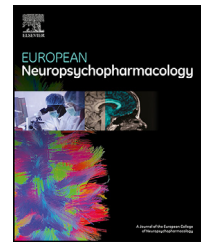




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# The effect of family environment and psychiatric family history on psychosocial functioning in first-episode psychosis at baseline and after 2 years

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Affective psychoses

## Abstract

The aim of the present study was to evaluate the contribution of family environment styles and psychiatric family history on functioning of patients presenting first-episode psychosis (FEP). Patients with FEP and healthy controls (HC) were assessed at baseline and after 2 years. The Functional Assessment Short Test (FAST) was used to assess functional outcome and the Family Environment Scale (FES) to evaluate family environment. Linear regressions evaluated the effect that family environment exerts on functioning at baseline and at 2-year follow-up, when FEP patients were diagnosed according to non-affective (NA-PSYCH) or affective psychoses (A-PSYCH). The influence of a positive parents' psychiatric history on functioning was evaluated through one-way between-groups analysis of covariance (ANCOVA) models, after controlling for family environmental styles. At baseline, FEP patients presented moderate functioning impairment, significantly worse than HC ( $28.65 \pm 16.17$  versus  $3.25 \pm 7.92$ ;  $p < 0.001$ ,  $g = 1.91$ ). At 2-year follow-up, the functioning of NA-PSYCH patients was significantly worse than in A-PSYCH ( $19.92 \pm 14.83$  versus  $12.46 \pm 14.86$ ;  $p = 0.020$ ,  $g = 0.50$ ). No specific family environment style was associated with functioning in FEP patients and HC. On the contrary, a positive psychiatric father's history influenced functioning of FEP patients. After 2 years, worse functioning in NA-PSYCH patients was associated with lower rates of active-recreational and achievement orientated family environment and with higher rates of moral-religious emphasis and control. In A-PSYCH, worse functioning was associated with higher rates of conflict in the family. Both family environment and psychiatric history influence psychosocial functioning, with important implications for early interventions, that should involve both patients and caregivers.

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## 1. Introduction

Patients suffering from a first-episode psychosis (FEP) present functional impairment, involving social and occupational activities (Parellada et al., 2015; Raghavan et al., 2017; Rosa et al., 2012; Stouten et al., 2017). Disability generally persists despite clinical symptom remission. Around 75% of FEP patients achieve symptomatic remission with antipsychotic treatment (Santesteban-Echarri et al., 2017). Nonetheless, social and vocational recovery was observed only in the 31% of the Early Psychosis Prevention and Intervention centre (EPPIC) cohort (Henry et al., 2010). Moreover, in a three-year Chinese longitudinal study, six out of ten FEP patients still exhibited functional disability after symptomatic remission (Chang et al., 2012).

Long-term functioning in FEPs was influenced by the duration of untreated psychosis (DUP), positive and negative symptoms and premorbid adjustment (Santesteban-Echarri et al., 2017). Furthermore, cognitive reserve (CR) (Amoretti et al., 2019, 2018, 2016), social cognition (González-Ortega et al., 2019) and coming from disadvantaged socioeconomic strata have been related to poor psychosocial functioning (Hall et al., 2019).

Moreover, the long-term functioning of FEP patients depends on the differentiation at follow-up in non-affective

(NA-PSYCH) and affective psychoses (A-PSYCH). The majority of affective patients show better functioning and lower negative symptoms than NA-PSYCH (Amoretti et al., 2018; Torrent et al., 2018). In addition, they differ in premorbid functioning, which was associated with clinical and psychosocial functioning in FEP patients, both in adults (White et al., 2009) and children and adolescents (Payá et al., 2013).

Family environment plays a major role in individual functioning. Among university students, higher rates of conflict and control were positively associated with depressive symptoms, while cohesion in the family was a protective factor (Yu et al., 2015). An increasingly large number of studies have found an association between negative family environment and poor prognosis in patients at high risk of suffering psychosis (O'Brien et al., 2006), in FEP patients (Lee et al., 2014; Norman et al., 2005) but also in bipolar disorder (BD) (Kim, 2004) and schizophrenia (Cañivé et al., 1995; Pitschel-Walz et al., 2001). Family exerts its effect as an environmental factor that is capable to act as a protective or a risk factor on long-term outcomes in FEP patients (Norman et al., 2005). Initial treatment seeking, adherence, and social support also depended on family environment (Quach et al., 2009).

In addition, the genetic load conferred by a positive psychiatric family history should be taken into account. A psy-

chiatric family history is considered to be a proxy measure of genetic risk (Lu et al., 2018). Moreover, it relies on familial-environmental factors (Kendler and Neale, 2009). A positive family history of psychosis was found to be associated with an higher risk of psychosis in siblings (Otero et al., 2011) who presented earlier age of onset (AAO), more severe negative symptoms and longer DUP (Esterberg and Compton, 2012).

The interaction of family environment and a positive family history of psychosis was evaluated. González-Pinto and colleagues (González-Pinto et al., 2011) identified that independently of the family history of psychosis, a negative family environment increased the risk of psychosis. Moreover, at baseline, the influence of a positive family environment exerted a protective effect on the presence of psychosis, particularly in those patients with a positive family history of psychosis, but not in those without.

Nonetheless, little is known about the implication of family environment and a psychiatric family history on functioning at follow-up of FEP patients, particularly depending on their final diagnosis (NA-PSYCH versus A-PSYCH). However, a better understanding of this interrelationship is essential for the development of future interventions focused on functional recovery and addressing not only FEP patients but also their families.

The aim of this study was to evaluate the contribution of the perceived family environment styles on functioning in a cohort of FEP patients compared to healthy controls (HC) at baseline, and of NA-PSYCH and A-PSYCH patients at 2 years. Furthermore, the possible influence on functioning exerted by a positive psychiatric family history has been assessed.

## 2. Experimental procedures

This study is part of the “Phenotype-genotype interaction. Application of a predictive model in first psychotic episodes” - PEPs Project, a multicentre, naturalistic and longitudinal study on FEP patients (Bernardo et al., 2013), under the umbrella of the Spanish Research Network on Mental Health (CIBERSAM) (Bernardo et al., 2019; Salagre et al., 2019). The PEPs Project was approved by the Clinical Research Ethics Committee of all participating centres. The procedures followed were in accordance with those of the World Medical Association and the Declaration of Helsinki. Informed consent was obtained from all participants. A total of 335 patients with a FEP and 253 healthy controls (HC) were recruited from 16 centres located throughout the Spanish territory from April 2009 to April 2011.

For the purpose of the present study only FEP patients 1. aged between 18 and 35 years, 2. With a functional assessment at baseline, 3. With a final diagnosis of A-PSYCH or NA-PSYCH after 2 years of follow-up, were included. The patients were matched with HC by age ( $\pm 10\%$ ), gender and parental socioeconomic status ( $\pm 1$  level). The exclusion criteria for HC were the same as for patients and also included 1. The presence of a current or past psychotic disorder or major depression and 2. Having one or both the parents suffering from a psychotic disorder.

Patients with a FEP and HC were evaluated at baseline and at follow-up with the Structured Clinical Interview for

DSM (SCID-I-II) (First et al., 1997, 1996) and diagnoses were determined according to DSM-IV criteria. The diagnoses of the patients who completed the study were based on information gathered up to the 2-year follow-up visit, taking into consideration potential changes across time and in order to ensure diagnostic stability. Diagnoses of schizophrenia, schizophreniform, schizoaffective disorders and psychoses that are not otherwise specified were categorized into NA-PSYCH, whereas BD or first manic episodes with psychotic symptoms were grouped as A-PSYCH.

## 3. Assessments

The complete assessment planning of the original cohort study is reported by Bernardo and colleagues (Bernardo et al., 2013).

### 3.1. Functional assessment

The overall functional outcome was assessed, both at baseline and at 2-year follow-up, by means of the Functioning Assessment Short Test (FAST) (Rosa et al., 2007). The FAST assessment refers to the last 15 days and comprises 24 items, which are divided in 6 specific areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. It has shown high internal consistency, high validity and strong test-retest reliability (Rosa et al., 2007), also in FEP patients (González-Ortega et al., 2010). The FAST total score (range 0-72) is calculated as the sum of each of the 24 item scores, with higher scores indicating worse functioning. Thresholds of severity are: no impairment in functioning (scores between 0 and 11), mild impairment (scores between 12 and 20), moderate impairment (scores between 21 and 40), and severe impairment (scores > 40) (Bonnín et al., 2018).

### 3.2. Family environmental styles

The Family Environment was assessed, both at baseline and at the 2-year follow-up, by the Family Environment Scale (FES) (Moos and Moos, 1976). FES is a self-reporting instrument focused on the measurement and description of the interpersonal relationships among family members. Three separate forms of the FES are available: the Real Form (Form R), which measures people’s perceptions of their actual family environments; the Ideal Form (Form I), which assesses individuals’ perceptions of their ideal family environment; the Expectations Form (Form E) in which participants indicate what they expect a family environment will be like. In the present study, the Real Form (Form R) was used. FES evaluates family emotional climate in different categories: COHESION (C) for mutual reliance; EXPRESSIVITY (EX), the extent to which family members express their feelings directly; CONFLICTS (CON) for open expression of anger, aggressiveness and conflict; INDEPENDENCE (IND), the extent to which family members are independent in their decisions; ACHIEVEMENT ORIENTATION (AO) for an achievement

orientated environment; INTELLECTUAL-CULTURAL ORIENTATION (ICO) for political, intellectual, cultural interests; ACTIVE-RECREATIONAL ORIENTATION (ARO) for participation in social activities; MORAL-RELIGIOUS EMPHASIS (MRE) for the importance given to ethical and religious practices and values; ORGANIZATION (ORG) for the organization in activities and responsibilities; and CONTROL (CTL), the extent to which the family considers rules and established procedures.

The first four subscales refer to personal growth; AO, ICO, ARO and MRE reflect the directions of personal growth emphasized in the family and the implication of the family in different activities whilst the last two subscales, ORG and CTL, are for system maintenance.

The 10 subscales show inter-correlations averaging around 0.20 and adequate internal consistency (Cronbach's alphas range from 0.64 to 0.79). Eight-week test-retest reliabilities ranged from 0.68 to 0.86 (Moos, 1990). The test-retest reliability of the Spanish version ranged from 0.68 to 0.86 for the 10 subscales (Moos, R.H., Moss, B.S., Trickett, E., 1995).

### 3.3. Parents' history of psychiatric disorders

The participants at baseline were asked to report family history of psychiatric disorders, namely affective and psychotic disorders. A positive family history for psychotic disorders was not present in HC since it represented an exclusion criterion of the study. Patients and HC were classified into two categories: (1) those with one or both parents suffering from a psychiatric disorder, and (2) those without parents' history of psychiatric disorders. A sub-classification of positive or negative psychiatric history in the mother or in the father was made.

## 4. Statistical analysis

The statistical analysis proceeded in different steps:

Step 1. Evaluation of functioning: FAST total score and subdomains scores were defined and compared for FEP patients and HC at baseline and for A-PSYCH and NA-PSYCH patients at 2-year follow-up. Functional differences among the groups were examined using unpaired t-tests and effect sizes were calculated (Hedges, 1981; Hedges and Olkin, 1985). Differences in functioning depending on socioeconomic status (SES) and cohabitation condition were assessed using the Kruskal-Wallis H test. The correlation between functioning at different time points and clinical variables (Positive and Negative Syndrome Scale-PANSS, Montgomery-Asberg Depression Rating Scale-MADRS and the Young Mania Rating Scale-YMRS and Clinical Global Impression-CGI scores) was assessed through Pearson correlation. An evaluation of the percentage of A-PSYCH or NA-PSYCH patients presenting at follow-up with a moderate or severe impairment in functioning (FAST total score  $\geq 21$ ) despite clinical remission (YMRS total score  $\leq 12$  + MADRS total score  $\leq 6$  + a score of  $\leq 3$  on the PANSS items P1, P2, P3, N1, N4, N6, G5, and G9) (Herrmann et al., 1998; Mohammadi et al., 2018; Os et al., 2006) was conducted.

Step 2. Evaluation of family environmental styles: Family environmental styles scores were defined for FEP patients and HC, at baseline, and for A-PSYCH and NA-PSYCH patients, at the 2-year follow-up. Differences between the groups were examined using unpaired t-tests. Differences in clinical variables depending on the family environmental styles were assessed for the different subgroups and at different time points. Significant clinical variables at bivariate analyses were entered in multiple regressions for the different family styles. Bonferroni correction was applied.

Step 3. Association of family environmental styles and functioning: Hierarchical multiple regressions were used to assess the ability of the different family environmental styles to predict functioning (FAST total score), at baseline, in FEP patients and HC, and at the 2-year follow-up, in A-PSYCH and NA-PSYCH patients, after controlling for the influence of SES and cohabitation condition, due to their influence on both individual functioning and family environment (Conger et al., 2010).

Step 4. Effect of positive parents' psychiatric history on functioning: Differences between the groups for positive parents' psychiatric history were examined using the Chi-square test. Clinical differences and environmental styles between those with or without a positive parents' psychiatric history were assessed. One-way between-groups analysis of covariance (ANCOVA) models were conducted to evaluate the effect exerted by a positive parent's psychiatric history on functioning. The independent variable was the presence or absence of a positive parents' psychiatric history and the dependent variable was the FAST total score (baseline or at 2-year follow-up). Scores on the different family environmental styles were used as covariates. The models were run only if at least one subject presented a positive parent's (or father's or mother's) psychiatric history.

Normality of distribution was assessed and held, otherwise non-parametrical alternatives were used. Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes, and reliable measurement of the covariates. All p-values were two-tailed and statistical significance was set at  $p < 0.05$ . Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, 23.0 version for Windows).

## 5. Results

### 5.1. Characteristics of the sample

According to the inclusion criteria of the present study, 283 FEP patients (mean age =  $25.40 \pm 5.30$ , 66.1% males) and 211 HC (mean age =  $25.83 \pm 5.68$ , 64% males) were considered. FEP patients reported a mean DUP of  $98.30 \pm 118.94$  days, the mean AAO was  $25.01 \pm 5.35$  years, the mean chlorpromazine equivalents (CPZ) were  $591.90 \pm 470.33$  doses and the mean CGI was  $4.04 \pm 1.55$ .

At the 2-year follow-up, the patient group divided in the NA-PSYCH ( $n = 244$ , 86.2%; mean age =  $25.42 \pm 5.21$ , 65.6% males) and the A-PSYCH ( $n = 39$ , 13.8%; mean age =  $25.28 \pm 5.88$ , 69.2% males) groups. NA-PSYCH patients and A-PSYCH patients did not differ in terms of AAO (NA-

PSYCH=25.10±5.21 versus A-PSYCH=24.91±6.17 years,  $t=-0.193$ ,  $p=0.847$ ), CPZ (NA-PSYCH=118.74±237.07 versus A-PSYCH=76.54±173.45 doses,  $t=-1.066$ ,  $p=0.287$ ) or CGI (NA-PSYCH=1.62±1.73 versus A-PSYCH=1.54±1.31,  $t=-0.338$ ,  $p=0.737$ ). The mean DUP of NA-PSYCH patients was significantly longer than for A-PSYCH patients (104.87±122.92 versus 58.51±81.78 days,  $t=-2.862$ ,  $p=0.006$ ,  $g=0.39$ ).

Subjects that did not undergo a functional assessment at follow-up were considered as drop-outs from the study and represented a percentage as high as 40.6% for FEP patients ( $n=115$ , of which at follow-up NA-PSYCH=102, 88.7% and A-PSYCH=13, 11.3%) and 31.8% ( $n=67$ ) for HC. The difference in drop-out rates between FEP patients and HC only reached a trend towards significance ( $X^2=3.726$ ,  $p=0.054$ ). In the comparison between NA-PSYCH versus A-PSYCH, the difference was not significant (NA-PSYCH: completers  $n=142$ , 58.2% versus non-completers  $n=102$ , 41.8%; A-PSYCH: completers  $n=26$ , 66.7% versus non-completers  $n=13$ , 33.3%;  $X^2=0.680$ ,  $p=0.410$ ). In all the groups, completers did not differ from those who did not complete the study in terms of FAST global scores. Among HC, non-completers had lower SES ( $X^2=11.706$ ,  $p=0.020$ ), education ( $X^2=10.913$ ,  $p=0.028$ ) and CR ( $t=4.350$ ,  $p<0.001$ ,  $g=0.66$ ) than those who completed the follow-up. Among FEP patients, lower CR ( $t=2.186$ ,  $p=0.030$ ,  $g=0.28$ ) was reported for those who did not complete the follow-up. The same happened in the NA-PSYCH group ( $t=2.013$ ,  $p=0.045$ ,  $g=0.28$ ) but no differences were identified in the A-PSYCH group.

## 5.2. Evaluation of functioning (Step 1)

Table 1 summarizes the functional characteristics and differences among groups.

In HC, FAST scores did not vary significantly between baseline and the 2-year follow-up ( $p=0.593$ ). At the 2-year follow-up, both A-PSYCH and NA-PSYCH patients presented average mild impairment but the functioning in NA-PSYCH patients was significantly worse than in A-PSYCH patients (mean ( $M$ )=19.92±14.83 versus  $M=12.46±14.86$ ;  $t=-2.355$ ,  $p=0.020$ ,  $g=0.5$ ), with significant differences particularly in the interpersonal relationships ( $M=4.78±4.07$  versus  $M=2.42±3.93$ ;  $t=-2.729$ ,  $p=0.007$ ,  $g=0.58$ ) and autonomy ( $M=2.91±2.86$  versus  $M=1.27±2.22$ ;  $t=-3.394$ ,  $p=0.002$ ,  $g=0.59$ ) subdomains.

Seventy (49.3%) out of 142 NA-PSYCH patients presented moderate or severe impairment. Among these, the 28.6% ( $n=20$ ) presented at the 2-year follow-up a moderate or severe impairment in functioning, despite clinical remission. 4 out of 26 (15.4%) A-PSYCH patients presented moderate or severe impairment, all despite clinical remission.

## 5.3. Evaluation of family environmental styles (Step 2)

Fig. 1 refers to family environmental styles across diagnostic groups and time periods.

The results of the bivariate analyses and of the multiple regression models assessing the association of specific clinical variables with the different family environmental styles are reported in the Supplementary Table (ST) 1 and 2, respectively.

## 5.4. Association of family environmental styles and functioning (Step 3)

At baseline, the linear models were not significant neither for HC ( $F(12,188)=0.701$ ,  $p=0.749$ ) nor for FEP patients ( $F(12,232)=1.282$ ,  $p=0.230$ ) and no family environment style was associated with functioning.

At the 2 years, in the NA-PSYCH group ( $F(12,86)=3.638$ ,  $p<0.001$ ), worse functioning was negatively associated with ARO ( $\beta=-0.304$ ,  $p=0.012$ ) and AO ( $\beta=-0.303$ ,  $p=0.004$ ) and positively associated with MRE ( $\beta=0.200$ ,  $p=0.045$ ) and CTL ( $\beta=0.268$ ,  $p=0.015$ ). SES and cohabitation condition were entered at Step 1, explaining 6.8% of the variance in functioning. After entry of the different family environmental styles, the total variance explained by the model was 24.4%.

In the A-PSYCH group ( $F(12,5)=5.249$ ,  $p=0.04$ ) worse functioning was associated with CON ( $\beta=0.718$ ,  $p=0.015$ ). SES and cohabitation condition were entered at Step 1, explaining 11% of the variance in functioning. After entry of the different family environmental styles, the total variance explained by the model was 75%.

## 5.5. Effect of positive parents' psychiatric history on functioning (Step 4)

Table 2 reports data on parents' history of psychiatric disorders with a comparison between diagnostic groups at different time points.

Differences in environmental styles among those with or without a family history of psychiatric disorders are reported in the ST3.

As for HC, after adjusting for environmental family styles scores, there was no significant difference on functioning at baseline between those with or without a parents' psychiatric history ( $p=0.496$ ). No relationship was found between any environmental family styles and FAST at baseline (see Fig. 2).

As for FEP, there was no significant difference on functioning at baseline between those with or without a parents' ( $p=0.550$ ) or a mother's ( $p=0.561$ ) psychiatric history after adjusting for environmental family styles scores. On the contrary, when father's psychiatric history was used as the independent variable, a significant difference was found between those with or without a father's psychiatric history on functioning at baseline (yes: adjusted mean (adjM)=39.93 versus no: adjM=27.42;  $F(1, 247)=6.601$ ,  $p=0.011$ , partial eta squared=0.027). No relationship was found between any environmental family styles and FAST at baseline. As for the association with clinical variables, FEP patients with a father's positive history presented higher PANSS negative symptoms (yes:  $M=23.4±6.74$  versus no:  $M=18.31±7.73$ ,  $t=-2.494$ ,  $p=0.013$ ,  $g=0.66$ ) and higher CPZ doses

**Table 1** Functioning across diagnostic groups.

Baseline	FEP (n = 283) Mean (SD)	HC (n = 211) Mean (SD)	t	P g
Overall functioning (FAST total score)	28.65 (16.17)	3.25 (7.92)	22.98	< 0.001 1.91
Autonomy	4.23 (3.33)	0.32 (1.12)	18.41	< 0.001 1.48
Occupational functioning	7.9 (5.3)	0.79 (2.34)	20.10	< 0.001 1.65
Cognitive functioning	5.96 (3.8)	0.9 (2.18)	18.64	< 0.001 1.57
Financial issues	1.63 (1.8)	0.25 (0.93)	11.03	< 0.001 0.92
Interpersonal relationships	6.73 (4.86)	0.69 (2.29)	18.32	< 0.001 1.52
Leisure time	2.20 (1.83)	0.3 (0.97)	15.27	< 0.001 1.24
	NA-PSYCH (n = 142)	HC (n = 144)		
2-year follow-up	Mean (SD)	Mean (SD)	t	p g
Overall functioning (FAST total score)	19.92 (14.83)	2.97 (8.52)	-11.825	< 0.001 1.40
Autonomy	2.91 (2.88)	0.33 (1.43)	-9.597	< 0.001 1.14
Occupational functioning	5.61 (5.13)	0.53 (1.74)	-11.199	< 0.001 1.33
Cognitive functioning	3.78 (3.58)	0.97 (2.17)	-8.037	< 0.001 0.95
Financial issues	0.99 (1.54)	0.15 (0.81)	-5.711	< 0.001 0.68
Interpersonal relationships	4.78 (4.07)	0.62 (2.29)	-10.637	< 0.001 1.26
Leisure time	1.85 (1.69)	0.38 (1.02)	-8.872	< 0.001 1.05
	A-PSYCH (n = 26)	HC (n = 144)		
2-year follow-up	Mean (SD)	Mean (SD)	t	p g
Overall functioning (FAST total score)	12.46 (14.86)	2.97 (8.52)	-3.163	0.004 0.97
Autonomy	1.27 (2.22)	0.33 (1.43)	-2.090	0.046 0.60
Occupational functioning	3.92 (4.79)	0.53 (1.74)	-3.571	0.001 1.38
Cognitive functioning	3 (3.75)	0.97 (2.17)	-2.685	0.012 0.82
Financial issues	0.69 (1.54)	0.15 (0.81)	-1.740	0.093 0.57
Interpersonal relationships	2.42 (3.93)	0.62 (2.29)	-2.273	0.031 0.69
Leisure time	1.15 (1.15)	0.38 (1.02)	-2.498	0.018 0.74
	NA-PSYCH (n = 142)	A-PSYCH (n = 26)		
2-year follow-up	Mean (SD)	Mean (SD)	t	p g
Overall functioning (FAST total score)	19.92 (14.83)	12.46 (14.86)	-2.35	0.020 0.50
Autonomy	2.91 (2.86)	1.27 (2.22)	-3.39	0.002 0.59
Occupational functioning	5.61 (5.13)	3.92 (4.79)	-1.56	0.121 0.33
Cognitive functioning	3.78 (3.58)	3 (3.75)	-1.01	0.311 0.21
Financial issues	0.99 (1.54)	0.69 (1.54)	-0.89	0.374 0.19
Interpersonal relationships	4.78 (4.07)	2.42 (3.93)	-2.72	0.007 0.58
Leisure time	1.85 (1.69)	1.15 (1.51)	-1.95	0.053 0.42

A-PSYCH= affective psychoses; FAST= Functioning Assessment Short Test; FEP= first episode psychosis; HC= healthy control; n= number; NA-PSYCH= non-affective psychoses; SD= standard deviation; g= Hedges' g effect size.

(yes:  $M = 868.23 \pm 532.21$  versus no:  $M = 575.51 \pm 462.42$ ,  $t = -2.362$ ,  $p = 0.019$ ,  $g = 0.63$ ).

In the NA-PSYCH subgroup, there was no significant difference between those with or without a parents' psychiatric history on functioning at the 2-year follow-up ( $p = 0.522$ ), after adjusting for environmental family styles scores. On the contrary, significant relationships were found between FAST at baseline and AO ( $F(1, 97) = 6.828$ ,  $p = 0.011$ , partial eta squared=0.072), ARO ( $F(1, 97) = 7.421$ ,  $p = 0.008$ , partial eta squared=0.078), MRE ( $F(1, 97) = 5.369$ ,  $p = 0.023$ , partial eta squared=0.057) and CTL ( $F(1, 97) = 4.982$ ,  $p = 0.028$ , partial eta squared=0.054). The same results were obtained when father's ( $F(1, 97) = 0.013$ ,  $p = 0.910$ , AO ( $F(1, 97) = 6.781$ ,  $p = 0.011$ , partial eta squared=0.072), ARO ( $F(1,$

$97) = 7.291$ ,  $p = 0.008$ , partial eta squared=0.077), MRE ( $F(1, 97) = 6.208$ ,  $p = 0.015$ , partial eta squared=0.066) and CTL ( $F(1, 97) = 4.959$ ,  $p = 0.029$ , partial eta squared=0.053) and mother's ( $F(1, 97) = 0.355$ ,  $p = 0.553$ , AO ( $F(1, 97) = 6.763$ ,  $p = 0.011$ , partial eta squared=0.071), ARO ( $F(1, 97) = 7.574$ ,  $p = 0.007$ , partial eta squared=0.079), MRE ( $F(1, 97) = 5.310$ ,  $p = 0.024$ , partial eta squared=0.057) and CTL ( $F(1, 97) = 5.504$ ,  $p = 0.021$ , partial eta squared=0.059) psychiatric history were used as the independent variables. As for the association with clinical variables, higher levels of CGI indicating higher severity of the disease were reported for those with a positive parents' psychiatric history (yes:  $M = 2.11 \pm 1.77$  versus no:  $M = 1.50 \pm 1.70$ ,  $t = -2.166$ ,  $p = 0.031$ ,  $g = 0.36$ ).

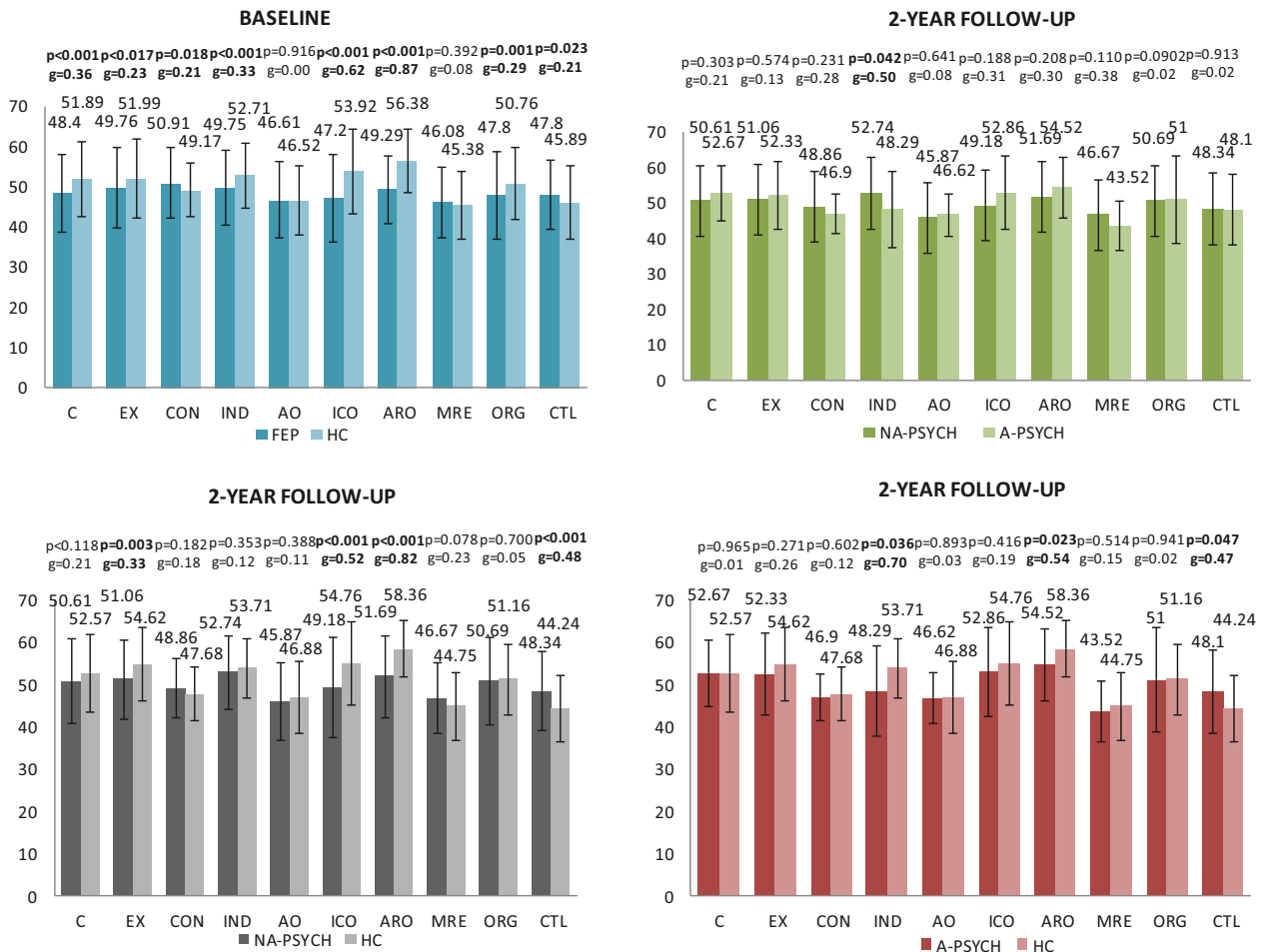


Fig. 1 Mean scores with error bars of family environment styles across diagnostic groups and time points.

Among A-PSYCH patients, there was no significant difference between those with or without a parents' psychiatric history on functioning at the 2-year follow-up ( $p = 0.537$ ), after adjusting for environmental family styles scores.

## 6. Discussion

In the present study, at baseline no specific family environmental style was associated with functioning in both FEP patients and HC, but in the FEP group worse functioning was related with positive father's history of psychiatric disorders. On the contrary, at the 2-year follow-up, worse functioning in NA-PSYCH patients was associated with the perception of higher rates of moral-religious emphasis and control in their family and lower rates of active-recreational and achievement orientation. Worse functioning was associated with higher conflicts in the family of A-PSYCH patients.

At the beginning of the study FEP patients presented moderate impairment that improved in 2 years, with mild impairment in both NA-PSYCH and A-PSYCH patients. Moreover, the global functioning of NA-PSYCH patients was significantly worse than in A-PSYCH, in line with previous literature (Thonse et al., 2018). Notably, half of the NA-

PSYCH patients presented moderate or severe functioning impairment at 2 years. In addition, a proportion of patients, both in the NA-PSYCH and in the A-PSYCH group, presented moderate or severe impairment in functioning at 2 years despite clinical remission (one out of three patients in the NA-PSYCH group, less than a quarter of the patients in the A-PSYCH group). Similar rates were reported in previous studies (Chang et al., 2012; Henry et al., 2010). As a consequence, the changes in functioning across time points can be partly explained by the clinical severity of the patients at baseline and their improvement at 2 years but the impairment in functioning at follow-up might not only be explained by their clinical condition. These findings indicate that functional recovery at follow-up in FEP patients does not only depend on clinical remission and it should be considered as important as symptomatic recovery (Santesteban-Echarri et al., 2017).

Previous literature identified that family environment plays a major role in longitudinal functioning in individuals at-risk of psychosis and FEP patients (O'Brien et al., 2006; Schlosser et al., 2010). Interestingly, in the present study environmental family styles perceived by the patients were significantly associated with functioning at follow-up in both NA-PSYCH and A-PSYCH patients. Particularly, higher

**Table 2** Parents' history of psychiatric disorders across diagnostic groups \*.

Baseline (yes reported)	FEP (n = 283) n (%)	HC (n = 211) n (%)	X <sup>2</sup> /FE	p
Parents' history of psychiatric disorders	51 (18)	26 (12.3)	2.566	0.109
- Psychotic disorders†	15 (-)	-		
- Bipolar disorders	2 (5.6)	4 (15.4)		
- Depressive disorders	34 (94.4)	22 (84.6)	1.669	0.196
Father's history of psychiatric disorders	15 (5.3)	15 (7.1)	0.412	0.521
- Psychotic disorders†	9 (-)	-		
- Bipolar disorders	1 (16.7)	2 (13.3)		
- Depressive disorders	5 (83.3)	13 (86.7)	0.039	1.000
Mother's history of psychiatric disorders	42 (14.8)	14 (6.6)	7.302	0.007
- Psychotic disorders†	9 (-)	-		
- Bipolar disorders	2 (6.1)	2 (14.3)		
- Depressive disorders	31 (93.9)	12 (85.7)	0.854	0.572
2-year follow-up (yes reported)	NA-PSYCH (n = 244) n (%)	A-PSYCH (n = 39) n (%)	FE	p
Parents' history of psychiatric disorders	47 (19.3)	4 (10.3)	1.846	0.260
- Psychotic disorders	13 (27.7)	2 (50)		
- Bipolar disorders	2 (5.9)	0	0.125	1.000
- Depressive disorders	32 (94.1)	2 (100)		
Father's history of psychiatric disorders	13 (5.3)	2 (5.1)	0.003	1.000
- Psychotic disorders	7 (53.8)	2 (100)		
- Bipolar disorders	1 (7.7)	0		
- Depressive disorders	5 (38.5)	0	1.538	0.463
Mother's history of psychiatric disorders	40 (16.4)	2 (5.1)	3.376	0.087
- Psychotic disorders	9 (22.5)	0		
- Bipolar disorders	2 (5)	0		
- Depressive disorders	29 (72.5)	2 (100)	0.745	0.540

A-PSYCH= affective psychoses; FE=Fisher's exact test; FEP=first episode psychosis; HC=healthy control; n=number; NA-PSYCH=non-affective psychoses; SD=standard deviation.

\*individuals can present more than one different psychiatric disorders in their parents' history.

†not included in the model because HC with a positive parents' history for psychotic disorders were excluded from the study.

rates of moral-religious emphasis and control in NA-PSYCH patients and the perception of conflicts in the family in A-PSYCH patients represented risk factors for worse individual functioning. These results met previous literature findings. In particular, families perceived as conflict-ridden or controlling were related to negative functioning in adolescents (Burt et al., 1988). Similarly, in the present study families of FEP patients in comparison with HC were characterized by higher rates of conflicts and control.

In previous studies assessing family environmental styles with the FES, the impact of family environment was also focused on evaluating longitudinal outcomes in terms of clinical features, such as relapses or re-hospitalizations. Interestingly, their findings on clinical outcomes resemble our findings on psychosocial functioning at follow-up. In a Spanish study assessing patients with schizophrenia outcomes after a nine-month follow-up, patients' perception of family control predicted psychotic relapses and re-hospitalization (Cañivé et al., 1995). Surprisingly, not only family control but also family independence predicted psychotic relapses (Cañivé et al., 1995). In the present study, independence was not significantly associated with functioning in NA-PSYCH patients, but NA-PSYCH patients scored significantly higher than A-PSYCH patients for their per-

ception of family independence. This finding might seem at odds with the fact that higher rates of family control were associated with worse functioning. Nonetheless, Spiegel and Wissler (Spiegel and Wissler, 1986), assessing a mixed cohort of patients during one year after an in-ward hospitalization, reported that patients whose families encouraged independence rated themselves as doing more poorly at follow-up and being less adapted. They conclude that this might reflect the poor self-perception of patients in family settings and might more acutely sense the limitations associated with their illness. In addition, psychotic relapses were predicted by the fathers' scores on moral-religious emphasis perceived in the family (Cañivé et al., 1995). Hafner and Miller (1991) identified that the fathers' scores on moral-religious emphasis were associated with higher number of days of hospitalization of siblings with schizophrenia. In terms of protective factors, in the same study higher fathers' scores on achievement orientation were associated with a better outcome (Hafner and Miller, 1991). In the present study, higher rates of achievement and active-recreational orientation within the family were protective factors from worse individual functioning in NA-PSYCH patients. In the subsample of patients suffering from schizophrenia of the study by Spiegel and



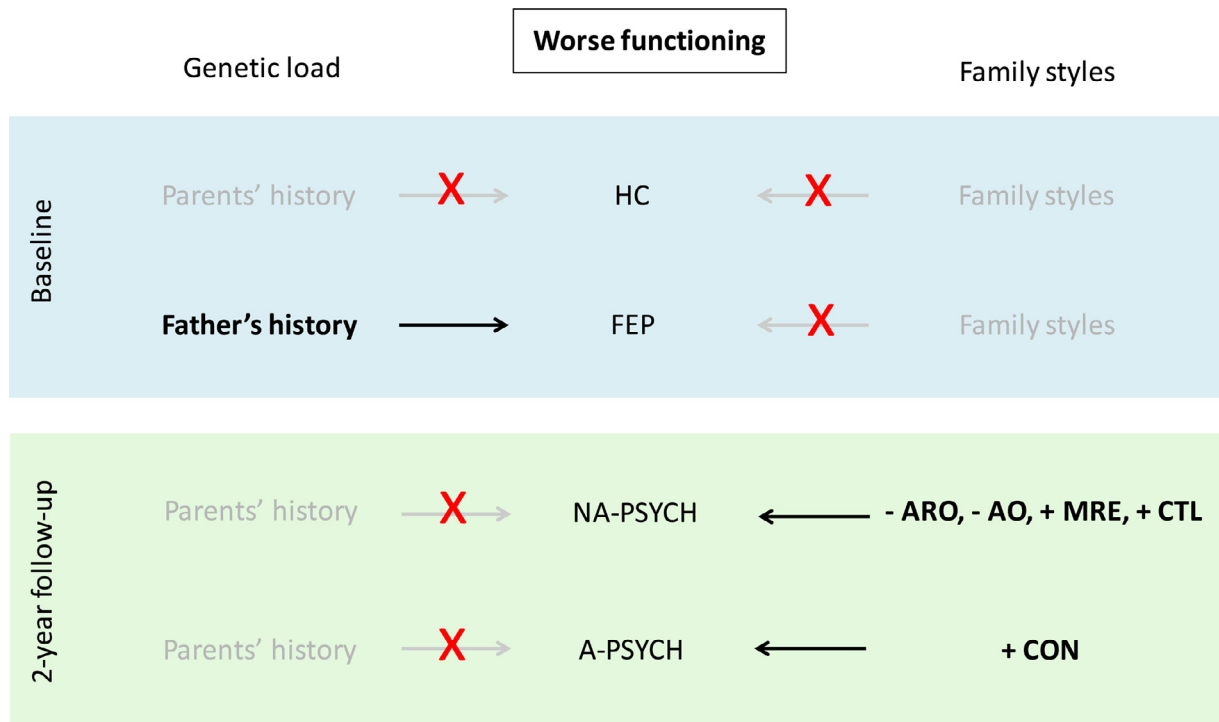


Fig. 2 The effect of family environmental styles or parents' history of psychiatric disorders on functioning.

Wissler (1986), a strong correlation was found between active-recreational orientation in the family at baseline and a better self-rated patient adjustment at short and long-term follow-up. In a research done in patients with history of psychosis (González-Pinto et al., 2011), it was found that families with affected relatives protect themselves from psychosis with positive environmental factors such as cohesion and intellectual-cultural activities. Consistently, in previous studies positive remarks, family warmth and an optimal level of family involvement predicted improved social functioning at follow-up in patients at risk of psychoses (O'Brien et al., 2006; Schlosser et al., 2010).

As for A-PSYCH patients, a more conflictive family environment represented a risk factor for worse individual functioning. High levels of conflicts were reported in the environment of BD families in previous studies (Barron et al., 2014; Reinares et al., 2016). Reinares et al. (2016) identified that individual psychosocial functioning positively correlated with cohesion and active-recreational orientation within the family and negatively correlated with control. Even though conflict was not directly associated with psychosocial functioning, it was related with substance use. As a consequence, the authors concluded that family conflict should be an important target for family intervention in BD (Reinares et al., 2016). In addition, in a cohort of patients with different psychiatric diagnoses, family conflict was seen to predict re-hospitalization at 3 months (Spiegel and Wissler, 1986). In a follow-up study assessing children and adolescents presenting a FEP (Otero et al., 2011), more problems in communication in families at baseline correlated with higher rates of psychopathology at one year. Moreover, less cohesion and poorer overall functioning was found in BD children with psychotic

symptoms in comparison with those without psychosis (Hua et al., 2011).

High rates of psychiatric disorders are commonly present in families of FEP patients, underlining the high vulnerability to psychiatric disorders in these families (Faridi et al., 2009). In the present study, at baseline FEP patients' functioning was not associated with any specific family environment style. Contrarily, worse baseline functioning was found for those FEP patients with a father's history of psychiatric disorder, even after controlling for the different family styles. A positive family history of psychosis was already seen to have a significant association with long-term occupational and global outcome in patients with schizophrenia (Käkelä et al., 2014). In a study assessing the possible effect exerted by positive or negative family styles against the development of psychosis, González-Pinto et al. (2011) found that the FES subscales with a significant effect on the presence of psychosis were CON and MRE, with a tendency to significance for CTL, whilst the protective factors on the presence of psychosis were ICO and ARO. These family styles were associated with functioning in NA-PSYCH and A-PSYCH patients in the present study. It seems that the genetic load conferred by a psychiatric family history has a higher influence on functioning at baseline, when the patient develops psychotic symptoms for the first time. Then, the family environment exerts its influence on functioning only when the illness was already established according to specific diagnoses, with manifested worse functioning in the presence of a disturbed family environment.

The reason why different family styles can confer a risk towards the development of an affective versus a non-affective psychosis is still not clear. In general, emotion-

ally neglectful and controlling parents' attitude were associated with an increased overall risk of psychiatric symptoms in children (Young et al., 2011). Adolescents suffering from BD acknowledged significantly more conflicts with their parents in comparison to either controls or adolescents suffering from unipolar depression. As for psychoses, caregivers who considered their relatives as chronic and who reported weaker beliefs in treatment generally use less coping strategies such as seeking social support and education and problem-solving with higher denial and disengagement (Gerson et al., 2011). Moreover, a positive family history does not only confer a genetic liability but might shape family relationship and interactions (Stapp et al., 2020). Patients with parent's history of psychiatric disorders tend to perceive more negative family environment styles in the present study. In previous literature, parents with psychosis reported that all domains of parenting appear to be affected by psychosis, i.e. the difficulty in concentration because of hallucinations had negative impact on their abilities to provide protection, expressivity and control (Strand et al., 2017). Furthermore verbal aggression was high in couples with an adult having BD (Serravalle et al., 2020) and this might have consequences on the relationship and development of siblings. Finally, a positive family history correlated with worse clinical indicators such as higher severity of negative symptoms and higher doses of treatment in FEP patients and higher severity of the disease in the group of NA-PSYCH patients at follow-up, in line with previous literature (Käkelä et al., 2018, 2017).

The present study has limitations. Data on trauma, abuse of drugs and early adjustment were retrospectively assessed at baseline, with the possibility of a recall bias. Recall bias could apply to the determination of the parents' history of psychiatric disorders. To reduce this risk, we considered a positive parents' history of psychiatric disorders only when a psychiatric disorder was formally diagnosed and required treatment. The small sample size of the A-PSYCH group can limit generalizability of the results and the possibility to compare A-PSYCH and NA-PSYCH. Only patients experiencing for the first time psychotic symptoms during an affective episode were included in the study, representing a selected group of A-PSYCH patients, with difficulty of recruitment. The family history of psychiatric disorders was not assessed through a semi-structured interview administered to the parents of the participants. Moreover, low rates of psychiatric family history were identified in the A-PSYCH group. Recruiting bias could be a risk. Indeed, drop-outs are a threat for any longitudinal study. The different potential sources of drop-outs, such as failure to contact research participants and to achieve cooperation, were partly reduced because patients were not only evaluated for research purposes but also for clinical reasons. Nonetheless, rates of drop-outs in the present study were moderately high but in line with the rates reported in previous longitudinal studies including FEP patients (Menezes et al., 2006). Furthermore, HC drop-outs and patients did not differ from completers in terms of functioning, which represented the main objective of the present study. Unfortunately, rates of re-hospitalization and relapses were not collected and future studies on the family environment of FEP patients should focus on these aspects. As for the family environmental styles, only patients were tested with the FES even

though it might have been interesting and informative if parents had completed the same scale as well. Nonetheless, in previous research significant levels of consistency in reports of family environment across family members were reported (De Ross et al., 1999; Kaur, 2013). The issue whether FEP patients experience a “bias” in the perception of the family environment in comparison to HC is unexplored in the current literature that actually deserve attention in future research. Similarly, the differences in the perception of the family environment in NA-PSYCH than in A-PSYCH should be further evaluated. The FAST severity thresholds were derived from the article by Bonnin et al. (2018), which stated severity groups considering a population of euthymic A-PSYCH patients. Anyway, no study was published so far establishing FAST severity thresholds for FEP patients. The final limitation would be the diagnostic instability of FEP. However, in this study the diagnoses were established in evaluations after 2 years of monitoring. Despite the limitations, this is the first study, to the best of our knowledge, to consider the effect exerted on functioning in FEP patients by family aspects, both environmental and derived from the genetic load to psychiatric disorders. Moreover, the study relies on a 2-year prospective follow-up period, allowing for causal interpretation of the results. Family environment has been poorly evaluated in previous studies. A recent study pairing polygenic risk score for schizophrenia with an aggregate environmental score provided evidence for gene-environment interaction in a FEP sample (Bernardo et al., 2017; Mas et al., 2020). Consequently, the exposome score for schizophrenia may be further enriched by inclusion of other exposures that have been associated with psychosis phenotype, such as family environment.

The present article underlined the importance of both perceived family environment and the genetic load on the functioning of patients presenting first-episode psychosis, with differences on the effect exerted at baseline or after 2 years, when specific diagnoses are established. Considering the worldwide initiatives to establishing preventive strategies, such as the European College of Neuropsychopharmacology Network on the Prevention of Mental Disorders and Mental Health Promotion (ECNP PMD-MHP) (Fusar-Poli et al., 2019), these findings shed light on the importance of identifying not only individuals at risk for developing a psychiatric disorder but also families with a higher dysfunctional load. Interventions apply both at the individual level, with a particular focus on functioning (Fowler et al., 2018), and to families (Dillinger and Kersun, 2019). Early interventions (Carvalho et al., 2020), and particularly family interventions aimed at improving the family environment by minimizing conflict and enhancing cohesion, organization, intellectual and recreational orientation might be useful in reducing the family burden and the patient's individual functioning.

## Role of the funding source

The funding sources were not involved in the study design, conduct, monitoring and preparation of the final database and had no influence on the final data analysis of this report.

## Contributors

NV and SA designed the study, managed the literature searches and analyses, undertook the statistical analysis, and wrote the first draft of the manuscript.

EV and MG revised the first draft and added critical comments to guide the redaction of the final manuscript.

GM, MJC, LP-C, CG-R, AL, AG-P, JM-N, IC, ES, IB, DB, MG, MBi, MS and CV revise the second draft of the article and provided critical comments to guide the redaction of the final manuscript.

All the authors within the PEPs Group recruited patients and healthy controls at their centers, provided the anonymous data and revise the final manuscript.

All authors approved the final manuscript.

## Declaration of Competing Interest

EV has received research support from or served as consultant, adviser or speaker for AB-Biotics, Actavis, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefónica, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute, unrelated to the present work.

MB has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, AMGEN, Eli Lilly, Ferrer, Forum Pharmaceuticals, Gedeon, Janssen-Cilag, Lundbeck, Otsuka, Pfizer and Roche.

MBi has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of, has received honoraria from talks and/or consultancy of Adamed, Angelini, Ferrer, Janssen-Cilag, Lundbeck, Otsuka, Pfizer and Sanofi.

AG-P has received grants and served as consultant, advisor or CME speaker for the following entities: Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Sanofi-Aventis, Alter, Angelini, Exeltis, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Government, and the European Framework Program of Research.

IB has received honoraria or travel support from Otsuka-Lundbeck, Angelini and Janssen, research support from Fundación Alicia Koplowitz and grants from Spanish Ministry of Health, Instituto de Salud Carlos III.

CG-R has received grants from/or served as consultant, advisor or speaker for the following entities Adamed, Angelini, Janssen-Cilag and Lunbeck.

MG served as consultant or advisor for Ferrer, Lundbeck and Janssen.

CDe-la-C. received financial support to attend scientific meetings from Janssen-Cilag, Almirall, Eli Lilly, Lundbeck, Rovi, Esteve, Novartis, and Astrazeneca.

RR-J has been a consultant for, spoken in activities of, or received grants from: Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS), Centro de Investigación

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VB-M has received grants and served as consultant, advisor, or continuing medical education speaker during the last 5 years for the following entities: Angelini Spain, Angelini Portugal, AstraZeneca, Bristol-Myers-Squibb, Ferrer, Janssen, Juste, Lundbeck, NutriciónMédica, and Otsuka.

AI has served as speaker or advisor for the following companies: Adamed, Bristol-Myers Squibb, Ferrer, Janssen-Cilag, Lundbeck, Pfizer, Servier and Otsuka.

IP has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag and Lundbeck.

The rest of authors report no biomedical financial interests or potential conflicts of interest related to the present article.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.euroneuro.2021.03.015](https://doi.org/10.1016/j.euroneuro.2021.03.015).

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