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Research paper

Predictive models for first-onset and persistence of depression and anxiety among university students☆

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ABSTRACT

Background: Depression and anxiety are both prevalent among university students. They frequently co-occur and share risk factors. Yet few studies have focused on identifying students at highest risk of first-onset and persistence of either of these conditions.

Methods: Multicenter cohort study among Spanish first-year university students. At baseline, students were assessed for lifetime and 12-month Major Depressive Episode and/or Generalized Anxiety Disorder (MDE-GAD), other mental disorders, childhood-adolescent adversities, stressful life events, social support, socio-demographics, and psychological factors using web-based surveys; 12-month MDE-GAD was again assessed at 12-month follow-up.

Abbreviations: aOR, Adjusted Odd Ratio; ASRS, Adult ADHD Self-Report Scales; AIC, Akaike's information criterion; AUDIT, Alcohol Use Disorders Identification Test; AUC, Area under the Curve; ADHD, Attention-deficit/hyperactivity disorder; UIB, Balearic Islands University; UPV-EHU, Basque Country University; UCA, Cádiz University; CIDI-SC, Composite International Diagnostic Interview Screening Scales; CI, Confidence Interval; GAD, Generalized anxiety disorder; ITC, International Test Commission; IPW, Inverse-probability weighting; MDE, Major Depressive Episode; MDE-GAD, Major Depressive Episode and/or Generalized Anxiety Disorder; UMH, Miguel Hernández University; MI, Multiple Imputation; OR, Odd Ratio; UPF, Pompeu Fabra University; SDS, Sheehan Disability Scale; SE, Standard Error; SD, Standard Deviation; WMH-ICS, World Mental Health International College Student initiative.

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Results: A total of 1253 students participated in both surveys (59.2% of baseline respondents; mean age = 18.7 (SD = 1.3); 56.0% female). First-onset of MDE-GAD at follow-up was 13.3%. Also 46.7% of those with baseline MDE-GAD showed persistence at follow-up. Childhood/Adolescence emotional abuse or neglect (OR= 4.33), prior bipolar spectrum disorder (OR= 4.34), prior suicidal ideation (OR=4.85) and prior lifetime symptoms of MDE (ORs=2.33-3.63) and GAD (ORs=2.15-3.75) were strongest predictors of first-onset MDE-GAD. Prior suicidal ideation (OR=3.17) and prior lifetime GAD symptoms (ORs=2.38-4.02) were strongest predictors of MDE-GAD persistence. Multivariable predictions from baseline showed AUCs of 0.76 for first-onset and 0.81 for persistence. 74.9% of first-onset MDE-GAD cases occurred among 30% students with highest predicted risk at baseline.
Limitations: Self-report data were used; external validation of the multivariable prediction models is needed.
Conclusion: MDE-GAD among university students is frequent, suggesting the need to implement web-based screening at university entrance that identify those students with highest risk.

1. Introduction

The transition to university may be stressful and increase the risk for onset of mental disorders (Arnett, 2000; Auerbach et al., 2018). Major depressive episode (MDE) and generalized anxiety disorder (GAD) are the most prevalent mental disorders among university students (Auerbach et al., 2018, 2016; Ibrahim et al., 2013; Vázquez et al., 2011). But less is known about their first-onset during the university period and the extent to which any of these disorders persist. Results from longitudinal studies among young adults and university students reported an incidence of MDE at 7% and of GAD at 4% (Beesdo et al., 2010; Ebert et al., 2019). Among adolescents, a longitudinal study found a 8-year incidence of MDE around 13% and GAD of 2% (Benjet et al., 2016). Also, depression and anxiety have been found to be persistent among college students (Zivin et al., 2009). Longitudinal studies are necessary to understand the course of these disorders to guide preventive interventions on campus.

Depression and GAD co-occur frequently (Garber and Weersing, 2010; Gorman, 1996; Kessler et al., 2008; Moffitt et al., 2007), have overlapping risk factors (Dozois et al., 2009), share similar symptoms (Goldberg et al., 2009) and non-specific cognitive and behavioral processes (Kotov, 2011). Additionally, similar efficacy of transdiagnostic interventions to disorder-specific treatments has been found (McEvoy et al., 2009; Newby et al., 2015), suggesting potential benefits of a single transdiagnostic protocol (Barlow et al., 2016). Notwithstanding the commonalities among these disorders, there are no studies focused on the broad occurrence of Major Depressive Episode and/or Generalized Anxiety Disorder (as from now, MDE-GAD) among university students.

There is robust evidence about a number of risk factors associated with depression and anxiety such as childhood adversities (Kessler et al., 2008), stressful life events (Spinhoven et al., 2010), prior history of mental disorders (Kessler et al., 2002) and previous symptomatology (Horwath, 1992; Rueter et al., 1999), as well as protective factors such as social support (Galatzer-Levy et al., 2012) and psychological factors (Crockett et al., 2007; Riskind et al., 1987). These known risk and protective factors could allow the development of prediction algorithms to early identify students at risk for the onset or persistence of MDE-GAD. In the mental health field, some efforts have been made to detect at-risk populations early, but most of them are directed to clinical or general adult populations (King et al., 2011; Wang et al., 2014). Developing an algorithm for both MDE-GAD may allow to deploy subsequent preventive interventions that may address their co-occurrence and common underlying factors (Nolen-Hoeksema and Watkins, 2011; Titov et al., 2011).

The present study aims to: (1) estimate 12-month incidence and persistence of MDE-GAD; (2) assess a broad range of risk and protective factors; and (3) develop and validate prediction models for the risk of first-onset and persistence of MDE-GAD among university students.

2. Methods

2.1. Study design

Longitudinal data were obtained from the UNIVERSAL project, a multi-center observational cohort study of university students in five Spanish universities. The UNIVERSAL project is part of the World Mental Health International College Student initiative (WHM-ICS, 2015). Information on the rationale and methods of the UNIVERSAL project has been published elsewhere (Blasco et al., 2016).

2.2. Participants and setting

The study was carried out in five public universities from different Autonomous Regions of Spain: Balearic Islands (UIB), Basque Country (UPV-EHU), Andalusia (UCA), Valencia (UMH), and Catalonia (UPF). These universities represented around 8% of the total number of students in public universities of Spain in the year 2014–15, and their distribution in terms of gender, nationality and academic field was similar to that of the overall population of students in public universities of Spain (Ballester et al., 2020).

In the academic year 2014–2015, all incoming first-year students at the participating universities aged 18 to 24 years old enrolled for the first time in a university were invited to participate in the baseline survey (N = 16,332). The baseline survey was carried out over the subsequent 12 months (October 2014–October 2015). Students were recruited in two stages. In the first stage of recruitment, all eligible students were invited to participate (i.e., census sampling). In order to increase participation, a second stage was carried out where a random subsample of eligible students who had not responded to the baseline survey (ranging from 6% to 11% of non-respondents depending on the University) was contacted by e-mail offering a direct economic incentive to complete the baseline survey. At UPV-EHU university, only the first stage was carried out. Baseline respondents were invited by e-mail with a personalized link to complete the follow-up survey twelve months after baseline evaluation. The data collection platform followed the international recommendations and guidelines for computerized assessment (International Test Commission -ITC-, 2005) (International Test Commission, 2019). Ethical approval was provided by the Parc de Salut Mar-Clinical Research Ethics Committee (Reference: 2013/5252/I).

2.3. Variables

Sociodemographic and university-related variables were asked at the beginning of the survey and included: gender, age, country of birth, parental education, urbanicity, religion, sexual orientation, university, academic field and first-term living location during the university period.

Mental disorders. Items taken from Composite International Diagnostic Interview Screening Scales (CIDI-SC) (Kessler et al., 2013a; Kessler and Üstün, 2004) were used to screen for lifetime and 12-month

DSM-IV Major Depressive Episode (MDE) and Generalized Anxiety Disorder (GAD) at baseline, and 12-month disorders at follow-up. CIDI-SC have shown good psychometric properties (Kessler et al., 2013b) and good concordance with blinded clinical diagnoses (Ballester et al., 2019; Kessler et al., 2013b). The outcome variable in this study was a positive screen for 12-month MDE and/or 12-month GAD at follow-up (i.e. 12-month MDE-GAD from now on). We distinguished between: a) first-onset MDE-GAD: 12-month MDE-GAD at follow-up among those without a baseline history of MDE and/or GAD (neither lifetime nor 12-month at baseline); and b) persistent MDE-GAD: 12-month MDE-GAD at follow-up among students with a baseline history of MDE and/or GAD (with or without 12-month diagnostic at baseline).

Bipolar spectrum disorder, panic disorder and drug use disorder were assessed with CIDI-SC. Alcohol use disorder was screened using a modified version of the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993). Adult Attention-deficit hyperactivity disorder (Adult ADHD) was assessed with the Adult ADHD Self-Report Scales (ASRS) referring to the previous 6 months (Kessler et al., 2005). Suicidal thoughts and behaviors were assessed with modified versions of the Self-Injurious Thoughts and Behaviors Interview (SITBI) (Nock et al., 2007) and the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). All of them were screened for lifetime and 12-month at baseline.

Childhood and adolescent adversities prior to the age of 17 were assessed using 20 items adapted from the CIDI-3.0 (Kessler and Üstün, 2004), the Adverse Childhood Experience Scale (Felitti et al., 1998), and the Bully Survey (Swearer and Cary, 2003) and included: breakdown of family structure (parental death, separation or divorce), family maladaptation (parental psychopathology or household dysfunction), childhood maltreatment (emotional abuse or neglect and physical or sexual abuse) (Blasco et al., 2019), bully victimization and dating violence. The presence of any specific adversity was considered when the response to the corresponding item was different than "never," except for bully victimization, where the cut-point was "sometimes" or more.

Childhood and adolescent perceived support prior to the age of 17 was assessed using 13 items adapted from the CIDI-3.0 (Kessler and Üstün, 2004), the Psychological Sense of School Membership Scale (Goodenow, 1993), the Adverse Childhood Experience Scale (Felitti et al., 1998), and the Childhood Trauma Questionnaire (Bernstein et al., 1997). Three constructs were considered: relationships within school, family, and peers/others. Confirmatory factor analysis showed good fit with the data (Comparative Fit Index = 0.986; Tucker-Lewis Index = 0.983; RMSEA = 0.055). Scores for the constructs were categorized into tertiles.

Psychological factors included: personality, positive coping strategies and student expectations. Personality was assessed using the Ten Item Personality Inventory (TIPI: Gosling et al., 2003). Scores were calculated as the mean of the two items in each dimension (Gosling et al., 2003). *Positive coping strategies* were assessed using 5 items adapted from the Hurricane Katrina Community Advisory Group Survey (Kessler et al., 2006), and the Army STARRS survey (Ursano, 2012). The five items were added together to give a total coping score. *Student expectations* were assessed using 2 items adapted from the Survey of Student Attitudes, Experiences and Expectations (Round, 2005). The items asked about expectations on academic demands and social life at university on a 7-point Likert scale. The score was obtained as the mean of the item responses.

12-month recent stressful events items were adapted from the Life Events Questionnaire (Brugha and Cragg, 1990), the Deployment Risk and Resilience Inventory (Vogt et al., 2008), and the Department of Defense Survey of Health-Related Behaviors (Bray et al., 2009). *Current severe stress* was assessed using 8 items adapted from the CIDI-3.0 (Kessler and Üstün, 2004) asking about how much stress the students currently had in different areas of their life. The presence of stress in any area of life was considered when the response to the corresponding item was "severe" or more.

Severe role impairment was assessed with an adapted version of the Sheehan Disability Scale (Leon et al., 1997). This scale is composed of four role domains: home management, college-related and other work, close personal relationships, and social. Severe self-reported role impairment was defined as having a 7–10 rating.

2.4. Analysis

Missing item-level data among respondents to both the baseline and follow-up assessment were imputed using multiple imputation (MI) by chained equations (van Buuren, 2012) with 43 imputed datasets, equivalent to the percentage of incomplete subjects (White et al., 2011), and 10 iterations per imputation.

Out of the 2118 baseline participants, we analyze here those that completed at least 40% of the follow-up survey, which include MDE and GAD sections (1253) (see Supplementary Table 1 for the characteristics of the 12-month follow-up sample). To correct the bias caused by lost to follow-up, inverse-probability weighting (IPW) (Seaman et al., 2012; Seaman and White, 2013) was calculated based on baseline covariates. Additionally, post-stratification weights were used to restore population distribution of gender, country of birth, and academic field within each university and across universities (further details available upon request).

For first-onset MDE-GAD, analyses were restricted to students reporting no history MDE-GAD at baseline (n = 794); for persistence, analyses were restricted to those with lifetime MDE-GAD at baseline (n = 459). Descriptive statistics are reported as weighted percentages and SE. Bivariate logistic regression analyses were performed to examine the association between hypothesized risk and protective factors and the outcome variable. Crude Odds Ratios (ORs) and MI-based 95% confidence intervals (CIs) were calculated, and statistical significance was assessed with F-test based on MI.

Multivariable logistic regression models were estimated for first-onset and persistence of MDE-GAD in the 12 months prior to follow-up. We identified the subset of variables that best explain first-onset and persistence of MDE-GAD using group lasso penalty (Tibshirani, 1996; Yuan and Lin, 2006) in the stacked imputed dataset (Zhao and Long, 2017), with gender forced into the model. We chose group lasso because this method has shown a good performance in terms of selection consistency (Bach and Org, 2008). Akaike information criterion (AIC) with effective degrees of freedom was used to select the regularization parameter λ (Harrell, 2001). The AIC criterion has shown to be an efficient selection method (Flynn et al., 2013) with lower computational cost than cross-validation (Gelman et al., 2014). Adjusted odds ratios (aORs) and MI-based CIs were obtained. Statistical significance was evaluated with two-side F test based on MI and α level of significance of 0.05. Firth's penalized likelihood estimation was applied to avoid overfitting due to data sparseness (Heinze, 2006). The area under the curve (AUC) was estimated to assess discriminant capacity of the models. To correct the over-estimation of prediction accuracy we used cross-validation with leave-one-out method (Efron and Gong, 1983).

Predicted probabilities were discretized into deciles and cross-classified with observed incident and persistent cases. Sensitivity was defined as the proportion of first-onset and persistent cases found among predefined proportions of respondents with the highest predicted probabilities as defined by the deciles. Positive predictive value was defined as the probability of first-onset MDE-GAD and of persistent MDE-GAD when estimated among respondents with the highest predicted probabilities based on each decile. MI was carried out using mice package from R (van Buuren and Groothuis-Oudshoorn, 2011). Analyses were performed using R v3.64 (RStudio Inc., 2017), SAS v9.4 (SAS Institute Inc., 2014) and Mplus v7.11 (Muthén and Muthén, 2015).

3. Results

3.1. 12-month first-onset and persistence of MDE-GAD

Fig. 1 shows the overall 12-month MDE-GAD prevalence, first-onset and persistence of MDE-GAD. A total of 24.9% of students had MDE-GAD at 12-month follow-up. Of students without a history of MDE-GAD at baseline, 13.3% (95% CI 10.6–15.9) had first-onset of MDE-GAD at 12-month follow-up. Of the students with MDE-GAD at baseline, 46.7% (95% CI 41.3–52.1) reported persistence at 12-month follow-up. No statistically significant differences by gender were found either in first-onset or persistence.

3.2. Risk and protective factors associated with the onset and persistence of MDE-GAD

Bivariate analyses revealed that most factors were statistically significantly associated with the onset and persistence of MDE-GAD, with the magnitude of associations being generally higher with the onset of MDE-GAD.

For first-onset of MDE-GAD, the strongest associations were childhood–adolescent emotional abuse or neglect (OR = 4.33; 95% CI 2.67–7.01), any childhood–adolescent adversity (OR = 4.08; 95% CI 2.40–6.94), current severe stress in any area of life (OR = 3.90; 95% CI 2.32–6.57) (Table 1); 12-month bipolar spectrum disorder (OR = 4.34; 95% CI 1.21–15.5), 12-month suicidal ideation (OR = 4.85; 95% CI 2.12–11.1) (Table 2); lifetime MDE symptoms (OR range = 2.33–3.63) and lifetime GAD symptoms (OR range = 2.15–3.75) (Table 3).

For persistence of MDE-GAD, the most important predictors were any 12-month stressful event (OR = 2.55; 95% CI 1.30–5.0) (Table 1); 12-month suicidal ideation (OR = 3.17; 95% CI 1.92–5.21) (Table 2); and lifetime GAD symptoms (OR range = 2.38–4.02) (Table 3).

Regarding protective factors examined, significant negative associations were found for perceived support with the onset of MDE-GAD (family: OR = 0.45; 95% CI 0.24–0.81, highest tertile and peers/others: OR = 0.30, 95% CI 0.16–0.58, highest tertile) and with persistence (peers/others: OR = 0.49; 95% CI 0.30–0.80, middle tertile and school: OR = 0.47, 95% CI 0.27–0.82, highest tertile) (Table 1). Also, positive coping strategies (OR = 0.94, 95% CI 0.89–0.99; OR = 0.93, 95% CI 0.89–0.97 for first-onset and persistence, respectively) and positive expectations (OR = 0.71, 95% CI 0.57–0.90; OR = 0.66, 95% CI 0.54–0.80 for first-onset and persistence, respectively) were found associated (Table 2).

As shown in Supplementary Table 2, sociodemographic and university-related variables did not significantly predict the onset of MDE-GAD. For persistence of MDE-GAD, only sexual orientation was associated.

3.3. Prediction models for the onset and persistence of MDE-GAD

The multivariable prediction models after lasso selection had a reasonable performance with a cross-validated AUC of 0.76 for predicting onset of MDE-GAD and 0.81 for predicting persistence. Table 4 shows cross-validated sensitivity and PPV estimates for different proportions of students at highest predicted risk based on the final baseline models. For instance, considering the 30% of students at highest baseline predicted risk for first-onset of MDE-GAD would include 74.9% (SE = 6.34) of all observed cases, being the probability of MDE-GAD onset of 33.4% (SE = 5.12) within this 30% of respondents. On the other hand, the 30% of students at highest baseline predicted risk of persistent MDE-GAD would include 54.6% (SE = 6.23) of all observed cases, with a probability of persistent MDE-GAD in this group of 85.1% (SE = 4.08).

The final prediction algorithm for first-onset of MDE-GAD (Supplementary Table 3) contained 21 variables in addition to gender. Independent predictors were: age of 18 years old (aOR = 0.5; 95% CI 0.3–1.0), childhood-adolescent emotional abuse or neglect (aOR = 3.2; 95% CI 1.7–5.7), current severe stress in any area of life (aOR = 3.0; 95% CI 1.7–5.3), a lifetime GAD symptom: worried about number of things or about everything (aOR = 2.4; 95% CI 1.4–4.0), a lifetime MDE symptom: sadness or depressed (aOR = 1.9; 95% CI 1.0–3.7), and neuroticism (aOR = 1.7; 95% CI 1.3–2.3).

The final prediction algorithm for persistence of MDE-GAD (Supplementary Table 4) contained 23 variables, in addition to gender, where the independent predictors were: family support (aOR = 2.8; 95% CI 1.3–5.9, highest tertile), a lifetime MDE symptom: diminished interest or pleasure (aOR = 2.1; 95% CI 1.2–3.9), 12-month suicidal ideation (aOR = 2.0; 95% CI 1.0–3.8), 3 lifetime GAD symptoms: more anxious, nervous or worried than other people (aOR = 1.9; 95% CI 1.1–3.6), worry or anxiety about things than other people wouldn't worry (aOR = 1.9; 95% CI 1.1–3.5) and restlessness or feeling keyed up or on edge (aOR = 2.2; 95% CI 1.2–4.2), neuroticism (aOR = 1.5; 95% CI 1.1–2.1) and openness to new experiences (aOR = 1.4; 95% CI 1.0–1.8).

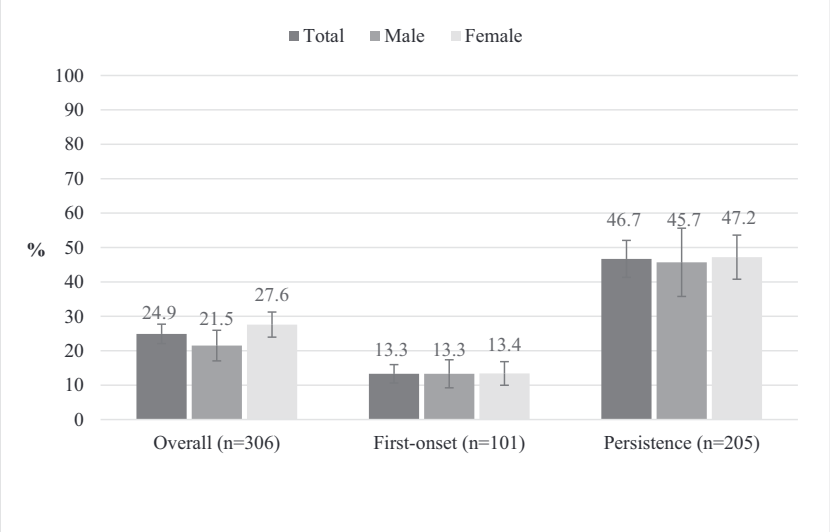

Fig. 1. First-onset and persistence of MDE-GAD at 12-month follow-up by gender. (% weighted).

Table 1
Bivariate associations of childhood-adolescent experiences and recent stressful events with first-onset and persistence of MDE-GAD at 12-month follow-up.

	First-onset				Persistence			
			Bivariate model				Bivariate model	
	%	SE	OR	95%CI	%	SE	OR	95%CI
Childhood-Adolescent experiences								
Adversities								
Breakdown of family structure	16.5	1.6	1.16	(0.65–2.05)	23.7	2.3	1.28	(0.77–2.11)
Family maladaptation	30.9	1.9	**2.14**	(1.33–3.45)	46.6	2.9	**1.74**	(1.15–2.63)
Physical or sexual abuse	10.1	1.2	**2.38**	(1.26–4.50)	17.3	2.1	1.36	(0.78–2.38)
Emotional abuse or neglect	20.8	1.7	**4.33**	(2.67–7.01)	33.4	2.5	1.47	(0.95–2.28)
Dating violence	2.2	0.6	1.01	(0.24–4.32)	5.9	1.2	1.60	(0.67–3.86)
Bully victimization	28.0	1.9	1.55	(0.95–2.56)	50.8	2.6	**2.06**	(1.35–3.16)
Any adversity	54.6	2.0	**4.08**	(2.40–6.94)	75.2	2.5	1.61	(0.97–2.69)
Perceived support[a]								
Family (ref = Low)								
High	38.1	1.9	**0.45**	(0.24–0.81)	29.0	2.3	1.11	(0.67–1.85)
Middle	32.4	1.8	**1.12**	(0.66–1.90)	34.8	2.6	1.19	(0.72–1.98)
Peers/others (ref = Low)								
High	26.6	1.7	**0.30**	(0.16–0.58)	23.2	2.2	**0.64**	(0.38–1.07)
Middle	40.3	2.0	**0.51**	(0.30–0.84)	33.6	2.4	**0.49**	(0.30–0.80)
School (ref = Low)								
High	31.6	1.8	0.90	(0.50–1.59)	19.8	2.0	**0.47**	(0.27–0.82)
Middle	40.8	1.9	0.65	(0.36–1.17)	34.3	2.4	**0.49**	(0.30–0.79)
Recent stressful events								
12-month stressful events								
Death illness injury or accident	50.8	2.0	**1.77**	(1.12–2.79)	57.9	2.6	1.38	(0.90–2.10)
Breakup or betrayal arguments	49.5	2.0	1.62	(1.01–2.62)	69.7	2.4	**1.85**	(1.14–3.01)
Seriously physically or sexually assaulted	5.6	0.9	**2.37**	(1.10–5.12)	3.7	0.9	1.77	(0.61–5.14)
Trouble with the police or serious legal problem	6.2	1.0	1.19	(0.44–3.19)	3.4	1.1	3.80	(0.86–16.8)
Another stressful event	5.1	0.9	1.18	(0.46–3.01)	11.3	1.7	2.18	(1.08–4.39)
Any stressful event	77.7	1.7	1.52	(0.85–2.72)	87.0	1.8	**2.55**	(1.30–5.00)
Current stress								
Severe stress in any area of life	17.3	1.5	**3.90**	(2.32–6.57)	46.4	2.6	1.45	(0.95–2.21)

Significant odds ratios are shown in bold (Raw *p*-value statistically significant after adjustment for multiple comparisons using Benjamini-Hochberg procedure with false discovery rate 0.05). P-value obtained from F-test to evaluate significant difference in estimates based on multiple imputations.
% weighted. SE: Standard Error; OR: odds ratio; CI: confidence interval; ref.: Reference category.
[a] Family: lowest tertile [1–3.75], middle tertile [3.75–4.5], highest tertile [4.5–5.0]; Peers/others: lowest tertile [1–2.75], middle tertile (2.75–3.5], highest tertile (3.5–5.0]; School: lowest tertile [1–3.33], middle tertile [3.33–4.17], highest tertile [4.17–5.0].

Table 2
Bivariate associations of psychological factors, impairment and mental health problems with first-onset and persistence of MDE-GAD at 12-month follow-up.

	First-onset				Persistence			
			Bivariate model				Bivariate model	
	Mean	SD	OR	95%CI	Mean	SD	OR	95%CI
Psychological factors								
Personality								
Extraversion	4.40	1.7	0.91	(0.77–1.07)	4.06	1.74	0.9	(0.79–1.02)
Agreeableness	4.34	1.0	**0.77**	(0.61–0.98)	4.27	0.94	1.09	(0.85–1.40)
Conscientiousness	5.30	1.4	0.89	(0.74–1.07)	5.02	1.18	**0.77**	(0.64–0.93)
Neuroticism	3.21	1.4	**1.65**	(1.37–1.98)	4.40	1.49	**1.74**	(1.45–2.07)
Openness to new experiences	5.23	1.3	1.11	(0.90–1.36)	5.11	1.41	**1.31**	(1.10–1.55)
Coping strategies								
Positive coping strategies	26.8	5.3	**0.94**	(0.89–0.99)	24.16	5.59	**0.93**	(0.89–0.97)
Student expectations								
Positive expectations	5.79	1.0	**0.71**	(0.57–0.90)	5.34	1.15	**0.66**	(0.54–0.80)
Impairment and mental health problems	%	SE			%	SE		
12-month role impairment								
Any severe role impairment	11.0	1.3	**2.63**	(1.44–4.81)	34.4	2.5	**2.08**	(1.34–3.23)
12-month mental health problems								
Bipolar spectrum disorder	2.1	0.6	**4.34**	(1.21–15.5)	7.1	1.4	2.26	(0.99–5.18)
Panic disorder	0.7	0.4	1.25	(0.11–14.7)	6.2	1.2	1.46	(0.63–3.38)
Alcohol abuse or dependence	5.0	0.9	0.38	(0.09–1.59)	3.9	1	0.67	(0.24–1.88)
Substance abuse or dependence	2.0	0.5	2.58	(0.71–9.37)	3.1	0.8	0.58	(0.17–1.98)
Adult Attention deficit hyperactivity disorder	7.7	1.1	**2.31**	(1.16–4.58)	23.7	2.2	**1.92**	(1.14–3.21)
Suicidal ideation	3.8	0.8	**4.85**	(2.12–11.1)	23.8	2.1	**3.17**	(1.92–5.21)

Significant odds ratios are shown in bold (Raw p-value statistically significant after adjustment for multiple comparisons using Benjamini-Hochberg procedure with false discovery rate 0.05). P-value obtained from F-test to evaluate significant difference in estimates based on multiple imputations.
% weighted; SD: Standard Deviation; SE: Standard Error; OR: odds ratio; CI: confidence interval; ref.: Reference category.

Table 3
Bivariate associations of lifetime symptoms of MDE and GAD with first-onset and persistence of MDE-GAD at 12-month follow-up.

	First-onset				Persistence			
			Bivariate model				Bivariate model	
	%	SE	OR	95%CI	%	SE	OR	95%CI
Lifetime symptoms								
Lifetime MDE symptoms								
Sadness or depressed	21.4	1.6	**3.63**	(2.24–5.88)	81.6	2.0	1.36	(0.80–2.32)
Discouraged	24.5	1.7	**3.19**	(2.00–5.10)	84.7	1.9	1.73	(0.96–3.13)
Diminished interest or pleasure	13.1	1.3	**2.49**	(1.39–4.49)	72.1	2.4	**1.73**	(1.09–2.76)
Worthlessness, feel down on yourself	16.0	1.4	**2.33**	(1.40–3.85)	73.6	2.2	**1.91**	(1.18–3.08)
Thoughts of death	4.6	0.9	1.65	(0.65–4.21)	35	2.5	1.58	(1.00–2.48)
Diminished concentration	6.8	1.0	1.92	(0.93–3.99)	50.8	2.7	**1.78**	(1.18–2.69)
Number of symptoms (ref = 0)								
1	16.5	1.4	**2.53**	(1.31–4.89)	3.5	1.0	**0.34**	(0.06–2.03)
2	13.7	1.3	**5.13**	(2.72–9.67)	6.4	1.3	**1.89**	(0.49–7.30)
3	11.2	1.3	**6.19**	(3.22–11.9)	17.2	2.0	**1.10**	(0.35–3.47)
4	2.3	0.6	**4.08**	(1.19–14.1)	28.3	2.3	**1.16**	(0.38–3.50)
5	0.0	0.0	n.a.	n.a.	26.3	2.2	**2.04**	(0.67–6.22)
6	0.0	0.0	n.a.	n.a.	14.3	1.8	**4.24**	(1.28–14.0)
Lifetime GAD symptoms								
Anxiety or nervousness	23.4	1.6	**2.68**	(1.67–4.32)	67.9	2.4	**2.38**	(1.49–3.80)
Worry about a number of different things or about everything	29.2	1.8	**3.75**	(2.37–5.95)	82	1.9	**4.02**	(2.18–7.43)
More anxious, nervous or worried than other people	7.4	1.0	1.12	(0.52–2.42)	61.5	2.5	**3.13**	(2.00–4.90)
Worry or anxiety about things other people wouldn't worry about	10.9	1.3	**3.23**	(1.81–5.76)	57.6	2.5	**3.48**	(2.23–5.43)
Difficulty to control the worry or anxiety	11.5	1.2	**3.22**	(1.84–5.62)	61.6	2.5	**3.66**	(2.29–5.87)
Restlessness or feeling keyed up or on edge	14.6	1.4	**2.98**	(1.76–5.06)	60.9	2.5	**3.02**	(1.91–4.76)
Irritability	17.2	1.5	**2.15**	(1.29–3.59)	68.4	2.5	1.36	(0.87–2.14)
Number of symptoms (ref = 0)								
1	14.4	1.4	**9.63**	(4.73–19.6)	4.9	1.1	**2.13**	(0.28–16.4)
2	11.3	1.3	**3.28**	(1.39–7.73)	6	1.2	**2.59**	(0.38–17.8)
3	11.6	1.2	**4.97**	(2.25–11.0)	7.7	1.4	**5.0**	(0.83–30.2)
4	6.7	1.0	**11.7**	(5.25–26.2)	10.8	1.9	**10.9**	(1.81–65.6)
5	3.3	0.7	**22.4**	(8.38–59.9)	15.2	1.9	**8.22**	(1.50–45.1)
6	1.4	0.5	**14.8**	(3.70–59.5)	16.6	1.9	**14.4**	(2.58–80.2)
7	0.0	0.0	n.a.	n.a.	18.7	2.0	**13.3**	(2.50–71.1)
8	0.0	0.0	n.a.	n.a.	14.7	1.9	**31.3**	(5.38–182.5)

Significant odds ratios are shown in bold (Raw p-value statistically significant after adjustment for multiple comparisons using Benjamini-Hochberg procedure with false discovery rate 0.05). *P*-value obtained from F-test to evaluate significant difference in estimates based on multiple imputations.
% weighted; SE: Standard Error; OR: odds ratio; CI: confidence interval; ref.: Reference category.

Table 4
Concentration of risk of MDE-GAD first-onset and persistence at 12-month follow-up in different proportions of university students.

% at highest predicted risk	First-onset				Persistence			
	Sensitivity[a]		PPV[b]		Sensitivity[a]		PPV[b]	
	%	SE	%	SE	%	SE	%	SE
100	100.0	0.00	13.3	2.01	100.0	0.00	46.7	3.73
90	99.6	0.58	14.8	2.19	99.1	0.70	51.4	3.92
80	97.8	1.45	16.3	2.44	97.8	1.08	57.1	4.06
70	94.7	2.28	18.1	2.71	94.3	2.08	62.9	4.19
60	91.2	3.32	20.3	3.10	86.9	3.01	67.6	4.38
50	86.4	4.49	23.1	3.51	80.5	3.75	75.3	4.28
40	81.8	5.22	27.4	4.24	69.9	4.70	81.7	4.04
30	74.9	6.34	33.4	5.12	54.6	6.23	85.1	4.08
20	64.9	7.57	43.4	6.59	37.5	6.31	87.6	4.73
10	45.5	9.04	60.7	8.58	19.2	6.33	89.5	6.84

SE: Standard error.
[a] Sensitivity = proportion of first-onset or persistent MDE-GAD cases found among respondents at highest predicted risk, based on cross-validated predicted probabilities.
[b] Positive Predictive Value (PPV) = probability of first-onset or persistent MDE-GAD when estimated among respondents at highest predicted risk, based on cross-validated predicted probabilities.

4. Discussion

4.1. Main findings

This study provides the first prospective data on first-onset and persistence of MDE-GAD among Spanish university students during their first academic year. These disorders are common during university, 13.3% of students had a first-onset of MDE and/or GAD during their first year in university, and 46.7% of those with a history of these mental disorders before entering college had MDE and/or GAD at 12-month follow-up. We found a higher than expected incidence of MDE-GAD in our study than the 6.9% previously reported for MDE in Belgian university students (Ebert et al., 2019) and for GAD among young adults in Germany of 4.3% (Beesdo et al., 2010). Also our prevalence estimates were higher than reported from a sample of adolescents from Mexico of 8-year incidence of 12.9% and 1.6%, for MDE and GAD respectively (Benjet et al., 2016). Regarding persistence, these were also somewhat higher than reported in prior studies of university students (MDE: 26.9%; anxiety: 30.4%) but slightly lower than those found among adolescents (MDE: 70.2%, GAD: 51.2%) (Kessler et al., 2012; Zivin et al., 2009). However, these results are not directly comparable due to the aggregation of MDE and GAD in our study. In general, our findings suggest that these disorders are common during university period, which had been previously reported in cross-sectional studies (Auerbach et al., 2018; Ballester et al., 2020; Eisenberg et al., 2007), highlighting the importance of early detection of young people at risk of common mental disorders.

We also found that, while most of the childhood adversities included in the study were associated with first-onset of MDE-GAD, fewer were associated with persistence. This is consistent with previous findings of a reduced impact of stressful events on mental disorders according to the increase of the number of previous episodes (Kessler et al., 2008; McLaughlin et al., 2010). It could be explained through some kind of kindling phenomenon, understood as a progressive neurobiological

sensitization (Post, 2007). Also consistent with previous research, lifetime MDE and GAD symptoms were predictors of first-onset (Fava and Tossani, 2007; Horwath, 1992; Liu et al., 2019). These symptoms may correspond to prodromal stages or subthreshold disorders (Murphy et al., 1989; Wolitzky-Taylor et al., 2014). Thus, early detection of students with subclinical symptoms could facilitate preventive interventions before the onset of a mental disorder. Otherwise, we found that GAD symptoms predicted persistence of MDE-GAD more strongly than did MDE symptoms. This finding is in line with Kessler et al. (2008), reporting that while GAD predicted onset and persistence of MDE, MDE did not predict persistence of GAD. One possible explanation could be to interpret GAD as a prodrome or severity marker of MDE when they are considered together (Kessler et al., 2008; Wittchen et al., 2001). Nevertheless, Moffitt et al. (2007) found that the reverse pattern also occurs with almost the same frequency (Moffitt et al., 2007). Finally, protective factors were associated with the onset and persistence of MDE-GAD. Consistent with previous studies, family relationships, peer support and connection to school were protective (Galatzer-Levy et al., 2012; van Voorhees et al., 2008) as well as positive coping strategies (Crockett et al., 2007; McLafferty et al., 2019) and student expectations (Brackney and Karabenick, 1995; Riskind et al., 1987). These findings suggest that the identification of modifiable protective factors could aid prevention efforts, beyond a focus on the reduction of potential risk factors and which could contribute to resilience (Steinhardt and Dolbier, 2008).

Our findings show that prediction models applied to freshmen could be useful in identifying students at high risk of onset and persistence of Major Depressive Episode (MDE) and/or Generalized Anxiety Disorder (GAD) over their first year of school. Also, in comparison to previous integrative models of MDE or GAD (Ebert et al., 2019; King et al., 2011), this model jointly adds personality traits, protective factors and previous symptomatology to compose the model. The multivariate algorithm for onset had good performance (AUC = 0.76), similar than AUCs obtained previously for MDE among university students, general population and primary care (AUC = 0.71–0.82) (Bellón et al., 2011; Ebert et al., 2019; Nigatu et al., 2016); and slightly higher than AUC for GAD among general population and primary care (AUC = 0.62–0.75) (King et al., 2011; Nigatu and Wang, 2019). Less evidence exists on multivariate models for persistence of MDE and GAD (King et al., 2011; van Loo et al., 2015, 2014). Based in the models, may be defined 30% or greater as "high risk", where over than 70% of MDE-GAD onset cases will occur and 55% of MDE-GAD persistent cases (an estimated of 79 students and 117 students respectively), which could be offered evidence-based interventions (Harrer et al., 2019; Rith-Najarian et al., 2019). However, the sensitivity could be increased, considering the prevalence of the persistence (46.7%), by targeting the top 50% at risk. Also on the other hand, the identification of false positives could be reduced by targeting the top 10% at risk (an estimate of 31 students for onset and 5 students for persistence). Notwithstanding, students at lower risk could benefit from awareness campaigns or universal prevention programs (Conley et al., 2015). Moreover, there is not yet evidence to support these threshold values to be used as intervention rules or the effectiveness of specific cut-off interventions, so a cost-effectiveness research should be conducted. Addressing these issues in future research will be important to enhance prediction tools on mental health in university settings.

4.2. Limitations

Several limitations should be taken into account when interpreting our results. First, a low response rate at baseline might have caused a biased representation of the total population of university students. Also, losses at 12-month follow-up were experienced in our study. These limitations were minimized by applying population-based adjustments through post stratification with a specific end-game strategy that resulted in the use of inverse-probability weights (Brick, 2013). Second, a convenience sample of universities was used; however, the characteristics of the included universities were very similar to all Spanish universities. However, as described in the methods section, the characteristics of the included universities were very similar to all public Spanish universities, and therefore we are confident that the results are generalizable within this context. Third, the assessment of mental disorders was based on self-reports. However, a clinical reappraisal was carried out showing good concordance with blinded clinical diagnoses (Ballester et al., 2019). Fourth, our study does not differentiate between pure MDE and GAD cases or comorbid cases at baseline, which limits the analyses of specific effects in terms of onset and persistence of both conditions at follow-up. This is the first study that analyses the conjunction of MDE-GAD and future research in this sample will be necessary to study these groups more in-depth. Also, the analysis of MDE-GAD aggregated in our study limits the comparability with the incidence and persistence rates previously found in the literature. However, the use of MDE-GAD to develop a single algorithm could be a potential tool in the university setting for the early detection of a large population with symptoms of these common mental disorders and the subsequent implementation of preventive interventions addressing common underlying factors (Titov et al., 2011). Fifth, we divided the sample in two groups (first-onset and persistence) based on whether the students had previous history of MDE-GAD or not. We collapsed all cases with a baseline history of MDE-GAD as "persistent cases", thus including a small proportion of recurrent cases (65 students had 12-month MDE-GAD at baseline). However, our definition of persistence is consistent with previous longitudinal studies among university students (Blasco et al., 2019; Mortier et al., 2017). Finally, the models were not validated with external samples. Leave-one-out method was used for cross-validation. Other methods, such as leave-one-site-out validation, could provide better evidence of the generalizability of the results. Because this method does not guarantee transportability to distinct samples, additional studies in other countries are necessary.

5. Conclusion

The current study provides relevant information on the high proportion of MDE-GAD among Spanish university students, highlighting the need to develop an active strategy for the detection and prevention of common mental disorders. University authorities should consider risk screening at university entrance to provide timely interventions or prevention strategies. The risk algorithms for MDE-GAD compared favorably with previous algorithms for prediction psychiatric outcomes and may be useful as prediction tools in university campuses.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, J.A., upon reasonable request.

CRediT authorship contribution statement

Jordi Alonso had full access to all of the data in this study and takes

responsibility for the integrity of the data, and the accuracy of the data analysis.

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Conflict of interest

In the past 3 years, Dr. Kessler was a consultant for Datastat, Inc., Holmusk, RallyPoint Networks, Inc., and Sage Therapeutics. Dr. Roca received research funds from Lundbeck and Janssen."

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