

Supplemental Material

Supplementary Methods

The three groups were defined using the DAWBA self-report. An additional criteria for healthy controls was a score lower than 4 on the Adolescent Depression Rating Scale (ADRS) at both follow-ups. To be diagnosed with MDD, participants had to endorse a total of at least 5 depressive symptoms on the DAWBA at one of the follow-up assessments (e.g. 5 of more of the following symptoms: sad mood, loss of interest, fatigue, changed appetite, weight loss/gain, insomnia, hypersomnia, psychomotor agitation, feelings of worthlessness or guilt, concentration problems, thoughts of death), with at least 1 of these symptoms including one of the two core depression criteria (sad mood and loss of interest) over a period of at least 2 weeks (1). In addition, they also had to score 50% or higher on the DAWBA computer prediction of depression (<http://www.dawba.info>). Subthreshold MDD was defined as experiencing at least 1 of the two core symptoms and at least 2 other depressive symptoms on the DAWBA at one of the follow-up assessments, without any restrictions on the duration or functional impact of these symptoms. Participants with comorbid bipolar disorder or psychosis at any timepoint were excluded from the MDD groups, however comorbid anxiety disorders were no exclusion criteria. There were no differences between age and sex distributions of participants in the included and excluded samples, however depressive symptoms were higher in the excluded participants since those with depression at baseline were removed from the sample

Demographic predictors

Sex was included as predictor variable. Age was not included since all participants were within the same age range (~14 years old at baseline).

Clinical predictors

Scores on five subscales of the strengths and difficulties questionnaire (SDQ) were included to measure psychopathology (2). A binary predictor was created indicating if the participants had a first degree relative with a history of psychiatric disorder (schizophrenia, bipolar disorder, depression, anxiety disorder, obsessive compulsive disorder or substance use disorder) or suicide attempt, based on the genetic screening and family history of psychiatric disorders interview filled out by participants'

parent or caregiver. A baseline depression score, ranging from 0 to 14, was created based on self-reported depressive symptoms assessed using the Development and Well-Being Assessment (DAWBA).

Cognitive predictors

Scores on eight subscales of the Wechsler Intelligence Scale for Children, fourth edition, (WISC-IV) were included, capturing verbal comprehension, visual spatial processing, inductive and quantitative reasoning and working memory (3). From the Cambridge Neuropsychological Test Automated Battery (CANTAB), the pattern recognition memory task, spatial working memory task and rapid visual information processing task were included (4). In addition, 12 predictors from the emotional dot probe task were used. In the emotional dot probe task, the participants are simultaneously shown two (emotional) faces, next a probe appears on the location of one of the faces. The participant has to indicate on which side the probe was displayed. The following 12 variables were used as predictors; reaction time and number of correct responses for the six different task conditions (angry, fearful and happy versus neutral; congruent and incongruent) (5).

Personality trait predictors

Scores on five subscales of the NEO Five-Factor Inventory (NEO-FFI) were included (6). Four subscales from the substance use risk profile scale (SURPS) were included (7).

Psychosocial predictors

To measure life events, the subscales for lifetime frequency and mean valence of life events in eight categories from the life-events questionnaire were included (8). In addition, six items of the Olweus Bully/Victim questionnaire were included that focused on situations where the participant were the victim (9).

Substance use predictors

Variables encapsulating substance use were based on four self-report questionnaires, including alcohol use in the past year based on the first question in the Alcohol Use Disorder Identification Test (AUDIT) (10), lifetime frequency of cannabis use and lifetime frequency smoking cigarettes on a scale

of 0 (never) to 6 (>40 times) (European School Survey Project on Alcohol and Drugs; ESPAD) (11) and total score on the Fagerström test for nicotine dependence (12).

Developmental predictors

The total score on the pubertal development scale was included to assess the stage of physical pubertal development at baseline (13).

Neuroimaging predictors

T1 weighted images were acquired on 3T scanners (Siemens, Munich, Germany; Philips, Best, The Netherlands; General Electrics, Chalfont St Giles, UK; Bruker, Ettlingen, Germany). Variance between sites was minimized and tested by scanning The American College of Radiology phantom and healthy volunteers at each site (14). For the current study we focused on the magnetization prepared gradient echo sequence (MPRAGE), which was based on the ADNI protocol (<http://adni.loni.usc.edu/methods/mri-tool/mri-analysis/>). The acquisition parameters were: repetition time (TR): 2300 ms, echo time (TE): 2.8 ms, flip angle: 8-9°, voxel size: 1.1x1.1x1.1 mm, pixel matrix: 256x256x170 mm.

FreeSurfer (version 5.3) was used to extract measures of cortical and subcortical brain structure (15), using the Desikan-Killiany atlas for cortical parcellations. The ENIGMA protocols were used to check the quality of the cortical parcellations and subcortical segmentations (<http://enigma.ini.usc.edu/protocols/imaging-protocols>) (16, 17). Cortical surface area (34 regions), cortical thickness (34 regions) and subcortical volumes (8 regions) was calculated per region and averaged across left and right hemisphere. In total 78 structural MRI measures were included as predictors. To correct for the effect of head size, intercranial volume (ICV) was regressed out of the cortical surface area and subcortical volume variables. This was not done for cortical thickness, because cortical thickness does not scale with head size (18). Participants missing more than 10% of neuroimaging data were excluded.

Prediction of depression excluding comorbid anxiety

To assess if depression could be predicted when subjects who developed comorbid anxiety were excluded, the analysis was repeated in a smaller sample (N = 393 in training set). However, excluding participants who developed a comorbid anxiety disorder at follow-up (in addition to depression) results in a non-representative sample, therefore we decided to keep these participants in the main analysis.

Supplementary Results

Prediction of MDD

When those with subthreshold depression were excluded, MDD onset could be predicted with an AUROC ranging between 0.86 and 0.88 across different levels of α (Supplementary Table S1). When subjects who developed subthreshold depression were included as healthy controls, the AUROC ranged between 0.54 and 0.59 (Supplementary Table S2).

Prediction of depression excluding comorbid anxiety

The performance measures of prediction of depression onset when those who developed comorbid anxiety were excluded were similar to the performance measures of the main analysis (AUROC: 0.69-0.70) (Supplementary Table S3).

Supplementary Figures and Tables

S1 Supplementary Table S1. Performance measures in penalized logistic regression for four different α (Ridge towards Lasso penalty) to predict MDD onset.

| α | AUROC | SD AUROC | Sensitivity | Specificity | Accuracy |
|----------|-------|----------|-------------|-------------|----------|
| 0.25 | 0.86 | 0.16 | 0.92 | 0.49 | 0.70 |
| 0.5 | 0.88 | 0.15 | 0.94 | 0.46 | 0.70 |
| 0.75 | 0.88 | 0.16 | 0.96 | 0.45 | 0.70 |
| 1 | 0.88 | 0.19 | 0.94 | 0.47 | 0.71 |

SD: standard deviation across folds

S2 Supplementary Table S2. Performance measures in penalized logistic regression for four different α (Ridge towards Lasso penalty) to predict MDD onset with subthreshold depression included as healthy controls.

| α | AUROC | SD AUROC | Sensitivity | Specificity | Accuracy |
|----------|-------|----------|-------------|-------------|----------|
| 0.25 | 0.59 | 0.10 | 0.70 | 0.43 | 0.57 |
| 0.5 | 0.55 | 0.09 | 0.74 | 0.34 | 0.54 |
| 0.75 | 0.56 | 0.10 | 0.75 | 0.32 | 0.54 |
| 1 | 0.54 | 0.09 | 0.76 | 0.29 | 0.53 |

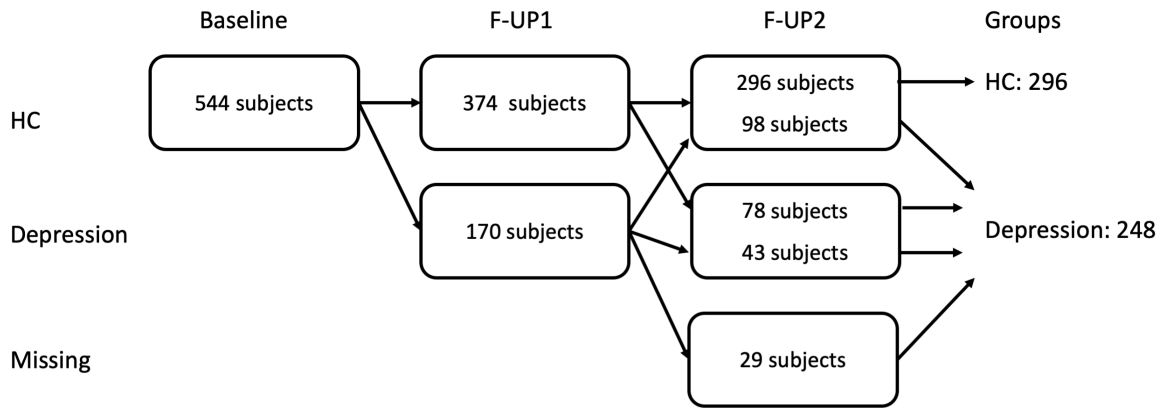
SD: standard deviation across folds

S3 Supplementary Table S3. Performance measures in penalized logistic regression for four different α (Ridge towards Lasso penalty) to predict depression (comorbid anxiety was excluded).

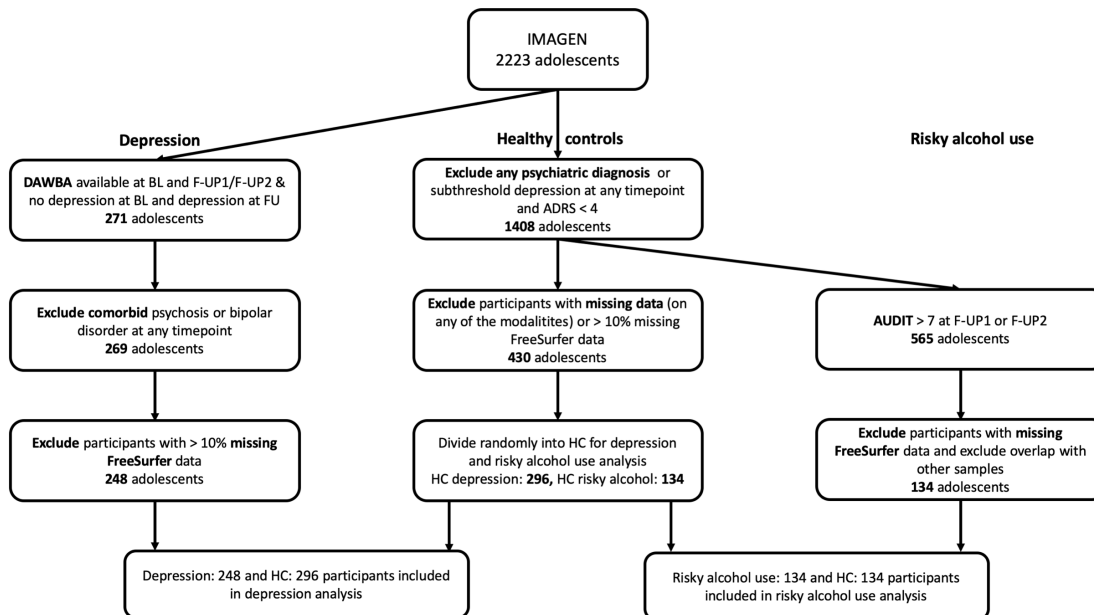
| α | AUROC | SD AUROC | Sensitivity | Specificity | Accuracy |
|----------|-------|----------|-------------|-------------|----------|
| 0.25 | 0.70 | 0.08 | 0.66 | 0.64 | 0.65 |

| | | | | | |
|------|------|------|------|------|------|
| 0.5 | 0.69 | 0.09 | 0.63 | 0.65 | 0.64 |
| 0.75 | 0.69 | 0.09 | 0.63 | 0.66 | 0.64 |
| 1 | 0.70 | 0.10 | 0.66 | 0.66 | 0.66 |

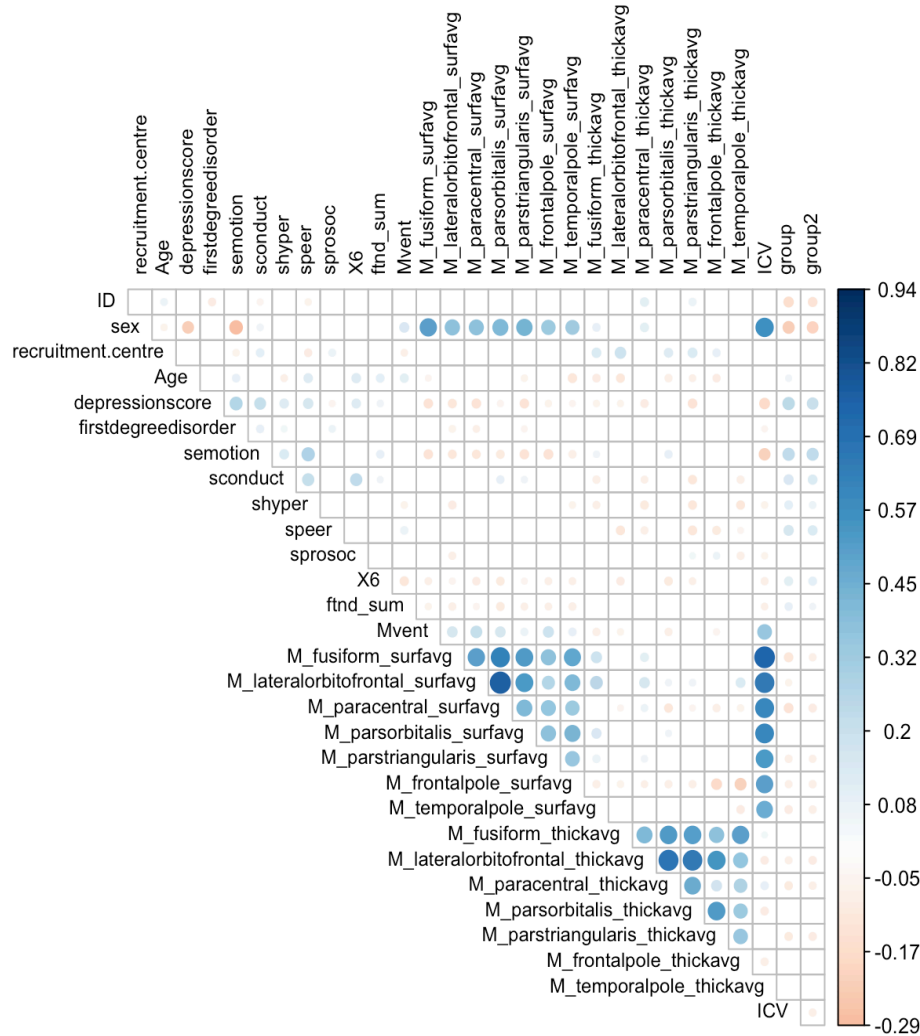
SD: standard deviation across folds



Supplementary Figure 1. Flowchart of participants across groups



Supplementary Figure 2. Flowchart of participants in study



Supplementary Figure 3. Strongest correlations between the features used to predict depression onset.

S2 Supplemental Table S2. Features used to predict depression onset

| Category | Feature | Explanation | Based on (measure) |
|----------------------|--|-----------------------|--------------------|
| Demographical | Sex | Male or Female | |
| | Recruitment center | 5 recruitment sites | |
| Clinical | Depression score | Total score | DAWBA |
| | Emotional symptoms | Subscale | SDQ |
| | Conduct problems | Subscale | SDQ |
| | Hyperactivity | Subscale | SDQ |
| | Peer problems | Subscale | SDQ |
| | Prosocial behavior | Subscale | SDQ |
| | First degree relative with history of psychiatric disorder | | GEN |
| Cognition | Block design | Spatial visualization | WISC IV |
| | Digit span backward | Memory span | WISC IV |
| | Digit span forward | Memory span | WISC IV |
| | Digit span longest backward | Memory span | WISC IV |
| | Digit span longest forward | Memory span | WISC IV |
| | Matrix reasoning | Perceptual reasoning | WISC IV |

| | | | | |
|----------------------|---|---|---------|-----|
| | Similarities | Verbal comprehension | WISC IV | |
| | Vocabulary | Verbal comprehension | WISC IV | |
| | Pattern recognition memory | Visual recognition memory, % correct | CANTAB | |
| | Rapid visual information processing | Sustained attention | CANTAB | |
| | Spatial working memory errors | Visual memory and manipulation | CANTAB | |
| | Spatial working memory strategy | Visual memory and manipulation | CANTAB | |
| | Angry – neutral congruent | Reaction time | EDPT | |
| | Angry – neutral incongruent | Reaction time | EDPT | |
| | Fear – neutral congruent | Reaction time | EDPT | |
| | Fear – neutral incongruent | Reaction time | EDPT | |
| | Happy – neutral congruent | Reaction time | EDPT | |
| | Happy – neutral incongruent | Reaction time | EDPT | |
| | Angry – neutral congruent | Number correct responses | EDPT | |
| | Angry – neutral incongruent | Number correct responses | EDPT | |
| | Fear – neutral congruent | Number correct responses | EDPT | |
| | Fear – neutral incongruent | Number correct responses | EDPT | |
| | Happy – neutral congruent | Number correct responses | EDPT | |
| | Happy – neutral incongruent | Number correct responses | EDPT | |
| Environmental | Bullied at school | | Bully | |
| | Called mean names/made fun of | | Bully | |
| | Left out or ignored | | Bully | |
| | Physically bullied | | Bully | |
| | Bullied by teacher | | Bully | |
| | Bullied by family member | | Bully | |
| | Family lifetime | Subscale total score of lifetime occurrence of (yes(1)/no(0) for each event): Parents: divorce, remarried, alcohol abuse, money problems, argues/fought | | LEQ |
| | Family valence | How did that make you feel? | | LEQ |
| | Accident/illness lifetime | Subscale total score of lifetime occurrence of (yes(1)/no(0) for each event):: Family accident/illness, given medication, death in family, serious accident/illness | | LEQ |
| | Accident/illness valence | | | LEQ |
| Sexuality lifetime | Subscale total score of lifetime occurrence of (yes(1)/no(0) for each event):: Fell in love, got/made pregnant, got/gave STD, started going out with girl/boyfriend, broke up with boy/girlfriend, had a gay experience, lost virginity | | LEQ | |

| | | | |
|----------------------|----------------------------|---|---------|
| | Sexuality valence | | LEQ |
| | Autonomy lifetime | Subscale total score of lifetime occurrence of (yes(1)/no(0) for each event):: Found new friends, began time-consuming hobby, decided about college/university, joined club or group, got own TV/computer, went on holiday without parents, started driving a motor vehicle, started making own money | LEQ |
| | Autonomy valence | | LEQ |
| | Deviance lifetime | Subscale total score of lifetime occurrence of (yes(1)/no(0) for each event):: Got in trouble with the law, stole something valuable, got in trouble at school | LEQ |
| | Deviance valence | | LEQ |
| | Relocation lifetime | Subscale total score frequency lifetime: Parents changed jobs, changed schools, family moved | LEQ |
| | Relocation valence | | LEQ |
| | Distress lifetime | Subscale total score of lifetime occurrence of (yes(1)/no(0) for each event):: Face broke out with pimples, started seeing therapist, thought about suicide, ran away from home, got poor grades in school, gained a lot of weight | LEQ |
| | Distress valence | | LEQ |
| | Other lifetime | Subscale total score of lifetime occurrence of (yes(1)/no(0) for each event):: Brother/sister moved out, met a teacher I liked a lot, found religion | LEQ |
| | Other valence | | LEQ |
| Developmental | Pubertal development scale | Total score | PDS |
| Personality | Neuroticism | Subscale total score | NEO-FFI |
| | Extraversion | Subscale total score | NEO-FFI |
| | Openness | Subscale total score | NEO-FFI |
| | Agreeableness | Subscale total score | NEO-FFI |
| | Conscientiousness | Subscale total score | NEO-FFI |
| | Anxiety sensitivity | Subscale total score | SURPS |

| | | | |
|-----------------------|--|--|------------|
| | Negative thinking | Subscale total score | SURPS |
| | Impulsivity | Subscale total score | SURPS |
| | Sensation seeking | Subscale total score | SURPS |
| Substance use | Smoking | Number of occasions smoking (lifetime) | ESPAD |
| | Smoking score | Total score | FTND |
| | Cannabis use | Number of occasions marijuana (lifetime) | ESPAD |
| | Alcohol use | Frequency alcohol use – question 1 | AUDIT |
| Structural MRI | Hippocampus | Volume | FreeSurfer |
| Subcortical | Amygdala | Volume | FreeSurfer |
| | Thalamus | Volume | FreeSurfer |
| | Nucleus accumbens | Volume | FreeSurfer |
| | Pallidum | Volume | FreeSurfer |
| | Putamen | Volume | FreeSurfer |
| | Caudate | Volume | FreeSurfer |
| | Ventricles | Volume | FreeSurfer |
| Cortical | Bank of superior sulcus of temporal lobe | Surface area & thickness | FreeSurfer |
| | Caudal anterior cingulate cortex | Surface area & thickness | FreeSurfer |
| | Caudal middle frontal cortex | Surface area & thickness | FreeSurfer |
| | Cuneus | Surface area & thickness | FreeSurfer |
| | Entorhinal cortex | Surface area & thickness | FreeSurfer |
| | Fusiform gyrus | Surface area & thickness | FreeSurfer |
| | Inferior parietal cortex | Surface area & thickness | FreeSurfer |
| | Inferior temporal cortex | Surface area & thickness | FreeSurfer |
| | Isthmuscingulate cortex | Surface area & thickness | FreeSurfer |
| | Lateral occipital cortex | Surface area & thickness | FreeSurfer |
| | Lateral orbitofrontal cortex | Surface area & thickness | FreeSurfer |
| | Lingual cortex | Surface area & thickness | FreeSurfer |
| | Medial orbitofrontal cortex | Surface area & thickness | FreeSurfer |
| | Middle temporal cortex | Surface area & thickness | FreeSurfer |
| | Parahippocampal cortex | Surface area & thickness | FreeSurfer |
| | Paracentral cortex | Surface area & thickness | FreeSurfer |
| | Pars opercularis | Surface area & thickness | FreeSurfer |
| | Pars triangularis | Surface area & thickness | FreeSurfer |
| | Pars orbitalis | Surface area & thickness | FreeSurfer |
| | Pericalcarine | Surface area & thickness | FreeSurfer |
| | Postcentral gyrus | Surface area & thickness | FreeSurfer |
| | Precentral gyrus | Surface area & thickness | FreeSurfer |
| | Posterior cingulate cortex | Surface area & thickness | FreeSurfer |
| | Precuneus | Surface area & thickness | FreeSurfer |
| | Rostral anterior cingulate cortex | Surface area & thickness | FreeSurfer |
| | Rostral middle frontal cortex | Surface area & thickness | FreeSurfer |
| | Superior frontal gyrus | Surface area & thickness | FreeSurfer |
| | Superior parietal lobule | Surface area & thickness | FreeSurfer |
| | Superior temporal cortex | Surface area & thickness | FreeSurfer |
| | Supramarginal | Surface area & thickness | FreeSurfer |
| | Frontal pole | Surface area & thickness | FreeSurfer |
| | Temporal pole | Surface area & thickness | FreeSurfer |
| | Transversetemporal | Surface area & thickness | FreeSurfer |

AUDIT: alcohol use disorders identification test, CANTAB: Cambridge neuropsychological test automated battery, DAWBA: development and well-being assessment, EDPT: emotional dot probe task, ESPAD: European school survey project on alcohol and other drugs, FTND: Fagerstrom test for nicotine dependence, GEN: genetic screening and family history of psychiatric disorders interview, LEQ: life events questionnaire, NEO-FFI: neuroticism-extraversion-openness five-factor inventory, PDS: pubertal development scale, SDQ: strengths and difficulties questionnaire, SURPS: substance use risk profile scale, WISC-IV: Wechsler intelligence scale for children – fourth edition.

S3 Supplemental Table S3. Demographic, clinical, cognitive, personality, environmental, substance use, developmental and neurobiological variables in three groups (healthy control, MDD, subthreshold MDD)

| | Training depression (n=180) | Training control (n=227) | Test depression (n=68) | Test control (n=69) |
|---------------------------------------|-----------------------------|--------------------------|------------------------|---------------------|
| Age | | | | |
| Mean (SD) | 14.5 (0.54) | 14.4 (0.44) | 14.4 (0.59) | 14.4 (0.61) |
| Sex | | | | |
| Female | 121 (67.2%) | 104 (45.8%) | 46 (67.6%) | 29 (42.0%) |
| Male | 59 (32.8%) | 123 (54.2%) | 22 (32.4%) | 40 (58.0%) |
| Site | | | | |
| Berlin | 34 (18.9%) | 17 (7.5%) | NA | NA |
| Dresden | 17 (9.4%) | 62 (27.3%) | NA | NA |
| Hamburg | 35 (19.4%) | 45 (19.8%) | NA | NA |
| London | 47 (26.1%) | 53 (23.3%) | NA | NA |
| Nottingham | 47 (26.1%) | 50 (22.0%) | NA | NA |
| Dublin | NA | NA | 21 (30.9%) | 11 (15.9%) |
| Mannheim | NA | NA | 20 (29.4%) | 27 (39.1%) |
| Paris | NA | NA | 27 (39.7%) | 31 (44.9%) |
| Depression score at BL (DAWBA) | | | | |
| Mean (SD) | 1.07 (1.23) | 0.59 (0.80) | 0.82 (0.88) | 0.36 (0.57) |
| SDQ | | | | |
| Emotion (mean (SD)) | 3.02 (2.01) | 2.32 (1.77) | 3.22 (2.23) | 1.59 (1.65) |
| Conduct problems (mean (SD)) | 2.20 (1.57) | 1.76 (1.32) | 2.18 (1.44) | 1.81 (1.39) |
| Hyperactivity (mean (SD)) | 4.31 (2.12) | 3.88 (2.03) | 4.24 (2.12) | 3.16 (2.30) |
| Peer (mean (SD)) | 2.07 (1.63) | 1.76 (1.62) | 1.93 (1.66) | 1.03 (1.11) |
| Prosocial (mean (SD)) | 7.87 (1.73) | 7.71 (1.59) | 7.99 (1.46) | 7.86 (1.56) |
| Familial psychiatric history | | | | |
| No | 156 (87%) | 197 (87%) | 59 (87%) | 62 (90%) |
| Yes | 24 (13%) | 30 (13%) | 9 (13%) | 7 (10%) |
| WISC-IV | | | | |

| | Training depression (n=180) | Training control (n=227) | Test depression (n=68) | Test control (n=69) |
|---|--|---|---------------------------------------|------------------------------------|
| Block design (mean (SD)) | 50.7 (9.67) | 52.6 (7.87) | 49.8 (9.24) | 54.2 (8.22) |
| Digit span backward (mean (SD)) | 8.78 (1.93) | 9.01 (2.20) | 8.18 (1.93) | 8.70 (1.97) |
| Digit span forward (mean (SD)) | 9.69 (1.92) | 9.59 (2.15) | 9.66 (1.99) | 9.94 (2.06) |
| Digit span longest back (mean (SD)) | 5.04 (1.27) | 5.18 (1.36) | 4.72 (1.03) | 4.97 (1.26) |
| Digit span longest forward (mean (SD)) | 6.35 (1.28) | 6.42 (1.27) | 6.28 (1.13) | 6.67 (1.21) |
| Matrix Reasoning (mean (SD)) | 26.6 (3.74) | 27.5 (3.35) | 26.3 (3.94) | 27.1 (4.21) |
| Similarities (mean (SD)) | 30.2 (5.84) | 31.5 (4.90) | 30.5 (4.45) | 31.6 (5.06) |
| Vocabulary (mean (SD)) | 51.0 (8.41) | 52.0 (8.07) | 47.4 (6.56) | 50.4 (6.70) |
| Executive functioning | | | | |
| Pattern recognition memory (mean (SD)) | 95.3 (6.25) | 95.4 (7.36) | 95.5 (7.04) | 94.4 (9.44) |
| Rapid visual information processing (mean (SD)) | 0.88 (0.05) | 0.89 (0.05) | 0.87 (0.05) | 0.88 (0.05) |
| Spatial working memory errors (mean (SD)) | 18.8 (13.2) | 17.8 (13.3) | 21.9 (15.0) | 17.6 (13.3) |
| Spatial working memory strategy (mean (SD)) | 31.0 (5.46) | 30.4 (5.76) | 31.8 (5.33) | 31.1 (4.88) |
| Emotional Dot Probe Task | | | | |
| Reaction time congruent angry neutral (mean (SD)) | 469 (218) | 458 (116) | 458 (79.4) | 451 (97.1) |
| Reaction time incongruent angry neutral (mean (SD)) | 450 (87.6) | 469 (149) | 475 (116) | 447 (77.9) |
| Reaction time congruent fear neutral (mean (SD)) | 455 (87.8) | 466 (126) | 482 (148) | 457 (111) |
| Reaction time incongruent fear neutral (mean (SD)) | 452 (76.4) | 470 (192) | 480 (168) | 448 (85.0) |
| Reaction time congruent happy neutral (mean (SD)) | 454 (94.7) | 466 (127) | 463 (93.7) | 451 (95.9) |
| Reaction time incongruent happy neutral (mean (SD)) | 456 (89.9) | 469 (170) | 483 (182) | 455 (93.9) |
| Score congruent angry neutral (mean (SD)) | 19.5 (1.55) | 19.5 (1.11) | 19.7 (0.58) | 19.6 (0.73) |
| Score incongruent angry neutral (mean (SD)) | 19.4 (1.35) | 19.5 (1.30) | 19.4 (0.74) | 19.7 (0.70) |
| Score congruent fear neutral (mean (SD)) | 19.4 (1.54) | 19.5 (1.22) | 19.5 (0.80) | 19.7 (0.68) |
| Score incongruent fear neutral (mean (SD)) | 19.5 (1.20) | 19.5 (1.00) | 19.7 (0.59) | 19.6 (0.69) |
| Score congruent happy neutral (mean (SD)) | 19.4 (1.54) | 19.5 (1.09) | 19.6 (0.61) | 19.7 (0.61) |

| | Training depression (n=180) | Training control (n=227) | Test depression (n=68) | Test control (n=69) |
|--|-----------------------------------|--------------------------------|------------------------------|---------------------------|
| Score incongruent happy neutral (mean (SD)) | 19.4 (1.73) | 19.6 (1.10) | 19.7 (0.62) | 19.6 (0.65) |
| I was bullied in school | | | | |
| None | 95 (52.8%) | 155 (68.3%) | 33 (48.5%) | 49 (71.0%) |
| Only once or twice | 59 (32.8%) | 46 (20.3%) | 26 (38.2%) | 16 (23.2%) |
| 2 or 3 times a month | 11 (6.1%) | 12 (5.3%) | 3 (4.4%) | 1 (1.4%) |
| About once a week | 9 (5.0%) | 7 (3.1%) | 3 (4.4%) | 2 (2.9%) |
| Several times a week | 6 (3.3%) | 7 (3.1%) | 2 (2.9%) | 1 (1.4%) |
| Missing | 0 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| I was called mean names by a peer | | | | |
| None | 107 (59.4%) | 162 (71.4%) | 37 (54.4%) | 48 (69.6%) |
| Only once or twice | 50 (27.8%) | 43 (18.9%) | 19 (27.9%) | 18 (26.1%) |
| 2 or 3 times a month | 5 (2.8%) | 11 (4.8%) | 7 (10.3%) | 0 (0%) |
| About once a week | 7 (3.9%) | 6 (2.6%) | 2 (2.9%) | 3 (4.3%) |
| Several times a week | 11 (6.1%) | 5 (2.2%) | 2 (2.9%) | 0 (0%) |
| Missing | 0 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| A peer left me out of things | | | | |
| None | 116 (64.4%) | 170 (74.9%) | 50 (73.5%) | 63 (91.3%) |
| Only once or twice | 50 (27.8%) | 44 (19.4%) | 14 (20.6%) | 6 (8.7%) |
| 2 or 3 times a month | 3 (1.7%) | 7 (3.1%) | 1 (1.5%) | 0 (0%) |
| About once a week | 4 (2.2%) | 3 (1.3%) | 2 (2.9%) | 0 (0%) |
| Several times a week | 7 (3.9%) | 3 (1.3%) | 0 (0%) | 0 (0%) |
| Missing | 0 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| I was hit by a peer | | | | |
| None | 152 (84.4%) | 194 (85.5%) | 55 (80.9%) | 64 (92.8%) |
| Only once or twice | 24 (13.3%) | 27 (11.9%) | 7 (10.3%) | 5 (7.2%) |
| 2 or 3 times a month | 1 (0.6%) | 2 (0.9%) | 2 (2.9%) | 0 (0%) |
| About once a week | 2 (1.1%) | 2 (0.9%) | 2 (2.9%) | 0 (0%) |
| Several times a week | 1 (0.6%) | 2 (0.9%) | 1 (1.5%) | 0 (0%) |
| Missing | 0 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| I have been bullied by a teacher | | | | |
| None | 140 (77.8%) | 201 (88.5%) | 59 (86.8%) | 65 (94.2%) |
| Only once or twice | 34 (18.9%) | 19 (8.4%) | 7 (10.3%) | 4 (5.8%) |

| | Training depression (n=180) | Training control (n=227) | Test depression (n=68) | Test control (n=69) |
|---|--|---|---------------------------------------|------------------------------------|
| 2 or 3 times a month | 2 (1.1%) | 5 (2.2%) | 0 (0%) | 0 (0%) |
| About once a week | 2 (1.1%) | 1 (0.4%) | 0 (0%) | 0 (0%) |
| Several times a week | 2 (1.1%) | 1 (0.4%) | 1 (1.5%) | 0 (0%) |
| Missing | 0 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| I have been bullied by a family member | | | | |
| None | 145 (80.6%) | 202 (89.0%) | 57 (83.8%) | 65 (94.2%) |
| Only once or twice | 25 (13.9%) | 16 (7.0%) | 7 (10.3%) | 1 (1.4%) |
| 2 or 3 times a month | 5 (2.8%) | 4 (1.8%) | 1 (1.5%) | 2 (2.9%) |
| About once a week | 2 (1.1%) | 2 (0.9%) | 0 (0%) | 1 (1.4%) |
| Several times a week | 3 (1.7%) | 3 (1.3%) | 2 (2.9%) | 0 (0%) |
| Missing | 0 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| Life events | | | | |
| Family lifetime (mean (SD)) | 1.69 (1.17) | 1.11 (1.03) | 1.12 (1.18) | 0.65 (0.78) |
| Family valence (mean (SD)) | -1.15 (0.44) | -1.14 (0.41) | -1.10 (0.46) | -1.07 (0.34) |
| Accident lifetime (mean (SD)) | 2.24 (1.03) | 2.09 (0.97) | 1.84 (1.11) | 1.77 (1.10) |
| Accident valence (mean (SD)) | -1.28 (0.32) | -1.21 (0.32) | -1.22 (0.29) | -1.19 (0.29) |
| Sexuality lifetime (mean (SD)) | 2.17 (1.20) | 1.76 (1.26) | 1.93 (1.30) | 1.99 (1.16) |
| Sexuality valence (mean (SD)) | -0.03 (0.39) | -0.02 (0.37) | -0.13 (0.38) | 0.02 (0.34) |
| Autonomy lifetime (mean (SD)) | 4.31 (1.33) | 4.37 (1.35) | 4.22 (1.35) | 4.16 (1.35) |
| Autonomy valence (mean (SD)) | 0.97 (0.34) | 0.97 (0.35) | 0.99 (0.37) | 0.99 (0.33) |
| Deviance lifetime (mean (SD)) | 0.90 (0.64) | 0.72 (0.62) | 0.68 (0.68) | 0.57 (0.65) |
| Deviance valence (mean (SD)) | -1.09 (0.50) | -0.99 (0.51) | -0.95 (0.56) | -0.97 (0.44) |
| Relocation lifetime (mean (SD)) | 1.45 (1.06) | 1.48 (0.95) | 1.15 (1.11) | 1.10 (0.96) |
| Relocation valence (mean (SD)) | -0.44 (0.60) | -0.37 (0.50) | -0.40 (0.53) | -0.43 (0.50) |
| Distress lifetime (mean (SD)) | 1.90 (1.13) | 1.41 (1.12) | 1.94 (1.17) | 1.30 (0.96) |
| Distress valence (mean (SD)) | 0.108 (0.44) | 0.15 (0.44) | 0.23 (0.45) | 0.19 (0.34) |
| Other lifetime (mean (SD)) | 1.06 (0.77) | 0.99 (0.82) | 0.94 (0.91) | 0.84 (0.78) |
| Other valence (mean (SD)) | -1.13 (0.40) | -1.12 (0.34) | -1.05 (0.37) | -1.03 (0.30) |
| Pubertal Development Scale | | | | |
| Mean (SD) | 2.69 (0.44) | 2.59 (0.44) | 2.71 (0.42) | 2.61 (0.45) |
| NEO-FFI | | | | |
| Neuroticism (mean (SD)) | 24.6 (6.71) | 21.9 (6.78) | 23.9 (8.27) | 20.5 (7.00) |
| Extraversion (mean (SD)) | 30.0 (5.67) | 30.5 (4.97) | 30.8 (5.79) | 31.0 (5.56) |
| Openness (mean (SD)) | 27.3 (5.54) | 26.3 (5.69) | 26.9 (5.59) | 24.6 (5.71) |

| | Training depression (n=180) | Training control (n=227) | Test depression (n=68) | Test control (n=69) |
|------------------------------------|--|---|---------------------------------------|------------------------------------|
| Agreeableness (mean (SD)) | 28.6 (5.78) | 30.1 (4.80) | 29.2 (5.16) | 30.2 (4.44) |
| Conscientiousness (mean (SD)) | 27.3 (6.55) | 28.3 (5.95) | 27.1 (7.51) | 29.1 (6.20) |
| SURPS | | | | |
| Anxiety sensitivity (mean (SD)) | 2.28 (0.44) | 2.24 (0.44) | 2.39 (0.49) | 2.10 (0.46) |
| Negative thinking (mean (SD)) | 1.85 (0.39) | 1.79 (0.33) | 1.89 (0.37) | 1.74 (0.34) |
| Impulsivity (mean (SD)) | 2.42 (0.43) | 2.34 (0.38) | 2.59 (0.42) | 2.32 (0.43) |
| Sensation seeking (mean (SD)) | 2.75 (0.55) | 2.76 (0.52) | 2.81 (0.57) | 2.79 (0.51) |
| Smoking (lifetime) | | | | |
| 0 | 125 (69.4%) | 185 (81.5%) | 43 (63.2%) | 44 (63.8%) |
| 1-2 | 24 (13.3%) | 19 (8.4%) | 6 (8.8%) | 11 (15.9%) |
| 3-5 | 12 (6.7%) | 9 (4.0%) | 4 (5.9%) | 5 (7.2%) |
| 6-9 | 3 (1.7%) | 3 (1.3%) | 3 (4.4%) | 0 (0%) |
| 10-19 | 4 (2.2%) | 2 (0.9%) | 4 (5.9%) | 4 (5.8%) |
| 20-39 | 3 (1.7%) | 4 (1.8%) | 1 (1.5%) | 2 (2.9%) |
| 40+ | 9 (5.0%) | 5 (2.2%) | 7 (10.3%) | 3 (4.3%) |
| FTND total | | | | |
| Mean (SD) | 0.03 (0.25) | 0.01 (0.13) | 0.12 (0.56) | 0.00 (0.00) |
| Cannabis (lifetime) | | | | |
| 0 | 165 (91.7%) | 215 (94.7%) | 62 (91.2%) | 64 (92.8%) |
| 1-2 | 7 (3.9%) | 10 (4.4%) | 1 (1.5%) | 3 (4.3%) |
| 3-5 | 3 (1.7%) | 1 (0.4%) | 3 (4.4%) | 2 (2.9%) |
| 6-9 | 0 (0%) | 1 (0.4%) | 0 (0%) | 0 (0%) |
| 10-19 | 5 (2.8%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 20-39 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 40+ | 0 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| Missing | 0 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| AUDIT question 1 | | | | |
| Never | 67 (37.2%) | 102 (44.9%) | 30 (44.1%) | 34 (49.3%) |
| Monthly or less | 85 (47.2%) | 91 (40.1%) | 28 (41.2%) | 30 (43.5%) |
| Two to four times a month | 24 (13.3%) | 32 (14.1%) | 8 (11.8%) | 5 (7.2%) |
| Two to three times a week | 3 (1.7%) | 2 (0.9%) | 1 (1.5%) | 0 (0%) |
| Four or more times a week | 1 (0.6%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Missing | 0 (0%) | 0 (0%) | 1 (1.5%) | 0 (0%) |
| Brain structure (mean (SD)) | | | | |

| | Training depression (n=180) | Training control (n=227) | Test depression (n=68) | Test control (n=69) |
|--|--|---|---------------------------------------|------------------------------------|
| ICV | 1510000 (151000) | 1540000 (137000) | 1520000 (155000) | 1560000 (122000) |
| Hippocampus | 4330 (377) | 4370 (386) | 4400 (445) | 4420 (383) |
| Amygdala | 1760 (220) | 1790 (229) | 1770 (249) | 1760 (207) |
| Thalamus | 7410 (708) | 7540 (695) | 7690 (736) | 7600 (637) |
| Nucleus accumbens | 778 (107) | 795 (102) | 810 (119) | 798 (108) |
| Pallidum | 1690 (225) | 1690 (205) | 1690 (229) | 1670 (193) |
| Putamen | 6570 (709) | 6600 (593) | 6440 (647) | 6560 (705) |
| Caudate | 4080 (506) | 4130 (455) | 4160 (514) | 4120 (413) |
| Ventricles | 4930 (2180) | 5130 (2630) | 4870 (2080) | 4950 (2390) |
| Banks of the superior temporal sulcus surface area | 1030 (144) | 1070 (141) | 1040 (147) | 1060 (138) |
| Caudal anterior cingulate surface area | 729 (132) | 742 (123) | 726 (133) | 741 (98.9) |
| Caudal middle frontal surface area | 2280 (361) | 2380 (360) | 2290 (357) | 2430 (314) |
| Cuneus surface area | 1530 (202) | 1550 (184) | 1510 (195) | 1530 (178) |
| Entorhinal surface area | 354 (67.9) | 370 (76.0) | 359 (63.1) | 362 (60.5) |
| Fusiform surface area | 3330 (416) | 3410 (377) | 3260 (427) | 3390 (377) |
| Inferior parietal surface area | 5160 (663) | 5370 (619) | 5250 (737) | 5380 (589) |
| Inferior temporal surface area | 3300 (481) | 3340 (426) | 3220 (538) | 3310 (372) |
| Isthmuscingulate surface area | 976 (147) | 1010 (172) | 1020 (172) | 1010 (151) |
| Lateral occipital surface area | 4810 (569) | 4940 (591) | 4760 (684) | 4850 (559) |
| Lateral orbitofrontal surface area | 2590 (310) | 2620 (320) | 2570 (334) | 2630 (289) |
| Lingual surface area | 3140 (358) | 3230 (380) | 3150 (439) | 3170 (353) |
| Medial orbitofrontal surface area | 1790 (228) | 1810 (206) | 1790 (223) | 1840 (199) |
| Middle temporal surface area | 3360 (409) | 3420 (406) | 3280 (466) | 3370 (383) |
| Parahippocampal surface area | 704 (91.5) | 731 (91.3) | 711 (83.3) | 721 (83.7) |
| Paracentral surface area | 1460 (175) | 1510 (179) | 1480 (173) | 1510 (196) |
| Pars opercularis surface area | 1610 (218) | 1640 (219) | 1600 (215) | 1630 (224) |
| Pars orbitalis surface area | 730 (90.1) | 736 (87.5) | 717 (96.8) | 719 (83.1) |
| Pars triangularis surface area | 1460 (212) | 1490 (211) | 1430 (194) | 1490 (190) |
| Pericalcarine surface area | 1450 (213) | 1440 (234) | 1420 (260) | 1440 (211) |
| Postcentral surface area | 4170 (458) | 4320 (474) | 4280 (530) | 4310 (414) |
| Posterior cingulate surface area | 1210 (169) | 1240 (162) | 1220 (169) | 1230 (130) |
| Precentral surface area | 4850 (530) | 4960 (510) | 4870 (481) | 5020 (537) |

| | Training depression (n=180) | Training control (n=227) | Test depression (n=68) | Test control (n=69) |
|--|--|---|---------------------------------------|------------------------------------|
| Precuneus surface area | 3970 (495) | 4110 (491) | 4060 (541) | 4140 (446) |
| Rostral anterior cingulate surface area | 742 (136) | 771 (128) | 754 (138) | 781 (111) |
| Rostral middle frontal surface area | 5920 (852) | 6130 (825) | 5750 (829) | 6070 (801) |
| Superior frontal surface area | 7220 (845) | 7470 (801) | 7310 (862) | 7500 (866) |
| Superior parietal surface area | 5570 (631) | 5710 (591) | 5680 (709) | 5670 (576) |
| Superior temporal surface area | 3800 (426) | 3890 (452) | 3720 (404) | 3840 (376) |
| Supramarginal surface area | 3900 (520) | 4090 (537) | 4010 (600) | 4040 (512) |
| Frontal pole surface area | 264 (33.5) | 271 (35.0) | 267 (31.8) | 268 (37.7) |
| Temporal pole surface area | 450 (52.2) | 459 (53.6) | 440 (67.5) | 452 (48.6) |
| Transversetemporal surface area | 409 (59.1) | 421 (64.4) | 408 (61.7) | 412 (58.0) |
| Insula surface area | 2060 (230) | 2090 (220) | 2050 (216) | 2090 (177) |
| Bank of the superior temporal sulcus thickness | 2.72 (0.18) | 2.74 (0.17) | 2.77 (0.19) | 2.80 (0.18) |
| Caudal anterior cingulate thickness | 2.89 (0.24) | 2.87 (0.25) | 2.95 (0.25) | 2.92 (0.22) |
| Caudal middle frontal thickness | 2.64 (0.18) | 2.64 (0.18) | 2.64 (0.18) | 2.68 (0.13) |
| Cuneus thickness | 2.04 (0.14) | 2.04 (0.15) | 2.06 (0.16) | 2.04 (0.11) |
| Entorhinal thickness | 3.50 (0.37) | 3.44 (0.36) | 3.42 (0.39) | 3.46 (0.37) |
| Fusiform thickness | 2.90 (0.15) | 2.90 (0.16) | 2.85 (0.17) | 2.87 (0.18) |
| Inferior parietal thickness | 2.62 (0.15) | 2.65 (0.14) | 2.66 (0.14) | 2.70 (0.14) |
| Inferior temporal thickness | 2.94 (0.23) | 2.92 (0.21) | 2.82 (0.23) | 2.86 (0.24) |
| Isthmuscingulate thickness | 2.79 (0.19) | 2.80 (0.19) | 2.80 (0.22) | 2.81 (0.20) |
| Lateral occipital thickness | 2.34 (0.12) | 2.36 (0.13) | 2.37 (0.13) | 2.37 (0.12) |
| Lateral orbitofrontal thickness | 2.85 (0.17) | 2.87 (0.19) | 2.80 (0.22) | 2.85 (0.18) |
| Lingual thickness | 2.25 (0.12) | 2.27 (0.12) | 2.27 (0.11) | 2.27 (0.12) |
| Medial orbitofrontal thickness | 2.67 (0.19) | 2.68 (0.19) | 2.64 (0.20) | 2.64 (0.16) |
| Middle temporal thickness | 3.04 (0.20) | 3.03 (0.20) | 2.97 (0.21) | 3.01 (0.21) |
| Parahippocampal thickness | 2.99 (0.29) | 2.94 (0.27) | 2.96 (0.28) | 2.93 (0.29) |
| Paracentral thickness | 2.53 (0.17) | 2.57 (0.16) | 2.60 (0.18) | 2.64 (0.16) |
| Pars opercularis thickness | 2.75 (0.16) | 2.78 (0.17) | 2.79 (0.15) | 2.82 (0.14) |
| Pars orbitalis thickness | 2.97 (0.24) | 2.94 (0.23) | 2.87 (0.24) | 2.86 (0.22) |
| Pars triangularis thickness | 2.62 (0.18) | 2.65 (0.16) | 2.63 (0.18) | 2.66 (0.14) |
| Pericalcarine thickness | 1.70 (0.13) | 1.71 (0.15) | 1.74 (0.15) | 1.72 (0.11) |
| Postcentral thickness | 2.13 (0.14) | 2.17 (0.13) | 2.18 (0.13) | 2.22 (0.13) |
| Posterior cingulate thickness | 2.79 (0.17) | 2.80 (0.15) | 2.85 (0.18) | 2.84 (0.14) |
| Precentral thickness | 2.62 (0.15) | 2.63 (0.15) | 2.63 (0.16) | 2.68 (0.14) |

| | Training depression (n=180) | Training control (n=227) | Test depression (n=68) | Test control (n=69) |
|--------------------------------------|--|-------------------------------------|-----------------------------------|--------------------------------|
| Precuneus thickness | 2.56 (0.14) | 2.60 (0.14) | 2.61 (0.15) | 2.66 (0.14) |
| Rostral anterior cingulate thickness | 3.10 (0.21) | 3.10 (0.24) | 3.10 (0.23) | 3.12 (0.21) |
| Rostral middle frontal thickness | 2.49 (0.16) | 2.49 (0.16) | 2.45 (0.16) | 2.47 (0.13) |
| Superior frontal thickness | 2.92 (0.16) | 2.92 (0.17) | 2.90 (0.15) | 2.95 (0.14) |
| Superior parietal thickness | 2.26 (0.15) | 2.30 (0.15) | 2.31 (0.15) | 2.35 (0.14) |
| Superior temporal thickness | 3.00 (0.19) | 3.01 (0.17) | 3.00 (0.21) | 3.03 (0.18) |
| Supramarginal thickness | 2.73 (0.15) | 2.74 (0.16) | 2.77 (0.16) | 2.82 (0.14) |
| Frontal pole thickness | 3.09 (0.31) | 3.08 (0.31) | 2.97 (0.33) | 3.01 (0.27) |
| Temporal pole thickness | 3.62 (0.35) | 3.58 (0.35) | 3.55 (0.42) | 3.67 (0.33) |
| Transversetemporal thickness | 2.66 (0.24) | 2.65 (0.20) | 2.63 (0.19) | 2.67 (0.21) |
| Insula thickness | 3.29 (0.13) | 3.30 (0.152) | 3.29 (0.13) | 3.33 (0.15) |

AUDIT: alcohol use disorders identification test, DAWBA: development and well-being assessment, FTND: Fagerstrom test for nicotine dependence, ICV: intracranial volume, MDD: major depressive disorder, N: sample size, NEO-FFI: neuroticism-extraversion-openness five-factor inventory, SD: standard deviation, SDQ: strengths and difficulties questionnaire, SURPS: substance use risk profile scale, WISC-IV: Wechsler intelligence scale for children – fourth edition.

S4 Supplemental Table S4. Demographics risky alcohol use

| | Healthy control (N=134) | Risky alcohol use (N=134) |
|---------------------------------------|------------------------------------|--------------------------------------|
| Age | | |
| Mean (SD) | 14.4 (0.40) | 14.4 (0.34) |
| Sex | | |
| Female | 66 (49.3%) | 55 (41.0%) |
| Male | 68 (50.7%) | 79 (59.0%) |
| Site | | |
| Berlin | 8 (6.0%) | 12 (9.0%) |
| Dresden | 31 (23.1%) | 7 (5.2%) |
| Dublin | 8 (6.0%) | 21 (15.7%) |
| Hamburg | 27 (20.1%) | 19 (14.2%) |
| London | 18 (13.4%) | 16 (11.9%) |
| Mannheim | 15 (11.2%) | 11 (8.2%) |
| Nottingham | 12 (9.0%) | 37 (27.6%) |
| Paris | 15 (11.2%) | 11 (8.2%) |
| Depression score at BL (DAWBA) | | |
| Mean (SD) | 0.455 (0.66) | 1.82 (2.91) |

DAWBA: development and well-being assessment, N: sample size, SD: standard deviation

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