sup> and in patients with MDD13. The subject's socioeconomic situation has been related to a worse perception in HRQoL in patients with MDD treated in community settings and followed up during a year<sup>11</sup>.

As we studied other factors associated with change in HRQoL, we have found a negative association between therapeutic effort or the use of additional therapies, like psychotherapy and change in HRQoL. Despite the publications that relate improvements in HRQol during the "acute" treatment phase<sup>11</sup>, this finding could be related to the fact that worse evolution asks for a higher therapeutic effort and thus the inverse relationship between the two.

It is worth mentioning that there were different courses in patients from different regions. In Madrid and the Canary Islands patients had a worse perception of basal HRQoL but they improved more during follow up, even after adjusting for the rest of variables including the step of care in which patients were being treated. Higher improvement in the place in which patients started off worse could be due to a regression toward the mean phenomenon<sup>38</sup> but it was still present after adjusting by the basal utility score. It has been debated whether differences observed in HRQoL between different regions could be explained by contextual or "compositional" differences. It seems that differences in the characteristics among the subjects from the different regions could explain a great proportion of the results<sup>30</sup>, therefore it is possible that on this occasion we did not collect one of these characteristics associated with the differences.

The study presents some limitations. Explicative models only look for associations that can not be assessed from a casual point of view. Also, participants were recruited in different places, throughout a year and at different steps in care, including some clinical and social profiles that contribute to representativeness but do not assure it. Other circumstances that can limit representativeness are lack of information about subjects that decline participation and the rate of loss to follow up.

Other limitations have to do with the inclusion criteria: recruiting patients with diagnosis of MDD excluding those with dysthymia diagnosis may interfere with representability, however, it is important to take into account that predictors of MDD and dysthymia are different. Female sex, anxiety disorder and depressive symptoms predict the onset of MDD, dysthymia is associated with multiple adverse events during childhood, low trust and chronic physical disorders<sup>39</sup>. Their impact in HRQoL may be different<sup>40</sup>. Patients were recruited according to DSM IV-TR diagnostic criteria. DSM-V does not modify significantly the diagnostic criteria of MDD but it does contemplate the possibility of a chronic MDD or with recurrent episodes, abandoning the requirement of not having suffered a MDD during the 2 years prior to the onset<sup>41</sup>. This may limit the generalization of these results.

It seems to us that these results have a clear application. It is important to know the characteristics of patients with MDD in which HRQoL perception is more affected. Being mindful of this group of patients when consulting and adjusting interventions based on their characteristics. Gender, age, low socioeconomic status and comorbidity influence negative HRQoL perception and those characteristics should be taken into account when establishing a therapeutic plan. Actually, some of these factors transcend a classical clinical intervention and highlight the need to intervene comprehensively in MDD, with a treatment that encompasses several therapeutic and social approaches.

In conclusion, it would seem once more that the impact of MDD in HRQoL is considerable. When the patient perceives clinical improvement, we find significant evidence of this improvement in their perceived HRQoL. Progression in time is worse for older people, those with comorbidities or with low socioeconomic background.

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