RESPOND (REducing Stress and Preventing Depression): web-based rumination-focused cognitive behavioural therapy (i-RFCBT) for high ruminating university students at risk for depression: a randomised controlled trial

Lorna Cook¹, Mohammod Mostazir², Edward Watkins*¹

* Corresponding author: E.R.Watkins@exeter.ac.uk

¹SMART Lab, Mood Disorders Centre, School of Psychology, University of Exeter, EX4 4QG, UK

²College of Life and Environmental Sciences (CLES), School of Psychology, University of Exeter, EX4 4QG, UK
Abstract

Background: Prevention of depression is a priority to reduce its global disease burden. Targeting specific risk factors, such as rumination, may increase the efficacy of preventive interventions. Rumination-focused CBT (RFCBT) was developed to specifically target depressive rumination. A prior randomised controlled trial (RCT) in Dutch 15-22-year-olds at risk because of elevated worry and rumination found that both guided web-based RFBCT (i-RFCBT) and group-delivered RFCBT equally reduced depressive symptoms and onset of depressive cases over 1-year follow-up, relative to usual care control.

Objective: The primary objective was to test whether guided i-RFCBT would prevent the incidence of major depression relative to usual care when extended to UK university students and using diagnostic interviews to improve the assessment of incidence of depression. The secondary objective was to test the feasibility and estimated effect sizes of unguided i-RFCBT.

Methods: To address the primary objective, a Phase III RCT was designed and powered to compare high risk university students (N = 235), selected with elevated worry/rumination, recruited via an open access website in response to circulars within universities and internet advertisement, randomised to receive either guided i-RFCBT (an interactive web-based version of RFCBT, supported by asynchronous written web-based support from qualified and specially trained therapists), or usual care control. To address the secondary objective, participants were also randomised to an adjunct arm of unguided (self-administered) i-RFCBT. Primary outcome was onset of a major depressive episode, assessed with structured diagnostic interview at 3 (post-intervention), 6 and 15 months post-randomisation, conducted by telephone, blind to condition. Secondary outcomes of symptoms of depression and anxiety and levels of worry and rumination were self-assessed through questionnaires at baseline and the same follow-up intervals.
Results: A total of 235 participants were randomised to guided i-RFCBT (N = 82), unguided i-RFCBT (N = 76) or usual care (N = 77). For the primary comparison, guided i-RFCBT reduced risk of depression by 34% relative to usual care. Participants with higher levels of baseline stress benefited most from the intervention (HR: 0.43, 95% CI [0.21, 0.87], P = .02). Significant improvements in rumination, worry and depressive symptoms were found in the short to medium term. Of six modules, guided participants completed a mean of 3.46 modules (SD = 2.25), with 46.34% (38/82) compliant (completing ≥4 modules). Similar effect sizes and compliance rates were found for unguided i-RFCBT.

Conclusions: These results confirm that guided i-RFCBT can reduce the onset of depression in high-risk young people reporting high levels of worry/rumination and stress. The feasibility study argues for formally testing unguided i-RFCBT as a preventive intervention: as a scalable intervention, if the observed effect sizes are robustly replicated in a Phase III trial, it has potential to significantly address the burden of depression.

Trial registration: Current Controlled Trials ISRCTN12683436. Date of registration: 27/10/2014

Keywords: Randomised Controlled Trial; Cognitive Behavioural Therapy (CBT); Rumination; Depression; Prevention; Internet-Delivery
Introduction

Depression is the leading cause of disease burden worldwide, accounting for 7.5% of all years lived with disability in 2015 [1], with considerable individual, societal and economic consequences. Although there are effective evidence-based acute treatments, their impact is limited because of poor access to treatments [2], high rates of non-response [3] and the recurrent nature of depression, with 50-80% of patients experiencing two or more episodes [4]. It is estimated that even with optimal acute treatment at full coverage, only 34% of the disease burden would be averted [5]. As a consequence, a strong case has been made that prevention is needed to reduce the global burden of depression [6].

There is robust evidence that preventive interventions, mainly using cognitive-behavioural therapy (CBT) approaches, can reduce symptoms of depression and prevent the incidence of depression (see meta-analyses [7-9]), with an average reduction in incidence rates of 21% [10]. These meta-analyses suggest that targeted interventions (incorporating (i) selective interventions aimed at subgroups with known risk factors and (ii) indicated interventions aimed at those with subclinical symptoms) produce larger and longer-lasting effects than universal interventions aimed at entire populations. For example, a meta-analysis [11] of 21 preventive interventions (15 using CBT approaches) found that selective interventions and indicated interventions had lower incidence rate ratios (IRR) (0.72 and 0.76 respectively) relative to controls than universal interventions (IRR = 0.90). Merry et al. [8] also found both universal and targeted interventions reduced incidence relative to no intervention in the short to medium term (3-9 months post-intervention) but only targeted interventions reduced incidence at 12 months. Thus, targeting at-risk groups may improve the efficacy of preventive interventions for depression [6], in part because the base rate is higher in targeted samples so it is easier to detect a significant effect with smaller sample sizes [12].

The incidence of depression rises steeply from the age of 14 through into young adulthood, with increased rates in females (2:1 female: male) emerging at around 12 years old.
and continuing into young adulthood [13]. For example, the UK Adult Psychiatric Morbidity Survey found increasing rates of common mental health disorders (CMDs: incorporating depression and anxiety disorders) among young women (16-24-year-olds), rising from 22.2% in 2007 to 28.2% in 2014 [14], with rates in young women almost three times those of young men (10.0%) in 2014. Because early onset is linked to greater chronicity [15] as well as other negative long-term outcomes, such as poorer academic performance [16] and subsequent occupational performance [1], prevention may be particularly effective and impactful for this age group.

Within this age range, there is evidence that university students are a particularly high-risk group, with a weighted mean prevalence for depression of 30.6% (range 10-85%) across 24 studies [17] relative to estimates of 10.8%-22% in non-students of the same age range [18, 19]. Such increased prevalence may be due to the specific pressures of university and associated lifestyle changes, such as leaving the family home for the first time, forming new friendships, more self-directed learning and irregular sleep patterns [20]. Students who experience mental health difficulties during their studies are at greater risk of poor academic outcomes [16] or of dropout [21].

Despite these challenges, students often do not seek help from relevant services [22, 23]. Alternative modes of delivery, such as web-based interventions, offer advantages that may be attractive to students, including: availability at any time and place, anonymity which may reduce the stigma of seeking help and more time to reflect on the treatment material [12, 24, 25]. A recent systematic review and meta-analysis of 17 web-based and computer-delivered interventions for higher education students (1 treatment, 5 universal prevention, 11 selective/indicated prevention) found reductions in depression, anxiety and stress when compared to inactive controls [26]. However, sample sizes were generally small and the
authors recommend further larger scale trials to assess the effectiveness of web-based interventions in university students.

One such relatively large-scale trial was conducted by Topper, Emmelkamp, Watkins and Ehring [27] and tested a guided web-based targeted preventive intervention for 251 high school and university students aged 15-22 with high levels of self-reported worry and/or rumination. Participants were randomised to face-to-face group rumination-focused cognitive-behavioural therapy (RFCBT), guided web-based RFCBT (i-RFCBT), or a no-intervention control group. This preventive intervention is based on rumination-focused cognitive-behavioural therapy (RFCBT), previously shown to be effective in treating residual depression [28]. RFCBT specifically targets repetitive negative thought (RNT), incorporating worry and rumination, defined as a thinking style that is repetitive, intrusive, difficult to disengage from, perceived as unproductive and that captures mental capacity [29]. There is strong evidence that RNT is a transdiagnostic process, involved in the onset and maintenance of a range of disorders including depression, anxiety and physical health issues [30, 31]. RNT prospectively predicts emotional disorders in children and adolescents [32-35]. Moreover, differences in rumination partially explain the gender bias in depression rates [36].

Targeting transdiagnostic risk factors has the potential to improve the efficacy of prevention by impacting on multiple disorders with a single intervention [27]. In support of this transdiagnostic approach, both web-based and group-delivered RFCBT reduced symptoms of depression and anxiety ($d = 0.36$ to $0.72$) relative to controls. Cumulative incidence rates at the final 12-month follow-up were significantly lower in both RFCBT intervention conditions for depression (14.7% web-based; 15.3% group) and generalised anxiety disorder (GAD; 16.0% web-based; 18.0% group) relative to the usual care control condition (32.4% depression; 42.2% GAD), with no difference between i-RFCBT versus group RFCBT. In support of the hypothesised mechanism of change, reductions in worry and
rumination were found to mediate the effects of the interventions on prevalence of depression and GAD.

Topper et al. [27] findings suggest that targeting rumination has transdiagnostic preventive effects and are consistent with evidence that targeted prevention can be effective. However, there were several key limitations: (a) there was no diagnostic interview to assess depression and anxiety and self-report measures were only able to estimate point prevalence caseness; (b) because history of depression was not assessed, participants’ prior history of depression was not known and therefore it was not possible to discriminate whether the intervention prevented first onset or relapse/recurrence of depression. Topper et al. [27] included both secondary and university students to form a heterogeneous sample. With evidence that undergraduates may form a distinct at-risk subgroup and that, within this demographic, rumination predicts change in depression over 6 months [37] and interacts with negative cognitions and stressful life events to predict the maintenance of depressive symptoms over 6 weeks [38], we hypothesised that the benefits of i-RFCBT at preventing depression in high ruminating young adults would also specifically apply to high ruminating undergraduates, especially those experiencing stressful life events. The RESPOND trial therefore sought to assess whether the preventive findings from Topper et al. [27] could be replicated in an undergraduate population in the UK whilst also addressing the aforementioned methodological limitations by including a well-validated diagnostic interview (Structured Clinical Interview for DSM-IV; SCID-I [39]) to increase accuracy of current diagnostic status and measure retrospective incidence. By assessing history of depression at the baseline diagnostic interview, RESPOND could further stratify participants by history of depression, and discriminate whether i-RFCBT prevented first onset of depression or relapse. The primary aim of the current phase III efficacy trial was to test whether the findings of
Topper et al. [27] comparing guided i-RFCBT to usual care could be extended to a selective UK high-risk undergraduate population.

Part of the rationale for web-based therapy, such as i-RFCBT, is to increase the coverage, availability, and accessibility of treatment: web-based treatment can potentially reach a large number of people and overcome hurdles to therapy attendance such as geographical distance, poor mobility, and difficulty in scheduling appointments in the working day. Topper et al., [27] used i-RFCBT that was guided and supported by a therapist because prior evidence suggested that, at least for acute treatment for depression, guided i-CBT is significantly more effective than unguided (i.e., self-help) i-CBT [40-42], and only guided i-CBT produces similar treatment effects to face-to-face therapy in patients with acute depressive symptoms [24]. However, there is a limit to the scalability of guided i-CBT because the coverage is determined by the number and availability of therapists. In contrast, an unguided form of web-based therapy has nearly limitless scalability as there are no such constraints, and, thus, even with smaller effect sizes than guided interventions, has significant potential to reduce the disease burden of depression [43]. Such an intervention would be particularly beneficial for preventing depression because effective prevention requires an intervention to be highly scalable and able to reach very high numbers of people. The secondary aim of this study was therefore to assess the feasibility and acceptability of an unguided version of i-RFCBT, as well as estimate effect sizes to inform a fully powered trial, with respect to incidence rates and symptom levels (descriptives and confidence intervals).

**Methods**

**Trial Design**

**Phase III efficacy study**

The phase III study consisted of a single (researcher) blind parallel-group RCT, comparing guided i-RFCBT versus a usual care control group. For full details, see the trial protocol paper [44] and Current Controlled Trials ISRCTN12683436.
Quasi-Phase II pilot arm
To assess the feasibility of unguided i-RFCBT, a separate adjunct arm of unguided i-RFBCT was included as a quasi-phase II pilot arm. For efficiency, participants were randomised to this arm within the overall trial design, but there was no direct comparison between the unguided and guided arms. The unguided arm was compared to the control group in order to estimate effect sizes of an unguided version of i-RFCBT for the planning of future efficacy trials.

Participants
Assuming a similar hazard ratio of 0.41 for the guided i-RFCBT vs. usual care control [27], 75 participants per arm would provide 0.86 power (two-tailed 5% alpha level) to detect this effect. For change in depressive symptoms, the observed effect size was $d = 0.51$ [27]. 78 participants per arm would be needed for 80% power to detect a similar effect at two-tailed 5% alpha level, allowing for 20% follow-up drop-out attrition. With no previous evidence for unguided i-RFCBT, no power or sample size calculations were conducted. We aimed to recruit the same number ($N = 78$) as the other two arms.

Participants were university students resident in the UK aged 18-24 with elevated repetitive negative thought (RNT), defined as scoring above the 75th percentile on at least one measure of worry/rumination: $\geq 50$ on Penn State Worry Questionnaire (PSWQ; [45]); and/or $\geq 40$ on the Ruminative Response Scale (RRS; [46]), using the same criteria as Topper et al., [27]. As a prevention study, participants were excluded if they met diagnostic criteria for a current (within past month) major depressive episode (MDE). Additionally, potential participants were excluded if they reported any of the following: current and significant substance abuse or dependence; current symptoms/diagnosis of psychosis or bipolar disorder; current psychological therapy or active suicide risk. In line with standard practice, receipt of antidepressant medication was not an exclusion criterion, providing the dose had been stable for at least one month.
The full recruitment procedure is outlined in Cook and Watkins [44]. Briefly, 1834 university departments in the UK were contacted between 14/11/2013 and 10/12/2014 (1527 contacted twice) and asked to advertise the study. Three hundred and thirty-six departments confirmed the study was advertised either by email or as a poster. This advert contained a link to an open access screening website. Twitter and Facebook were also used to circulate the advert to young people who expressed an interest in the following terms: stress; worry; rumination; mental health; self-esteem; wellbeing; research; psychology; cognitive-behavioural therapy; online therapy. Additionally, three organisations working with young people and/or in the field of mental health agreed to advertise the study.

A two-step procedure identified eligible participants. In the first step, an open access screening website with conditional automated feedback identified potential participants for further screening by screening in those with elevated RNT (> 75th percentile) using shortened versions of the PSWQ (4 items, range 4-20, cut-off ≥12) and RRS (5 items, range 5-20, cut-off ≥ 10), as developed by Topper et al. [47]. A conservative cut-off of 15 on PHQ-8 [48] excluded individuals likely to be experiencing a current MDE. Eligible participants provided contact details as consent to be contacted for further telephone screening.

In the second step, a telephone interview consisted of brief screening questions for alcohol and drug use, symptoms of bipolar disorder and psychosis (Psychosis Screening Questionnaire, PSQ; [49]), assessment of any relevant past or current treatments, and the SCID-I [39] sections on current and past depressive episodes, dysthymia, and any relevant anxiety disorders and eating disorders. As the primary objective was to investigate the prevention of depression, diagnoses of anxiety disorders and eating disorders were recorded but participants meeting criteria for any of these disorders were not excluded from the study. Consent to interview was obtained verbally and included providing their general practitioner’s (GP) contact details so that appropriate clinical support could be obtained in the
event of disclosure of suicidal risk. The interview was audio-recorded, with consent, so that
diagnostic status could be independently checked. The same researcher conducted the
baseline and follow-up telephone interview assessments ensuring continuity of contact
between research team and participants. Two hundred and fifty-four participants were
eligible, of whom 235 returned written informed consent and were randomised to guided i-
RFCBT \( N = 82 \), unguided i-RFCBT \( N = 76 \) or usual care control \( N = 77 \). The
CONSORT diagram (Figure 1) indicates the numbers excluded at baseline for each of the
exclusion criteria.
Interventions

**Guided i-RFCBT**

The guided intervention was an English version of i-RFCBT (called MindReSolve), translated and adapted from the version used by Topper et al. [27] to include case examples relevant to university students (see Multimedia Appendix 1). RFCBT differs from standard CBT by seeking to change the process of thinking rather than the content of individual
thoughts [50]. RFCBT [51] was developed from theoretical models and experimental findings indicating distinct types of repetitive thought (RT) with different consequences [31]: unconstructive RT involves an abstract, evaluative processing mode focused on the meaning and evaluation of events and difficulties, leading to a range of negative consequences such as poorer problem-solving and greater emotional reactivity, relative to constructive RT, which involves concrete, specific and action-oriented processing [52]. RFCBT therefore aims to shift participants from an abstract and evaluative style to a concrete, specific and action-oriented style [31], consistent with evidence that concreteness training reduces depression [53].

RNT is also theoretically conceptualised as a mental habit acting as a form of avoidance and maintained by negative reinforcement [54]. RFCBT therefore involves counterconditioning the avoidant ruminative response with more helpful coping strategies and approach behaviours [51]. In practice, this involves functional analysis of rumination to help users spot triggers for rumination, to distinguish between helpful and unhelpful RT and to countercondition unhelpful RT with more functional responses through the formulation of contingency ‘If-Then’ plans [51].

The internet treatment was delivered on the internet platform and software owned, programmed, and hosted by Minddistrict [55], accessed by a research licence purchased from Minddistrict by the research team. The specific content of the i-RFCBT intervention was developed and entered into the platform using its Content Management System (CMS) by the research team led by Edward Watkins, using the same key intervention principles and techniques as face-to-face RFCBT as described in Watkins [51], adapted for the internet. I-RFCBT contains the same key components as face-to-face RFCBT [51], split into six one-hour modules, each in turn split into 3 or 4 sessions consisting of a single webpage, with one to two weeks recommended per module for practice of the techniques. The content includes
psycho-education, mood diaries, experiential audio exercises, pictures, and video vignettes of university students talking about their own experiences of the intervention. Modules follow the same basic structure: reflection on previous module; introduction of new technique; experiential in-session exercises; plans for implementation. The specific behaviour-change techniques are drawn from the following groups in the BCT Taxonomy (v1) [56]: goals and planning (goal setting, action planning, review behavior and behavioural contract), feedback and monitoring (self-monitoring of behaviour and outcomes), shaping knowledge (information about antecedents), natural consequences (information about social and environmental consequences and monitoring of emotional consequences), associations (prompts/cues and associative learning), repetition and substitution (behavioural practice/rehearsal, behaviour substitution, and habit formation), antecedents (restructuring physical and social environment, avoiding/reducing cues for the behaviour), and self-belief (mental rehearsal of successful performance, focus on past success, and self-talk). The key strategies include coaching participants to spot warning signs for rumination and worry, and then to make IF THEN plans in which an alternative strategy is repeatedly practised in response to the warning signs. These strategies include being more active, slowing things down, breaking tasks down, opposite action, relaxation, concrete thinking, becoming absorbed, self-compassion and assertiveness.

The intervention was accessed individually, for free, on a secure, password-protected website. Access was granted by email link, inviting the participant to set up a personal account and password. The intervention was supported by qualified clinicians who had received additional specific training in RFCBT. This support consisted of asynchronous written feedback provided by the clinician at the end of each module. Feedback served to highlight positive steps and identified areas to focus on in the following module. Feedback was constrained by template responses for each module, faithful to the RFCBT model, which
could be adapted to individual participants’ responses. All content and module order was identical across participants, ensuring treatment fidelity. Each module was self-paced but the participants were advised to spend one to two weeks on each and could only access the next module once feedback from the clinician was received, typically within 2 working days. Clinicians monitored log-ons and sent personalised reminder emails if there was no log-on for over a week. The platform also sent an automatic weekly reminder if the platform had not been accessed for a week. Suicidal risk was also monitored using a well-established departmental protocol to determine level of risk and seek clinical support as appropriate.

Therapists were provided with regular supervision with the developer of RFCBT (EW) to further encourage treatment fidelity. All (100%) feedbacks reviewed by EW were faithful to the intervention model (over 10% of therapist feedbacks sampled – a minimum of the three initial feedbacks for each therapist, plus a random sub-set of later feedbacks).

Unguided i-RFCBT

The content of unguided i-RFCBT was almost identical to guided i-RFCBT with minor adaptations for self-help to include some automatic online conditional feedback addressing common challenges with the exercises. Access was granted via email link to set up a personal account and password. Participants could then access all modules without restriction but were advised to spend one to two weeks on each to allow time for practice. Responses were not monitored except for weekly checks of questionnaires to identify and follow up suicidal risk as necessary.

Usual care control condition

Participants in the usual care control condition were permitted to access any other treatments during the study, as necessary. They were also offered access to unguided i-RFCBT at the end of the follow-up period.
Measures
All measures were completed at baseline, 3 months, 6 months and 15 months unless otherwise stated. Diagnostic measures were conducted by telephone, with the option to return the self-report questionnaire measures by email/post.

The Structured Clinical Interview for DSM-IV (SCID-I; [39]) is a semi-structured diagnostic interview for Axis I DSM-IV Diagnoses. The SCID-I was used to assess MDE (current and/or past), anxiety disorders and eating disorders. Inter-rater reliability for Axis I diagnoses is fair to excellent, with a mean Kappa of 0.71 [57]. In the event of disclosure of suicidal risk during the diagnostic interview, the researcher followed a well-established departmental protocol to assess risk and obtain clinical support as needed.

The Episodic Life Event Interview, part of the UCLA Life Stress Interview [58], assessed the number and impact of stressful events since the previous assessment (for previous 3 months at baseline). Participants provided a list of events experienced and a subjective rating of stress experienced as a result of the worst event. The original scale ranges from 1 ‘none’ to 5 ‘severe’. Participants scored 0 if no events were experienced. To aid analysis and interpretation, stress was recoded to collapse 0 ‘no event’ and 1 ‘event experienced but no stress’ into a single ‘no stress’ category. The recoded stress scale therefore ranges from 0 ‘no stress’ to 4 ‘severe stress’.

The Penn State Worry Questionnaire (PSWQ; [45]) is a 16-item self-report questionnaire assessing frequency, intensity and automaticity of worry (e.g. ‘My worries overwhelm me’; ‘I know I shouldn’t worry about things, but I just can’t help it’). It is scored from ‘1’ (not at all typical of me) to ‘5’ (very typical of me), with higher scores indicating higher levels of worry. Internal consistency is high with good test-retest reliability [45]. The PSWQ has also been shown to have good predictive validity for symptoms of anxiety and depression [59].

The Ruminative Response Scale (RRS; [46]) is a self-report measure of frequency of ruminative responses to depressed mood, with items relating to the self (e.g. ‘Think about all
your shortcomings, failings, faults and mistakes’), one’s symptoms (e.g. ‘Think about how hard it is to concentrate’) and possible causes and consequences of one’s mood (e.g. ‘Go away by yourself and think about why you feel this way’). Items are scored from 1 (almost never) to 4 (almost always). Higher scores indicate higher levels of rumination. The RRS has good internal consistency, moderate test-retest reliability, acceptable convergent validity and good predictive validity [46, 60, 61].

*The Patient Health Questionnaire (PHQ-9; [62])* is a nine-symptom measure of depressive symptoms. Scores range from 0-27, with higher scores indicating greater severity. The PHQ-9 is a reliable and valid measure of severity of depressive symptoms [62].

*The Generalised Anxiety Disorder Screener (GAD-7; [63])* is a standardised self-report measure of symptoms of anxiety. Scores range from 0-21 and higher scores indicate more severe symptoms. Spitzer, Kroenke, Williams and Löwe [63] demonstrated good validity and reliability of the GAD-7.

**Demographics and Treatment** At baseline, participants were asked if they had any family history of depression (including whom and how recently) and whether they had experienced any physical, sexual or emotional abuse before the age of 16 (yes/no questions with no further details requested). Participants were asked to report whether they had received any mental health treatments (medication, therapies, use of self-help materials) prior to or during the trial. Timing, duration and (for medication) dosage was recorded.

**Randomisation, allocation concealment and blinding**
Independent computer-generated block randomisation (block size of 3), stratified by sex (male vs. female) and history of depression (presence or absence of past depressive episodes) was used to allocate participants to the guided i-RFCBT, unguided i-RFCBT or usual care control in a 1:1:1 ratio. Varying block sizes were not used as the 2 levels of stratification ensured it would be difficult for the researcher to anticipate or determine allocation. A third
party not involved in assessing or treating the participants implemented the random allocation sequence and informed the therapist of the condition for each participant. The researcher responsible for recruitment and screening was blind to allocation and unable to influence the order of consents. As a single blind trial, the researcher conducting outcome assessments was blind to allocation. The researcher was not involved with any element of treatment delivery. To preserve researcher blinding, participants were notified of their treatment allocation by a trial therapist. Due to the nature of the intervention, participants and therapists could not be blinded.

**Statistical analysis for phase III efficacy trial**

Data cleaning followed the protocol set out by Tabachnick and Fidell [64]. Unplanned missing data was handled via Multiple Imputation (MI). Sensitivity analysis, assuming a variety of MI models (Missing at Random; Missing Not at Random), verified the likely impact of missing data. Auxiliary variables were used to improve the estimation of missing data. Primary analyses were conducted on the Intention-To-Treat (ITT) sample. Additional analyses assessed the effect of compliance using the Complier Average Causal Effect (CACE) analysis [65]. CACE provides an unbiased estimate of the benefits of compliance by comparing the compliers in the intervention group to a comparable subgroup of the control group who would have complied had they been offered the intervention. Compliance was defined in the protocol as completing at least 4 of 6 modules [44]. Analyses were carried out using statistical software Stata (version-15.1[66]).

As a prevention study, the primary outcome was the occurrence and time to onset of any depressive episode. In order to investigate this, Cox-proportional hazard models were fitted to the depression event data, with diagnosis of an episode of major depression at any point during the follow-up period as the outcome and time to onset measured in weeks from randomisation date. Participants were censored upon measurement dropout or end of study. Secondary outcomes of symptom severity and levels of rumination/worry were examined
using mixed model ANCOVAs: between group (ITT/CACE) and repeated measures (3-15-month follow-ups), controlling for baseline symptom levels.

**Feasibility and acceptability (Quasi-Phase II pilot arm)**
Feasibility of data collection procedures were assessed by measuring missing items on clinical outcome measures, number and timing of drop-outs and whether these varied across arms. The acceptability of the intervention was assessed using a behavioural index, measuring the number of online modules completed.

**Ethical approval and informed consent**
Ethical and professional guidelines were followed at all times, in line with Good Clinical Practice guidelines. Ethical approval was obtained from the Ethics Committee of the School of Psychology, University of Exeter (Ref: 2012/554). Participants returned written informed consent including permission to contact their general practitioner (GP) if significant risk was disclosed (see Multimedia Appendix 2).

**Results**

**Demographics**
For brevity, baseline demographics for the three arms are included in Table 1. As noted earlier, the primary comparison is guided i-RFCBT versus usual care control, with a separate analysis of the feasibility and acceptability of the adjunct unguided i-RFCBT arm.

**Survival analysis: guided i-RFCBT vs. usual care control**
Twenty-seven participants in the primary comparison of guided i-RFCBT vs. control completed no follow-ups and no minimum survival time could be estimated, so the ITT survival analyses were conducted on $N = 132$ (guided $N = 63$, control $N = 69$). Participants with a family history of depression were more likely to be lost to follow-up than those without: $\chi^2(1) = 3.89, P = .049$. No other baseline variables were linked to loss to follow-up: all $t$s on continuous measures $< 1.70$; all $\chi^2$ on categorical variables $< 1.74$; all $P$s $> .09$.

<p>| Table 1. Baseline characteristics of usual care, guided i-RFCBT and unguided i-RFCBT ITT samples |
|------------------------------------------|------------------------------------------|------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Usual Care (n=77)</th>
<th>Guided i-RFCBT (n=82)</th>
<th>Unguided i-RFCBT (n=76)</th>
</tr>
</thead>
</table>
There was no overall difference in incidence of depression ($P = .64$): 29% ($N = 18$) of participants receiving guided i-RFCBT and 33% ($N = 23$) of participants receiving usual care experienced MDE during the follow-up period. A Cox proportional hazard model was conducted, adjusting for past depression as a stratification variable. Gender, as the other stratification variable, was also considered for inclusion in the model. Because the majority (83%) of participants were female and there was no significant effect of gender, this was not included in the analysis. Additionally, as baseline stress was expected to increase risk of depression and Topper et al. [27] controlled for stressful life events, we included severity of baseline stress in the model. As expected, history of depression significantly increased risk, with participants with a history of depression over two and a half times more likely to experience an MDE than participants without: $HR = 2.62$, 95% CI [1.37, 5.01], $P = .004$.

Baseline stress marginally increased risk of MDE: $HR = 1.40$, 95% CI [0.99, 1.99], $P = .06$.

When controlling for both past depression and baseline stress, there was a 34% reduced risk

<table>
<thead>
<tr>
<th></th>
<th>Guided i-RFCBT</th>
<th>Usual Care</th>
<th>usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: N Female (%)</td>
<td>64 (83)</td>
<td>68 (83)</td>
<td>64 (84)</td>
</tr>
<tr>
<td>Age in years: M (SD)</td>
<td>20.27 (1.55)</td>
<td>20.43 (1.65)</td>
<td>20.53 (1.30)</td>
</tr>
<tr>
<td>Ethnicity: N White (%)</td>
<td>70 (91)</td>
<td>77 (94)</td>
<td>67 (88)</td>
</tr>
<tr>
<td>English mother tongue: N (%)</td>
<td>71 (92)</td>
<td>75 (91)</td>
<td>64 (84)</td>
</tr>
<tr>
<td>Previous major depressive episode: N Yes (%)</td>
<td>29 (38)</td>
<td>34 (41)</td>
<td>29 (38)</td>
</tr>
<tr>
<td>Received previous mental health treatment: N Yes (%)</td>
<td>38 (49)</td>
<td>38 (46)</td>
<td>31 (41)</td>
</tr>
<tr>
<td>Family history of depression: N Yes (%)</td>
<td>39 (51)</td>
<td>42 (51)</td>
<td>33 (43)</td>
</tr>
<tr>
<td>Parent with history of depression: N Yes (%)</td>
<td>34 (44)</td>
<td>34 (41)</td>
<td>29 (38)</td>
</tr>
<tr>
<td>Reported history of sexual abuse: N Yes (%)</td>
<td>7 (9)</td>
<td>5 (6)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Reported history of physical abuse: N Yes (%)</td>
<td>7 (9)</td>
<td>1 (1)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Reported history of emotional abuse: N Yes (%)</td>
<td>17 (22)</td>
<td>10 (12)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>PHQ-9: M (SD)</td>
<td>5.6 (4.1)</td>
<td>5.6 (3.2)</td>
<td>5.4 (3.6)</td>
</tr>
<tr>
<td>GAD-7: M (SD)</td>
<td>6.6 (4.3)</td>
<td>7.3 (4.2)</td>
<td>7.1(4.0)</td>
</tr>
<tr>
<td>PSWQ: M (SD)</td>
<td>61.9 (9.0)</td>
<td>62.0 (9.5)</td>
<td>60.3 (10.5)</td>
</tr>
<tr>
<td>RRS: M (SD)</td>
<td>47.9 (11.1)</td>
<td>49.8 (10.6)</td>
<td>47.2 (10.7)</td>
</tr>
<tr>
<td>Number of stressful events in past 3 months: M (SD)</td>
<td>3.6 (2.3)</td>
<td>3.8 (2.4)</td>
<td>3.4 (1.8)</td>
</tr>
<tr>
<td>Subjective rating of worst event</td>
<td>2.20 (1.11)</td>
<td>2.57 (0.96)</td>
<td>2.53 (0.92)</td>
</tr>
</tbody>
</table>

Note. ITT=intention-to-treat; PHQ-9 = Patient Health Questionnaire; GAD-7 = Generalised Anxiety Disorder Screener; PSWQ = Penn State Worry Questionnaire; RRS = Ruminative Response Scale.
of depression in the guided i-RFCBT condition relative to usual care, although this difference was not significant: HR = 0.66, 95% CI [0.35, 1.25], \( P = .20 \) (see Figure 2).

*Figure 2.* Survival curves for guided i-RFCBT and usual care controls, adjusted for past depression and baseline stress

Because the i-RFCBT intervention is designed to reduce habitual rumination in response to stress, because rumination interacts with stressful life events to predict depression [38], and given the impact of stress and history of depression on incidence of MDE, we hypothesised that high-ruminators with greater levels of baseline stress would experience a greater benefit from the intervention, and therefore examined the potential interactions between intervention condition and baseline stress, and intervention condition and history of depression within the Cox-proportional hazard analysis. There was no differential effect of
intervention between first onset (i.e., no history of depression) or relapse/recurrence (i.e., prior history of depression) for incidence of major depression and this interaction was removed from the final model (HR: 0.54, 95% CI [0.15, 1.94], $P = .34$; guided i-RFCBT: 38.9% first onset; 61.1% relapse vs. usual care: 36.4% first onset; 63.6% relapse). Both the effects of past depression (HR: 2.52, 95% CI [1.32, 4.81], $P = .005$) and baseline stress (HR: 1.99, 95% CI [1.22, 3.24], $P = .006$) remained significant. As hypothesised, there was a significant interaction of intervention condition by baseline stress (HR: 0.43, 95% CI [0.21, 0.87], $P = .02$), indicating a greater benefit of guided i-RFCBT relative to usual care (risk of MDE decreased by 57%) for undergraduates with higher baseline stress.

Plotting the interaction between intervention group and baseline stress (see Figure 3) suggests that at higher levels of stress, guided i-RFCBT markedly reduces the risk of a depressive episode relative to usual care, with this effect reversing at low levels of stress. However, since only a small number of participants reported low levels of baseline stress (13.1% scoring either 0 or 1), this reversal is based on low power, and needs to be treated with caution.
As further sensitivity analyses, to investigate the effect of compliance on outcomes, we conducted a complier average causal effect (CACE) analysis, using the Loeys and Goetghebur [65] method, which only allows for inclusion of the randomisation variable in the model, and using regression based adjustments to include past depression and baseline stress, which compares compliers in the intervention group to all other participants [67]. The mean completion for guided i-RFCBT was 3.46 (SD = 2.25) for the full ITT sample (N = 159), with 46.34% (38/82) compliant by completing at least 4 of the 6 modules. Rates of compliance were higher among those with follow-up outcome data (N = 132) as used for the CACE.
analysis, at 60.32% (38/63). The results of the CACE analyses (see Supplement 1) were equivalent to the ITT analysis. We therefore only report the primary ITT analysis.

**Secondary analyses on PHQ, GAD, RRS and PSWQ**

Baseline adjusted ANCOVAs were conducted for each of the symptom measures, at each of the three follow-ups. Estimated means, between-group differences and confidence intervals are displayed in Table 2 for the case completers and following multiple imputations (50 imputations). For the complete cases, at 3 months, rumination scores were significantly lower for guided i-RFCBT relative to usual care; at 6 months, both worry and depression scores were significantly lower for guided i-RFCBT relative to usual care, and there was no evidence of significant between-group differences at 15 months. Similar patterns were found when using multiple imputation to account for differing levels of missing data across the follow-ups.

**Retention, acceptability and effect sizes of unguided i-RFCBT**

Nineteen (25%) unguided participants did not complete any follow-up assessments. Participants were significantly more likely to be lost to follow-up in unguided i-RFCBT than in usual care: $\chi^2(1) = 4.53, P = .03$.

Due to the exploratory nature of the unguided version of i-RFCBT, no formal CACE analysis of compliance was undertaken for the unguided intervention. In the full ITT sample, unguided participants completed an average of 2.66 modules ($SD = 2.35$). Rates of compliance (38.16% unguided) were not significantly different from guided i-RFCBT ($\chi^2(1) = 1.08, P = .30$).
Table 2. Baseline adjusted symptom measures at 3, 6 and 15 months: guided i-RFCBT vs. usual care controls

<table>
<thead>
<tr>
<th>Time-point</th>
<th>Measure</th>
<th>Guided i-RFCBT</th>
<th>Usual care</th>
<th>Difference [95% CI]</th>
<th>MI-Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean [95% CI]</td>
<td>Mean [95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up 1 (3 months)</td>
<td>PHQ9</td>
<td>4.75 [3.74, 5.76]</td>
<td>5.40 [4.48, 6.33]</td>
<td>-0.65b [-2.02; 0.72]</td>
<td>-0.55b [-2.05- 0.96]</td>
</tr>
<tr>
<td>N = 114</td>
<td>GAD7</td>
<td>5.58 [4.51, 6.66]</td>
<td>6.27 [5.28, 7.25]</td>
<td>-0.69b [-2.15; 0.78]</td>
<td>-0.53b [-2.14, 1.09]</td>
</tr>
<tr>
<td></td>
<td>PSWQ</td>
<td>57.27 [54.85, 59.69]</td>
<td>58.45 [56.23, 60.67]</td>
<td>-1.18b [-4.46, 2.11]</td>
<td>-0.75b [-4.35, 2.86]</td>
</tr>
<tr>
<td></td>
<td>RRS</td>
<td>44.34 [41.66; 47.02]</td>
<td>48.21 [45.73, 50.68]</td>
<td>-3.87b [-7.53, -0.21]</td>
<td>-3.69b [-8.01, 0.63]</td>
</tr>
<tr>
<td>Follow-up 2 (6 months)</td>
<td>PHQ9</td>
<td>3.70 [2.48, 4.92]</td>
<td>5.52 [4.42, 6.62]</td>
<td>-1.82b [-3.46, -0.18]</td>
<td>-1.97b [-3.87, -0.063]</td>
</tr>
<tr>
<td>N = 105</td>
<td>GAD7</td>
<td>4.72 [3.44, 5.99]</td>
<td>6.06 [4.91, 7.20]</td>
<td>-1.34b [-3.05, 0.38]</td>
<td>-1.15b [-3.16, 0.85]</td>
</tr>
<tr>
<td></td>
<td>PSWQ</td>
<td>54.83 [52.19, 57.48]</td>
<td>58.41 [56.03, 60.79]</td>
<td>-3.58b [-7.14, -0.02]</td>
<td>-2.71b [-6.68, 1.25]</td>
</tr>
<tr>
<td></td>
<td>RRS</td>
<td>41.74 [38.15, 45.34]</td>
<td>46.35 [43.12, 49.58]</td>
<td>-4.60a [-9.47, 0.26]</td>
<td>-3.98a [-9.48, 1.52]</td>
</tr>
<tr>
<td>Follow-up 3 (15 months)</td>
<td>PHQ9</td>
<td>4.47 [3.23, 5.71]</td>
<td>4.82 [3.73, 5.91]</td>
<td>-0.35a [-2.00, 1.30]</td>
<td>-0.38a [-2.30, 1.55]</td>
</tr>
<tr>
<td>N = 108</td>
<td>GAD7</td>
<td>4.42 [3.16, 5.68]</td>
<td>5.73 [4.62, 6.83]</td>
<td>-1.31b [-2.99, 0.38]</td>
<td>-1.10b [-2.10, 0.80]</td>
</tr>
<tr>
<td></td>
<td>PSWQ</td>
<td>54.81 [51.71, 57.91]</td>
<td>58.11 [55.39, 60.84]</td>
<td>-3.30b [-7.43, 0.82]</td>
<td>-1.74b [-6.53, 3.06]</td>
</tr>
<tr>
<td></td>
<td>RRS</td>
<td>46.15 [42.59, 49.72]</td>
<td>44.65 [41.53, 47.78]</td>
<td>1.50b [-3.28, 6.28]</td>
<td>1.16b [-3.99, 6.31]</td>
</tr>
</tbody>
</table>

Note. PHQ-9 = Patient Health Questionnaire; GAD-7 = Generalised Anxiety Disorder Screener; PSWQ = Penn State Worry Questionnaire; RRS = Ruminative Response Scale.

*Estimates of hazard ratios for unguided i-RFCBT vs. usual care*

No formal significance analyses were undertaken, but hazard ratios and confidence intervals were estimated relative to usual care. Using a Cox-proportional hazard model including past depression and baseline stress, unguided i-RFCBT showed a 36% reduced risk of developing a depressive episode relative to controls: HR: 0.64; 95% CI [0.33, 1.24]. A similar interaction between intervention and baseline stress was found as for guided i-RFCBT (HR: 0.48, 95% CI [0.23, 1.00], such that unguided i-RFCBT had larger effect sizes for undergraduates with moderate to severe levels of baseline stress (see Figure 3).

Between group differences for unguided i-RFCBT vs. usual care were estimated with baseline adjusted ANCOVAs for both case completers and using multiple imputations (50 imputations). Estimated means and confidence intervals are displayed in Table 3. Due to the exploratory nature of this comparison, significance testing was not conducted. Patterns of
change and confidence intervals indicate similar symptom changes to those found in the guided i-RFCBT vs. usual care control ANCOVAs.

Table 3. Baseline adjusted symptom measures at 3, 6 and 15 months: unguided i-RFCBT vs. usual care controls

<table>
<thead>
<tr>
<th>Time-Point</th>
<th>Measure</th>
<th>Unguided i-RFCBT</th>
<th>Usual care</th>
<th>Difference</th>
<th>MI-Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up 1 (3 months)</td>
<td>PHQ9</td>
<td>4.02 [3.07, 4.96]</td>
<td>5.21 [4.33, 6.10]</td>
<td>-1.20 [-2.49, 0.10]</td>
<td>-1.18 [-2.65, 0.28]</td>
</tr>
<tr>
<td></td>
<td>GAD7</td>
<td>4.94 [3.90, 5.99]</td>
<td>5.98 [5.01, 6.96]</td>
<td>-1.04 [-2.47, 0.39]</td>
<td>-1.06 [-2.60, 0.49]</td>
</tr>
<tr>
<td></td>
<td>PSWQ</td>
<td>55.77 [53.26, 58.28]</td>
<td>57.60 [55.26, 59.95]</td>
<td>-1.84 [-5.28, 1.61]</td>
<td>-1.35 [-4.87, 2.17]</td>
</tr>
<tr>
<td></td>
<td>RRS</td>
<td>44.47 [41.89, 47.06]</td>
<td>47.01 [44.60, 49.42]</td>
<td>-2.54 [-6.08, 1.01]</td>
<td>-2.42 [-6.19, 1.34]</td>
</tr>
<tr>
<td>Follow-up 2 (6 months)</td>
<td>PHQ9</td>
<td>4.38 [3.20, 5.56]</td>
<td>5.35 [4.30, 6.40]</td>
<td>-0.97 [-2.56, 0.61]</td>
<td>-1.04 [-2.89, -0.81]</td>
</tr>
<tr>
<td></td>
<td>GAD7</td>
<td>4.20 [2.96, 5.44]</td>
<td>5.93 [4.83, 7.03]</td>
<td>-1.73 [-3.38, -0.07]</td>
<td>-2.09 [-3.92, -0.28]</td>
</tr>
<tr>
<td></td>
<td>PSWQ</td>
<td>54.51 [51.60, 57.42]</td>
<td>58.06 [55.47, 60.65]</td>
<td>-3.55 [-7.46, 0.36]</td>
<td>-3.35 [-7.36, 0.67]</td>
</tr>
<tr>
<td></td>
<td>RRS</td>
<td>41.27 [38.07, 44.47]</td>
<td>45.20 [42.35, 48.04]</td>
<td>-3.93 [-8.22, 0.37]</td>
<td>-4.12 [-8.94, 0.69]</td>
</tr>
<tr>
<td>Follow-up 3 (15 months)</td>
<td>PHQ9</td>
<td>4.20 [3.00, 5.40]</td>
<td>4.69 [3.64, 5.73]</td>
<td>-0.49 [-2.08, 1.11]</td>
<td>-0.92 [-2.61, 0.77]</td>
</tr>
<tr>
<td></td>
<td>GAD7</td>
<td>4.49 [3.28, 5.70]</td>
<td>5.52 [4.46, 6.57]</td>
<td>-1.03 [-2.63, 0.58]</td>
<td>-1.36 [-3.23, 0.52]</td>
</tr>
<tr>
<td></td>
<td>PSWQ</td>
<td>53.78 [50.75, 56.81]</td>
<td>57.56 [54.93, 60.19]</td>
<td>-3.78 [-7.79, 0.24]</td>
<td>-4.34 [-8.57, -0.09]</td>
</tr>
<tr>
<td></td>
<td>RRS</td>
<td>42.07 [38.59, 45.54]</td>
<td>43.85 [40.84, 46.86]</td>
<td>-1.78 [-6.40, 2.83]</td>
<td>-2.61 [-7.93, 2.71]</td>
</tr>
</tbody>
</table>

Note. PHQ-9 = Patient Health Questionnaire; GAD-7 = Generalised Anxiety Disorder Screener; PSWQ = Penn State Worry Questionnaire; RRS = Ruminative Response Scale.

Discussion

The main aim of RESPOND was to test if guided i-RFCBT could be effective in preventing depression in undergraduate students in the UK over one-year follow-up. When controlling for both past depression and baseline stress, guided i-RFCBT reduced the risk of experiencing an MDE by 34% relative to usual care. Whilst this effect size was not significant and smaller than that found by Topper et al. [27], it is broadly consistent with the wider prevention literature, which reports an average reduction in incidence of 21% [10] and a 28% (IRR = .72) reduction in incidence relative to controls for selective, predominantly CBT, interventions [11]. It may be that the current study was underpowered to detect a main preventive effect of i-RFCBT as it used a larger effect size estimate derived from Topper et al. [27].
Guided i-RFCBT was significant at preventing the onset of MDE in high-risk undergraduates relative to usual care when they experienced moderate or above levels of baseline stress, with a hazard ratio of 0.43 when moderated by baseline stress. This is consistent with theoretical models of rumination and the RFCBT treatment approach. The tendency to ruminate about difficulties or low mood is more likely to increase risk for depression in the context of stressful events, which activates that habitual tendency and provides subject matter to ruminate about: even someone with a habitual tendency to ruminate is less likely to have frequent rumination in the absence of any difficulties. Furthermore, one key mechanism by which rumination is proposed to increase vulnerability to depression is by exacerbating and prolonging negative affect and distress [31, 36]: rumination does not have deleterious effects in the absence of negative mood, and it is thus the confluence of stressful events that lower mood and the tendency to ruminate that particularly confers risk for depression [38]. This pattern of results suggests a partial replication of Topper et al. [27], by indicating that guided i-RFCBT may be a helpful preventive intervention for young adults with high levels of rumination and worry, who also experience at least moderate levels of stress.

The findings on the symptom measures suggest guided i-RFCBT was effective in the short to medium term, by reducing rumination, worry, and symptoms of depression at 3 and 6 months relative to usual care, but that these improvements were not sustained over the longer term. Watkins and Nolen-Hoeksema [54] hypothesised that rumination could be conceptualised as a learnt habit, triggered by particular cues such as low mood. Within this analysis, successful long-term reduction of the ruminative habit requires extensive repetition and rehearsal of alternative more adaptive responses to the triggers for rumination. It may be that i-RFCBT was too brief or that participants did not practise enough to produce long-term change in the ruminative habit. It may also be that further engagement and booster sessions
some months after the initial intervention phase would enhance the longer-term effects of the intervention [68]. These could take the form of explicit reminders to practice techniques (flashcards, text/email reminders; [69]) and/or increasing the generalisability of the new more helpful techniques across a broader range of contexts [69].

One possible reason for the difference in findings between the current study and Topper et al. [27] is the means of assessing onset of depression: RESPOND used structured clinical interview, whereas Topper et al. [27] used cut-offs on self-report questionnaires, which may overestimate incidence. Another potential explanation is the different samples. Although their sample included university students, the average age was 17.5 years, compared to 20.4 years in RESPOND. Cases of depression begin to rise steeply from the age of 14 [13] so it may be that the developmental risks during mid to late adolescence differ from those in university students and either that i-RFCBT was more efficacious in younger participants or the base-rate was higher in the younger sample, increasing the power of the trial.

Compliance rates and the pattern of findings and preliminary effect sizes and confidence intervals for unguided i-RFCBT were similar to those for guided i-RFBCT. These findings are in contrast to the literature on web-based acute treatment for depression, which generally demonstrates larger effect sizes for guided interventions relative to unguided [40-42]. This benefit of therapist guidance has also previously been found for indicated preventive interventions in university students [70]. However, the scalability of guided treatments is constrained by the time and availability of therapists. Given the need for widespread dissemination of preventive interventions, an efficacious unguided intervention would be valuable, even if it had somewhat reduced effect sizes relative to the guided version, because it would not be constrained by therapist numbers or availability and could be enormously scaled up to increase accessibility [43].
Additionally, unguided interventions may benefit a previously unreached population as many university students do not seek professional help for mental health difficulties [22, 23] and could therefore be more attracted to self-help interventions. In support of this increased reach, an unguided preventive intervention for students with elevated distress ratings reduced depressive symptoms relative to usual care at 2 months follow-up [71], with two thirds of the trial completers reporting unmet need (needing but not seeking help) in the previous year. As i-RFCBT targets worry and rumination, rather than focusing on depression, this may further attract those who prefer self-help to manage their symptoms as worry is a common experience without the perceived stigma of mental illness [27]. These initial findings on the acceptability and effect sizes of the unguided version provide some promise in terms of potential benefits and suggests the value of further studies to formally test unguided i-RFCBT as a preventive intervention.

Despite the need for larger scale trials to test the robustness of these findings, several strengths of RESPOND are identified. Firstly, the RESPOND trial addressed some of the methodological limitations of the Topper et al. [27] trial by including diagnostic interviewing. This allowed for retrospective diagnoses, capturing any episodes occurring between follow-up interviews, as well as baseline history of depression to assess the effect of prior history on risk of a further MDE.

The use of online and telephone-based measures allowed for recruitment throughout the UK, with participants from a wide range of university departments and geographical locations, increasing the generalisability of the findings within this demographic. The target sample size was achieved through this recruitment strategy and this would therefore be a suitable approach for a larger scale trial of i-RFCBT.

There were several limitations to the study. First, the sample was disproportionately female, limiting the generalisability of the findings. However, females consistently report
higher levels of rumination [72] and higher levels of depression, so a trial selecting on this basis will necessarily attract more female participants.

Second, despite a successful recruitment strategy, there was a considerable proportion of missing data at follow-up, particularly in the intervention conditions. Additionally, follow-up assessments were sometimes incomplete as participants did not always return the questionnaires after the follow-up interview, despite reminders being sent. Future trials should therefore further emphasise to participants the importance of follow-up data during the baseline assessment and ensure all measures are completed during the interview. Third, common to many e-Mental health trials, the participants were not blind to the treatment condition, and, as such, results could have been influenced by response bias and expectancy effects.

Despite these limitations, taken together, the findings from the Topper et al. [27] trial and from the current RESPOND trial, suggest that i-RFCBT is an effective and acceptable intervention for preventing depression in adolescents and undergraduates experiencing high levels of rumination and worry. This demonstrates the value in targeting a preventive intervention at identified risk factors. This intervention may be particularly effective in individuals experiencing high levels of stress. The initial findings relating to unguided i-RFCBT suggest this could also be efficacious in preventing depression, which, if shown to be robust in a fully powered trial, would have significant implications for the scalability of i-RFCBT.

Acknowledgements
This work was supported by University of Exeter, UK, through a matched funded PhD studentship to a successful Wellcome Trust Capital Bid. The funders had no involvement in the research or the submission of this manuscript for publication.
We are grateful to Jenny Cadman, Dr Yusuke Umegaki (therapists for guided therapy and assisting with randomisation) and Rosario Melero (assisting with recruitment and therapist for guided therapy).

Conflicts of Interest
Edward Watkins developed the original RFCBT intervention. The other authors declare they have no competing interests.

Abbreviations
CACE: Complier average causal effect; CBT: Cognitive-behavioural therapy; CMD: Common mental health disorder; CONSORT: Consolidated standards of reporting trials; GAD: Generalised anxiety disorder; GAD-7: Generalised anxiety disorder 7-item scale; GP: General practitioner; HR: Hazard ratio; (i-)RFCBT: (Web-based) Rumination-focused cognitive-behavioural therapy IRR: Incidence rate ratio; ITT: Intention-To-Treat; MDE: Major depressive episode; MI: multiple imputation; PHQ-8/PHQ-9: Patient health questionnaire-8 item or 9 item; PSQ: Psychosis Screening Questionnaire; PSWQ: Penn State Worry Questionnaire; RCT: Randomised controlled trial; RNT: repetitive negative thought; RRS: Ruminative Response Scale of the Response Styles Questionnaire; RT: repetitive thought; SCID-I: Structured Clinical Interview for DSM-IV

References


44. Cook L, Watkins E. Guided, internet-based, rumination-focused cognitive behavioural therapy (i-RFCBT) versus a no-intervention control to prevent depression in high-ruminating young adults, along with an adjunct assessment of the feasibility of unguided i-RFCBT, in the REducing Stress and Preventing Depression trial (RESPOND): study protocol for a phase III randomised controlled trial. Trials 2016;17:1 PMID: 26725476.


