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ABSTRACT

BACKGROUND: Adolescent onset of depression is associated with long-lasting negative consequences. Identifying adolescents at risk for developing depression would enable the monitoring of risk factors and the development of early intervention strategies. Using machine learning to combine several risk factors from multiple modalities might allow prediction of depression onset at the individual level.

METHODS: A subsample of a multisite longitudinal study in adolescents, the IMAGEN study, was used to predict future (subthreshold) major depressive disorder onset in healthy adolescents. Based on 2-year and 5-year follow-up data, participants were grouped into the following: 1) those developing a diagnosis of major depressive disorder or subthreshold major depressive disorder and 2) healthy control subjects. Baseline measurements of 145 variables from different modalities (clinical, cognitive, environmental, and structural magnetic resonance imaging) at age 14 years were used as input to penalized logistic regression (with different levels of penalization) to predict depression onset in a training dataset (n = 407). The features contributing the highest to the prediction were validated in an independent hold-out sample (three independent IMAGEN sites; n = 137).

RESULTS: The area under the receiver operating characteristic curve for predicting depression onset ranged between 0.70 and 0.72 in the training dataset. Baseline severity of depressive symptoms, female sex, neuroticism, stressful life events, and surface area of the supramarginal gyrus contributed most to the predictive model and predicted onset of depression, with an area under the receiver operating characteristic curve between 0.68 and 0.72 in the independent validation sample.

CONCLUSIONS: This study showed that depression onset in adolescents can be predicted based on a combination multimodal data of clinical characteristics, life events, personality traits, and brain structure variables.

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Major depressive disorder (MDD) usually has its onset in adolescence and young adulthood (1), which can have deleterious consequences for a young person's educational and occupational functioning and personal and social life (2). Moreover, adolescent-onset depression can have adverse economic consequences for society because depression onset in adolescence is associated with poorer social and occupational functioning and recurrent or persistent mental illness in adulthood (3,4). Predicting onset of depression at an early stage is of high clinical relevance because it might guide the deployment of early interventions and preventions, thereby reducing the negative long-term consequences associated with adolescent-onset depression.

Various studies have examined clinical, cognitive, and environmental predictors of depression onset (5,6). However, most of these studies examined cross-sectional associations and hence did not provide information on directionality (7,8). Longitudinal studies are required to study the predictive value of these factors for the onset of depression, but few studies exist that have investigated the longitudinal association between clinical, cognitive, and environmental risk factors and subsequent onset of depression in young people. These

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studies have shown that risk factors such as anxiety symptoms, diagnosis of another psychiatric disorder, stressful life events, and neuroticism precede the onset of depression (9–14). There are few studies that have examined the predictive characteristics of neuroimaging markers, and of those, most were conducted with small sample sizes (15–19). Our recent review showed that findings have been inconsistent, although there is some consistent preliminary evidence for blunted (ventral striatum) response to reward processing as a predictor for later depression (20).

Most of the longitudinal studies investigating clinical, environmental, and neurobiological risk factors for the onset of depression in adolescence have examined these risk factors in isolation. It remains to be investigated whether a combination of risk factors may yield better predictive performance, and which risk factors are most predictive. In addition, most of the studies have used a traditional group comparison approach. However, a statistically significant variable at group level will not necessarily be useful for individual prediction because of low effect size or because of its redundancy with respect to other variables. Conversely, even seemingly insignificant variables may become important when combined with other variables. Some studies, however, have used a multimodal approach to predict depression and have identified important predictors such as sex, neuroticism, rumination, negative affect, low self-esteem, childhood abuse, and familial history of mood disorders, among others (5,21–23). Machine learning–based predictive models are also well suited for combining a large amount of data and different data modalities into a single model. In addition, contrary to traditional multivariate prediction methods, they are optimized for evaluating the model's predictive value for previously unseen individuals ("new" individuals). Thus, they allow evaluation of the predictive model at the level of the individual.

A recent machine learning study in 15-year-old adolescents using psychosocial variables as predictors showed that school failure, social isolation, involvement in physical fights, drug use, running away from home, and maltreatment were predictive of MDD onset within 3 to 4 years after baseline, with the area under the receiver operating characteristic curve (AUROC) between 0.76 and 0.79 (24). Importantly, the predictive model was externally validated in two separate datasets. With regard to neurobiological risk factors, Foland-Ross *et al.* (25) showed that cortical thickness can predict onset of depression within 5 years after a baseline scan with 70% accuracy when 55% of the girls developed depression. Thickness of the right precentral and medial orbitofrontal cortex, left anterior cingulate cortex, and insula were the most predictive features in their predictive model.

These machine learning studies are an important first step toward the development of a predictive model that enables identification of adolescents at risk for depression. A critical next step is to elucidate whether we can predict depression onset in adolescents using a combination of risk factors found in these studies described above (neurobiological, clinical, cognitive, and environmental). Therefore, in this study, we examined the predictive value of multimodal data, using clinical, cognitive, environmental, and neurobiological variables, for the onset of MDD, including subthreshold MDD. We included subthreshold MDD because the DSM diagnostic criteria for adolescent MDD have low diagnostic validity and specificity, with unclear diagnostic boundaries (26,27). In addition, earlier studies have shown that subthreshold MDD is associated with a higher risk for developing future MDD and other adverse effects that are associated with MDD (28), highlighting the clinical importance of considering subthreshold MDD when predicting onset of depression in adolescence. We employed a machine learning method (penalized logistic regression) because this machine learning algorithm is appropriate to identify, in combination with a feature selection approach, the optimal set of measures that prospectively predict onset of depression over 5 years in a subsample of 407 subjects from the IMAGEN study who were aged 14 years at baseline (29). The predictive model was validated in an independent hold-out sample from the IMAGEN study (n = 137), and specificity for depression onset was tested in a sample with risky alcohol use (n = 268). To our knowledge, this is the first machine learning study in adolescents that combines a number of different modalities to predict depression onset.

METHODS AND MATERIALS

Participants

The IMAGEN cohort study is a multisite study, in which the baseline sample consisted of 2223 adolescents (around 14 years old) who were followed up at age 16 (FU1), 19 (FU2), and 22 (FU3; these data are still being collected) (29). The participants were recruited from schools, and their diversity in terms of academic performance, socioeconomic status, and behavioral and emotional functioning was maximized. Exclusion criteria included the following: receiving treatment for schizophrenia or bipolar disorder, IQ $<$ 70, autism diagnosis, nutritional or metabolic diseases, neurological conditions (e.g., brain tumor, epilepsy), and other medical diagnoses. The data were collected from eight sites in Europe (France, Germany, Ireland, and United Kingdom). Ethics was approved by local ethics committees. Participants' parents signed informed consent, and participants gave written assent. Participants older than 18 years gave informed consent at FU2. Detailed information about the study protocol can be found in prior literature (29).

At each time point, participants filled out a psychiatric symptom self-assessment using the Development and Well-Being Assessment (DAWBA) (30). We used the self-report version of the DAWBA instead of the clinical version to be consistent with previous reports. Three groups were created based on the DAWBA self-assessment: 1) healthy control subjects who did not meet criteria for any mental disorder or subthreshold MDD at any of the assessments (n = 430), 2) those who developed subthreshold MDD at follow-up (FU1 and/or FU2; n = 177) or full-threshold MDD at follow-up (n = 71). We excluded participants who met criteria for a psychiatric diagnosis or subthreshold MDD at baseline. Full-threshold MDD and subthreshold MDD were defined based on earlier research in the IMAGEN sample (Supplemental Methods and Figure S1) (31,32). We use the term "depression" when referring to the combined group of subthreshold MDD and full-threshold MDD. We kept a subset of healthy control subjects (n = 134) for a sensitivity analysis with regard to predicting onset of risky alcohol use (described below). Therefore, 296

healthy control subjects were included for the main analysis (Figure S2).

To investigate whether our model's performance was specific to the prediction of onset of depression or was broadly predictive of psychopathology, additional groups (nonoverlapping) were defined based on onset of risky alcohol use at follow-up. A risky alcohol group (n = 134) was defined as having a total score of 8 or above on the Alcohol Use Disorders Identification Test at FU1 and/or FU2, while not meeting criteria for any other psychiatric disorder (including MDD and subthreshold MDD) at baseline and follow-up. The healthy control subjects for this analysis were a randomly selected subsample (to match the number of participants in the risky alcohol use group, n = 134) of those participants who did not meet criteria for psychiatric disorders and had a score lower than 8 on the Alcohol Use Disorders Identification Test at baseline and follow-up.

Predictor Variables

All measures were collected at multiple time points; however, only baseline variables were included as predictors in this study. Two demographic, 7 clinical, 24 cognitive, 9 personality, 22 environmental, 4 substance use, 1 developmental, and 76 structural magnetic resonance imaging (i.e., surface-based morphometry) variables were used as predictors. In total, 145 predictors were included from these different modalities, described in the Supplemental Methods and Table S1.

Statistical Analysis

Splitting the Sample Into Training and Validation Sets. The dataset for the main analysis was divided into a training dataset (n = 407) and independent validation dataset (n = 137) based on recruitment site. Data from three randomly selected recruitment sites (Dublin, Mannheim, and Paris) were kept separately as the independent validation set (between-site split). The other five sites formed the training dataset. A between-site split instead of within-site split was chosen to examine if the model would generalize to completely new sites, which is especially relevant for neuroimaging, because machine learning models can be influenced by scanner effects. The age, sex, and diagnosis distribution did not differ between training and validation set. The group labels that we aimed to predict were 1) healthy control subjects versus 2) those who developed depression at follow-up.

Prediction of Depression Onset at Follow-up in Training Dataset. Penalized (to prevent overfitting) logistic regression was performed on the training dataset including all predictors to predict depression onset at follow-up (Figure 1) (33). We tested model performance across four different values for α (1 to 0.25, with 0.25 decreases) in the penalized logistic regression. When α was 1, the Lasso penalty was applied, and when α decreased, a combination of Lasso and Ridge penalties were applied. Lasso facilitates feature selection as it shrinks coefficients of features to zero, thereby removing these features from the model. Multiple values of α were used to examine which features were selected consistently. The hyperparameter λ value, the weight of the penalty, was determined by selecting the optimal λ associated with the minimum Brier score in an inner cross-validation (CV) loop. Using the R package "glmnet," a sparse model that uses feature selection was created (34). We applied a 10-fold CV, which was repeated 10 times. For the CV, the training data was divided into 10 sets, and within each CV fold, 9 sets formed the training set while the 10th was held out for testing. We ensured that the distribution of scanning sites within each group was the same across all 10 CV folds to correct for possible site effects. In each CV fold, a random subsample of healthy control subjects was selected to match the number of participants in the depression group. All variables were scaled and centered in the fold, and missing values were imputed in the training sets based on data of the five nearest neighbors (35). The parameters of the training set were used to impute the test set separately to prevent data leakage.

To identify features that contributed most to the prediction, the models (at different levels of α) were fitted 10 times in

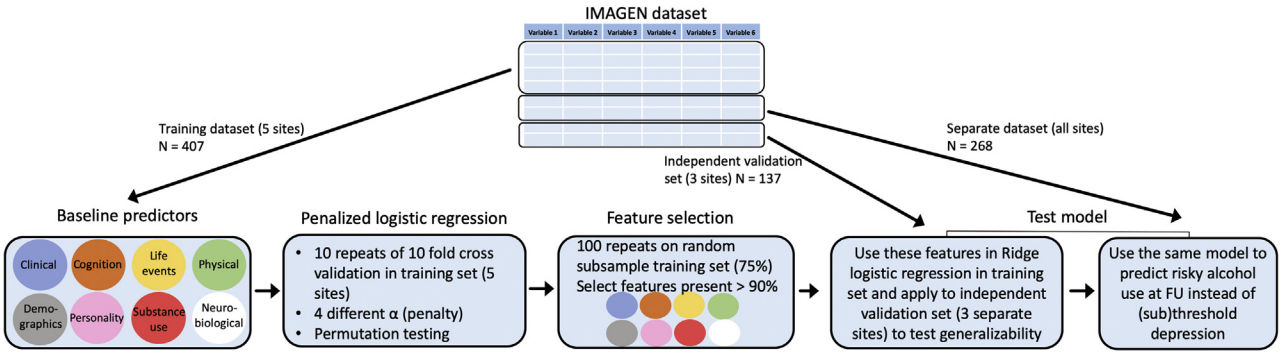

Figure 1. Statistical procedure for penalized logistic regression. Step 1: Baseline predictors from different domains were used to predict subthreshold major depressive disorder or major depressive disorder onset at follow-up (FU). Step 2: Penalized logistic regression with 10-fold cross-validation was applied to the training dataset (five sites) and repeated 10 times with four different levels of α. Permutation testing was used to test the statistical significance of the model. Step 3: Features that were selected in 90% or more in 100 random subsamples of the training data were selected to be tested in the independent validation set. Step 4: The selected features from step 3 were used as input to Ridge logistic regression in the whole training set that was then used to predict depression onset in the validation set (three independent sites) to test the generalizability of the model in the three sites that were left out from the training set. Step 5: The same Ridge model was used to evaluate its predictive value for onset of risky alcohol use in unseen individuals.

random subsamples within the 10 folds (75% of the training dataset in the fold). Features that were selected in 90% or more of the 100 repeats were identified (36).

Replication in Independent Validation Dataset. The features that were identified as most predictive (i.e., selected at least 90% of the time in the random subsamples) were subsequently used to build a Ridge logistic regression (α = 0) model using the whole training dataset. The Ridge regression approach ensured that all features were used in the model. This model was then applied to the independent validation dataset (three recruitment sites as a separate hold-out sample) to evaluate the predictive value of this subset of features for onset of depression in participants from independent sites.

Performance Measures. Performance of the models was examined using the AUROC, sensitivity, specificity, and balanced accuracy (average of sensitivity and specificity). The AUROC represents the probability that a subject from the depression group is ranked lower than a randomly selected healthy control subject across all classification thresholds. An AUROC higher than 0.5 is performing better than chance level. Permutation testing was used to test if the models performed statistically better than chance level prediction (1000 permutations with randomly permuted group labels). A nonparametric significance–level *p* value was estimated as the proportion the randomly permuted groups that had a higher AUROC than the AUROC for the original groups.

Prediction of Future Risky Alcohol Use. To evaluate if the features that were selected in the training set were specific to predicting onset of depression or whether they predict onset of psychopathology more generally, we used the Ridge model with the selected feature to predict risky alcohol use at follow-up.

Prediction of MDD. To assess if we could predict onset of MDD, we did an exploratory penalized logistic regression in a CV predicting MDD in the whole IMAGEN dataset (eight sites) (see Supplement), once excluding subthreshold depression (*n* = 349) and once with those with subthreshold depression included in the healthy control group (*n* = 513).

RESULTS

Demographic and clinical characteristics of the healthy control subjects and participants who developed depression can be found in Table 1 and Table S2.

Prediction of Depression Onset

In the training dataset, depression onset (subthreshold and full-threshold MDD combined) could be predicted with an AUROC ranging between 0.70 and 0.72 across different levels of α (Table 2). This was significantly different from chance level (all *p* values = .001).

Feature Selection

With an α of 1, four features were selected in the feature selection procedure (Table 3) as well as one recruitment site (Dresden). The features selected were depression score at baseline, sex, lifetime frequency of events in the family (sum score of the presence or absence of events such as parents divorced, abused alcohol, fought or argued, remarried, or had money problems), and distress (seeing therapist, thought about suicide, face broke out in pimples, ran away, gained a lot of weight, got poor grades in school) categories. At α of .75 and .50, the same features were selected but with the addition of surface area of the supramarginal gyrus. Being bullied at school, neuroticism, and verbal comprehension were additionally selected when α was .25.

Table 1. Demographics and Clinical Characteristics of the Groups in the Training and Validation Datasets

Characteristics	Training Depression, *n* = 180	Training Control, *n* = 227	Validation Depression, *n* = 68	Validation Control, *n* = 69
Age, Years, Mean (SD)	14.5 (0.54)	14.4 (0.44)	14.4 (0.59)	14.4 (0.61)
Sex, *n* (%)				
Female	121 (67%)	104 (46%)	46 (68%)	29 (42%)
Male	59 (33%)	123 (54%)	22 (32%)	40 (58%)
Site, *n* (%)				
Berlin	34 (19%)	17 (8%)	NA	NA
Dresden	17 (9%)	62 (27%)	NA	NA
Hamburg	35 (19%)	45 (20%)	NA	NA
London	47 (26%)	53 (23%)	NA	NA
Nottingham	47 (26%)	50 (22%)	NA	NA
Dublin	NA	NA	21 (31%)	11 (16%)
Mannheim	NA	NA	20 (29%)	27 (39%)
Paris	NA	NA	27 (40%)	31 (45%)
Depression Score at Baseline (DAWBA)[a], Mean (SD)	1.07 (1.23)	0.59 (0.80)	0.82 (0.88)	0.36 (0.57)

DAWBA, Development and Well-Being Assessment; NA, not applicable.
[a]Score based on number of depressive symptoms present according to youth self-report; DAWBA ranges between 0 and 14.

Table 2. Performance Measures in Penalized Logistic Regression for Four Different α Levels (Ridge Toward Lasso Penalty) to Predict Depression Onset in the Training Set

	Performance Measures				
α Levels	AUROC	SD AUROC	Sensitivity	Specificity	Accuracy
0.25	0.70	0.10	0.66	0.66	0.66
0.5	0.70	0.08	0.66	0.65	0.65
0.75	0.72	0.08	0.67	0.66	0.66
1	0.71	0.07	0.65	0.66	0.66

AUROC, area under the receiver operating characteristic curve; SD, standard deviation across folds.

Generalization to Independent Validation Dataset

The features that were selected in the penalized logistic regression were used to predict depression onset in the independent validation dataset (three independent IMAGEN sites), and an AUROC ranging between 0.68 and 0.72 was achieved (Table 4).

Generalization to Onset of Risky Alcohol Use at Follow-up

Demographic and clinical characteristics of the participants who had risky alcohol use at follow-up can be found in Table S4. The model was able to discriminate between participants with risky alcohol use at follow-up and healthy control subjects with AUROC of 0.62 when using the features selected at different levels of α in the model predicting onset of depression (Table 4).

DISCUSSION

In a large longitudinal sample of young people, we were able to prospectively predict depression onset with an AUROC ranging between 0.70 and 0.72 using penalized logistic regression applied to a large set of clinical, cognitive, developmental, personality, and neurobiological characteristics. Importantly, our prediction model was validated in an independent validation sample consisting of participants of the IMAGEN study assessed at independent sites (AUROC range 0.68–0.72), confirming the validity of the predictive model and its generalizability to independent recruitment sites.

Monitoring risk factors identified in this study could lead to early identification of those at risk for developing depression, which could help the development of risk-factor–specific strategies for prevention of onset of depression. However, the question arises whether an AUROC of 0.72 is high enough for a predictive model to be clinically relevant. Of note, the AUROC range is concordant with validated prognostic studies in psychosis (0.73–0.79), bipolar disorder (0.76), and cardiovascular disease (0.76–0.79) (37–39). The clinical utility of a machine learning model should be assessed by considering the cost-effectiveness of monitoring risk factors for depression identified by the prediction model. Because of the high levels of disability that depression can cause, with consequences for not only the individual but also the broader community, monitoring low-cost risk factors such as clinical characteristics or life events that can predict depression onset in adolescents with an AUROC of 0.70 might be sufficient.

The relative contribution of the predictors should be interpreted with caution because the model performance is based on multivariate data, and features with small weights still contribute to the overall performance of the model. However, using only the subset of features that made substantial contributions to the prediction in the training set to predict depression onset in an independent validation dataset yielded similar AUROCs as in the training set (0.68–0.72). Higher depressive symptoms at baseline, being bullied at school, neuroticism, female sex, and more negative life events were found to be among the largest contributors to depression onset, which is in line with previous research that examined these preexisting risk factors in isolation, using multivariate non–machine learning methods or a machine learning method (5,11,14,24,28). We found that a higher level of depressive symptoms was an important predictor for subsequent onset of depression, even though participants with subthreshold depression at baseline were excluded, and thus the mean level

Table 3. Selected Features in Penalized Logistic Regression for Prediction of Depression Onset at Different α Levels in Training Dataset

	Parameter Threshold			
Predictor Category	α = 0.25	α = 0.5	α = 0.75	α = 1
Clinical	DAWBA depression	DAWBA depression	DAWBA depression	DAWBA depression
Life Events	LEQ family lifetime	LEQ family lifetime	LEQ family lifetime	LEQ family lifetime
	LEQ distress lifetime	LEQ distress lifetime	LEQ distress lifetime	LEQ distress lifetime
	Bullied at school	–	–	–
Personality	Neuroticism	–	–	–
Cognitive	WISC-IV similarities	–	–	–
Biological	Sex	Sex	Sex	Sex
	Supramarginal gyrus surface area	Supramarginal gyrus surface area	Supramarginal gyrus surface area	–

DAWBA, Development and Well-Being Assessment; LEQ, Life Events Questionnaire; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition.

Table 4. Performance Measures of Ridge Logistic Regression With the Features That Were Selected in the Training Dataset Across Different Levels of α to Predict Depression at Follow-up in the Independent Validation Dataset

Number of Features (Selected at Which α in Training Set)	AUROC	Sensitivity	Specificity	Accuracy
Predicting Depression in Independent Validation Dataset				
8 (α = 0.25)	0.72	0.51	0.83	0.67
5 (α = 0.50 and 0.75)	0.68	0.49	0.77	0.63
4 (α = 1)	0.71	0.50	0.81	0.66
Predicting Risky Alcohol Use in Independent Dataset				
8 (α = 0.25)	0.62	0.41	0.74	0.57
5 (α = 0.50 and 0.75)	0.62	0.43	0.79	0.61
4 (α = 1)	0.62	0.42	0.78	0.60

AUROC, area under the receiver operating characteristic curve.

of depressive symptoms at baseline was low (mean: 0.75, on a scale from 0 to 14). This may be due to shared method variance. The selection of negative life events seems to suggest that early-life stress is an important predictor of depression onset and that experiencing stressful life events could be a valid prospective risk factor to monitor. In addition, the use of machine learning methods including internal and external validation in this study strengthens the hypothesis that the predictive characteristics could be extrapolated to new individuals (40). However, the performance of the predictive model will likely have to be improved for it to be clinically useful. Future studies could focus on sex-specific predictors of depression, which might help improve the performance.

With regard to brain measures, we found that lower surface area of the supramarginal gyrus contributed to the model's predictive performance. Previous research has shown that cortical surface area alterations may play a particular role when depressive symptoms are experienced early in adolescence (41,42). Given that cortical surface area, compared with cortical thickness, has a higher genetic heritability (43), is determined earlier in development, and is less strongly affected by later environmental influences (44), cortical surface area reductions may represent a preexisting risk factor for depression, shaped by genetic factors and/or early-life adversity (45). Of note, surface area of the supramarginal gyrus, involved in complex higher-order cognitive processes, was not identified to be associated with MDD in adolescents in a large consortium study (N = 505 adolescents) (41,46,47). Because the supramarginal gyrus was not selected at the highest α, thus not affecting the AUROC, and the supramarginal gyrus has been identified as an important brain region in adolescent depression in previous literature, the predictive role of the surface area of the supramarginal gyrus is most likely marginal. This is in contrast to a previous study by Foland-Ross *et al.* (25), who found a similar AUROC including only cortical thickness measures to predict depression onset in a relatively small sample (N = 33) of young adolescent girls. An important difference between the study by Foland-Ross *et al.* (25) and this study is that we also included participants with subthreshold depression and included multimodal predictors with other modalities that might be more informative than cortical thickness. Given that no other surface area regions, cortical thickness, or subcortical volumes measures were identified in our feature selection approach, and because it is costly to acquire structural neuroimaging measures, structural imaging might not be a useful predictor for depression onset in young people. However, this does not implicate that structural brain changes in young people with depression cannot provide information about the underlying mechanisms of depression.

The model was not specific to predicting depression onset at follow-up but could successfully predict risky alcohol use in an independent sample, with a slightly lower AUROC (0.62). This may not be surprising, given the high comorbidity between alcohol use disorder and MDD, with an increase in comorbidity in young adulthood (46). In addition, a risky lifestyle in adolescence, including risky alcohol use, is predictive of depressive symptoms (47). Finally, risky alcohol use occurred in the depression group, which might have contributed to the lack of specificity of the predictors. Beyond this, comorbidity of mental disorders is common; most people who experience mental illness will be diagnosed with more than one psychiatric disorder during their lifetime, and an early age of onset of the first psychiatric disorder has been associated with having more comorbid psychiatric disorders during the lifetime (48). We anticipate that our model could be similarly predictive for the onset of mental disorders other than depression or alcohol abuse, in line with previous longitudinal studies showing that other psychiatric disorders are associated with similar risk factors as the risk factors identified in this study such as bullying, neuroticism, depressive symptoms, and stressful life events (28,49–51). However, because the prevalence of other disorders such as bipolar disorder and psychosis was limited in the IMAGEN sample, the hypothesis about the nonspecificity for depression of the model requires further investigation in other samples.

When the analysis was restricted to patients with MDD and those with subthreshold depression were excluded, the AUROC was higher than in the main analysis. Unfortunately, the sample size of the MDD group was too small to allow validation in an independent dataset. This increase in AUROC when excluding subthreshold depression could be because adolescents who will develop MDD are more differentiated from healthy adolescents than adolescents developing subthreshold depressive symptoms. When those who developed subthreshold depression were treated as healthy control subjects, the AUROC decreased. These findings further support the postulation that depression based on a cutoff for a diagnosis of MDD is arbitrary because young people with a full-threshold MDD diagnosis cannot reliably be distinguished from those with subthreshold depression as indicated by our findings.

This study has major strengths, including its large sample size, longitudinal design, and integration of predictors across multiple modalities. However, an important limitation is that the diagnostic information was based on the self-report DAWBA, a measure that only captures a period of 4 weeks before each follow-up assessment. Because there was no information available on possible depressive episodes in the periods between the follow-ups, we may have missed depression in the healthy control group, which might have affected the classification performance of our model (though likely in the direction of weakening it). It could also have led to underdiagnosing depression at baseline, potentially leading to a less healthy group at baseline. In addition, the DAWBA is clinically reliable (30), although because of the use of a self-report measure, symptoms might have been underreported (52).

There are still challenges with translating these types of models into clinical practice, including that the rate of depression is high in the selected sample. Participants with a psychiatric diagnosis were removed from the healthy control group, which limits the clinical utility of the model as people in the general population might show nondepression psychiatric diagnoses. Therefore, future studies should test if a predictive model works in the general population that includes people who have already experienced episodes of mental ill health. In addition, the depression group might include young people with comorbid diagnoses such as anxiety disorders with similar risk factors, which could increase the predictive power. However, in a sensitivity analysis, excluding those who developed comorbid anxiety disorder at follow-up showed that the predictive performance measures were similar.

In conclusion, this study showed that depression onset in adolescents can be predicted based on multimodal data, including clinical, cognitive, life events, personality traits, and neurobiological variables. The variables contributing most to the predictive model were found to be depressive symptoms at baseline, neuroticism, cognition, supramarginal gyrus surface area, and stressful life events. Because the model was also predictive of onset of risky alcohol use, these risk factors may likely be predictive more generally of onset psychopathology during adolescence.

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