









# BMJ Open Effectiveness of a guided online mindfulness-focused intervention in a student population: Study protocol for a randomised control trial

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## ABSTRACT

**Background** Previous studies show that university students experience higher psychological stress than the general population, resulting in increased vulnerability for mental disorders for the student population. Online mindfulness interventions will be delivered to students as a potentially promising and more flexible approach compared to face-to-face interventions with the aim of improving their mental health. This study purposes to investigate the effectiveness of a guided online mindfulness-focused intervention for university students by using both self-reported and psychobiological measures.

**Methods and analyses** In this multicentre, two-armed randomised controlled trial with a parallel design, a guided version of the online mindfulness-focused intervention ‘StudiCare Mindfulness’ will be compared with a waitlist control group. In total, 120 participants will be recruited at different universities (of Applied Sciences) in (Neu-) Ulm. Data will be assessed prior to randomisation, after eight weeks (post-intervention) and six months after randomisation (follow-up). The primary outcome measure is mindfulness. The secondary outcome measures include depression, anxiety and stress levels, well-being, interoceptive sensibility, emotion regulation and alexithymia. Psychobiological parameters comprise interoceptive accuracy, hair cortisol and FKBP5 genotype. Sociodemographic variables, treatment expectations, side and adverse side effects, as well as intervention satisfaction and adherence will be assessed. All data analyses will be conducted according to the intention-to-treat principle.

**Ethics and dissemination** All study procedures have been approved by the Ethics Committee of Ulm University (application No. 48/18). The findings will be disseminated widely through peer-reviewed publications and conference presentations.

**Trial registration number** DRKS00014701.

## BACKGROUND

Stress is highly prevalent among university students. Previous studies showed that compared to the general population, students have significantly higher stress levels.<sup>1–3</sup> The

## Strengths and limitations of this study

- ‘StudiCare Mindfulness’ is an online mindfulness-focused intervention programme with the aim to increase mindfulness and simultaneously decrease stress levels in order to reduce mental disorders in university students.
- This study considers psychobiological parameters in addition to the common participants’ self-report data prior to randomisation as well as eight weeks and six months after randomisation.
- A follow-up measurement six months after randomisation is administered.
- Because of the use of psychobiological parameters, the study will only be conducted at universities (of Applied Sciences) in (Neu-)Ulm which could reduce generalisability.

increased clinical levels of stress in university students have been linked to a range of stressors such as new experiences and challenges in addition to new social relationships, academic pressures and exams.<sup>2–7</sup> Moreover, such high stress levels have the potential to trigger mental illness such as anxiety and/or depression or to exacerbate a pre-existing mental health condition.<sup>8–14</sup> For example, Auerbach *et al*<sup>15</sup> found in an international WHO survey that more than 20% of university students reported a mental disorder. However, it should be noted that 83% of these students had a mental illness onset before commencing their studies. Similar results were found in another survey, indicating that 23% of university students met the criteria for a mental disorder.<sup>16</sup> The development of a mental disorder is related to a more severe and chronic disease trajectory, a higher risk of developing comorbidities, decreased academic performance, as well as

an increased probability for dropouts during the university career.<sup>5 9 17-19</sup>

Accordingly, it is crucial to prevent elevated stress levels to reduce the risk of university students developing a mental health disorder. In this context, previous studies revealed that most university students do not use face-to-face interventions and do not seek professional help, although most of the universities provide free health and counselling services.<sup>8 14 20-25</sup> Prohibitive factors to accessing services reported by university students included: lack of time, fear of stigma, the preference to get help and support from family or friends as well as lack of knowledge regarding available services at the university. Thus, internet-based and mobile-based psychological interventions (IMIs) may offer a promising approach to close the gap between these barriers and to provide additional advantages (eg, no need for therapist availability, low-threshold access, stigma-reduction, cost-effectiveness as well as flexibility regarding time and place).<sup>21 22 26-30</sup> Emerging evidence from different studies has also demonstrated that online interventions can be as effective as face-to-face programmes in healthy and clinical populations.<sup>31-33</sup> Furthermore and most importantly, nowadays young people grow up in a digital world and show a preference for using the internet and smartphones daily.<sup>34-36</sup> They are also searching for health information online.<sup>37</sup> However, a study with an Australian sample (mean age 36.6 years) showed that 77% prefer face-to-face interventions.<sup>38</sup> In another study by Ryan and colleagues,<sup>25</sup> findings indicate that nearly 50% of university students (mean age 23.7) in Australia have a preference for online interventions. Consequently, the age range and the context seem to be crucial for understanding the preferences of the type of therapy delivery in different populations.<sup>25</sup> Moreover, Stallman and Kavanagh<sup>39</sup> as well as Ebert *et al*.<sup>26</sup> observed that university students show a high acceptance for and usability of online interventions. A growing body of research found that online interventions are helpful to improve mental health conditions.<sup>26 40-45</sup> These effects can be enhanced by therapeutic guidance, meaning that participants receive additional support from an expert, either online or face-to-face while receiving the online intervention.<sup>6 46</sup>

One opportunity to improve mental and physical health is mindfulness. Mindfulness is the awareness of the present moment in an open, accepting and non-judgmental way with the focus on internal bodily signals (eg, ones' breathing and other bodily sensations<sup>47-49</sup>) as well as external stimuli (eg, sounds, pictures, behaviour<sup>50</sup>). Several studies found positive effects of a mindfulness-based intervention on mental and physical health conditions, independent of whether these included healthy or clinical participants.<sup>51-59</sup> Furthermore, Wahbeh *et al*.<sup>59</sup> observed in their study sample that there was a preference for online mindfulness-based interventions compared to group or one-by-one interventions. As there are clear benefits of mindfulness-based interventions as well as online interventions such as e-health programmes,

it seems timely to combine these approaches to reduce stress and, therefore, to improve mental health in a student population.

Numerous studies<sup>43 60-63</sup> and meta-analyses<sup>64 65</sup> found evidence for the efficacy of online mindfulness-based interventions with the focus on self-reported health variables (eg, depression, anxiety, and stress). For example, Spijkerman *et al*.<sup>64</sup> compared 15 randomised control trials and showed small to medium effect sizes regarding the reduction of anxiety ( $g=0.22$ ; 95% CI: 0.05 to 0.39), improvement of depression ( $g=0.29$ ; 95% CI: 0.13 to 0.46), well-being ( $g=0.23$ ; 95% CI: 0.09 to 0.38), and mindfulness ( $g=0.32$ ; 95% CI: 0.23 to 0.42) in healthy samples as well as samples with mental disorders. Especially for stress reduction, a large effect was shown ( $g=0.51$ ; 95% CI: 0.26 to 0.75). Similar results were found in another meta-analysis conducted by Jayewardene *et al*.<sup>65</sup> The authors compared eight studies focusing on the effects of online mindfulness interventions in non-clinical populations with subclinical mental health conditions ( $g=0.28$  to 0.42; 95% CI: 0.15 to 0.67). Moreover, these results showed further improvements in mental health at follow-up ( $g=0.47$  to 0.70; 95% CI: 0.14 to 1.13). Even though these findings are promising, self-report data might substantially overestimate the effectiveness of interventions. Hence, the field should move forward to include more objective data to verify the promising results by including assessments of psychobiological variables.

Until now, there are no studies regarding the effectiveness of online mindfulness-focused training on psychobiological variables which represent objective markers of mental health conditions. Such variables are not influenced by social desirability, memory problems or a conscious perception.<sup>66</sup> Consequently, psychobiological data provide additional markers to complement the self-reported data and should, therefore, be included in mindfulness and stress-related intervention studies. In this study, we will include psychobiological measurements of interoceptive accuracy as well as cortisol and dehydroepiandrosterone (DHEA). Interoceptive accuracy represents the behavioural assessment of an individual's ability to perceive internal bodily changes which is mostly assessed via the heartbeat perception task.<sup>67</sup> Moreover, interoceptive accuracy is associated with other health-related variables such as emotion perception and regulation, alexithymia, stress, depression, anxiety symptoms and eating behaviour.<sup>68-73</sup> and can be influenced by the mentioned health-related variables. Recent studies focusing on interoceptive accuracy showed mixed results regarding the impact of different offline mindfulness interventions.<sup>74-76</sup>

Two biological indicators of the body's physiological stress response are cortisol and DHEA. While cortisol is a steroid hormone released by the hypothalamic-pituitary-adrenal (HPA) axis in response to stress,<sup>77</sup> DHEA represents an endogenous steroid hormone on the stress response that can antagonise the effect of cortisol.<sup>78</sup> To assess long-term effects of stress, collecting hair samples

is superior to fluid biomaterial (eg, saliva, blood) because hair samples reflect stress levels of weeks or even months and are not influenced by acute stress before or during the measurements, the body's circadian rhythm or hormone levels.<sup>79–82</sup> Accordingly, the ratio between cortisol and DHEA seems to be important. There is only one study showing positive effects of an 8-week body-scan training (one approach of the mindfulness-based stress reduction programme) on cortisol, DHEA and the ratio.<sup>83</sup> Several other studies reveal inconsistent results concerning the effect of mindfulness interventions on stress parameters assessed via saliva or plasma cortisol.<sup>84–89</sup> Moreover, there is no other evidence in previous research of a mindfulness training on DHEA. Besides the study of Schultchen *et al*<sup>83</sup>, some studies measured the sulfated form of DHEA (DHEA-S) and found no effect on DHEA-S after an 8-week mindfulness-based stress programme in a population diagnosed with cancer. To combine both stress markers, different researchers suggest the cortisol/DHEA ratio as a parameter for the endocrine imbalance of HPA regulation.<sup>90–94</sup> Comparable to DHEA, there is only the study of Schultchen *et al*<sup>83</sup> examining the change of the ratio through the body scan and another study by Cruess *et al*<sup>93</sup> that has investigated the cortisol/DHEA-S ratio. The study by Cruess *et al*<sup>93</sup> indicated that men diagnosed HIV positive had an improved ratio after participating in a cognitive-behavioural stress management programme in comparison to a waitlist control group. To sum up, studies examining psychobiological parameters in mindfulness-based programmes are very sparse, though there are some promising results. Nonetheless, such investigations are essential to characterise the long-term effects of mindfulness on psychobiological processes.

Another interesting marker is the gene FKBP5 coding for FK506 binding protein 51 (FKBP51). FKBP51 is a co-chaperone of the glucocorticoid receptor, changing its affinity for cortisol and therefore influencing the reactivity of cortisol-mediated stress signalling in the body. Compared to C-allele carriers (wild type) at position rs1360780, individuals with the T-allele show a higher risk for depression and less clinical responsiveness to antidepressant treatment.<sup>95</sup> Also, T-allele carriers show more pronounced changes in hair cortisol levels with increasing childhood maltreatment compared to C-allele carriers, demonstrating a gen x environment interaction with a dose–response relationship between adverse childhood experiences, a strong predictor for late-life depression and steroid hormones of the body's stress response.<sup>96</sup> In comparison to the other psychobiological stress markers, FKBP5 is usually assessed once because there is no fluctuation. Consequently, this marker will be included as a covariate variable.

An additional focus of the present trial is the effectiveness of guidance during the online mindfulness-focused intervention. Research in this context provides evidence that guidance enhances the efficacy of online interventions on health-related variables.<sup>64 97</sup> In the context of an online mindfulness training for students, only the study of

Mak *et al*<sup>61</sup> provided telephone or email support without a control group.

Taken together, we hypothesise that

1. The primary outcome mindfulness will be improved after the intervention in comparison to a waitlist control group.
2. The secondary outcomes of depression, anxiety, stress levels, interoceptive sensibility, emotion regulation, and alexithymia will also be improved. We assume similar results for the psychobiological variables, including interoceptive accuracy (assessed via the heartbeat perception task) as well as cortisol and DHEA levels in hair.

Further, it should be noted that outcomes can be influenced by various covariates. For example, interoceptive accuracy can be influenced by emotion regulation, alexithymia or depression and anxiety symptoms.<sup>68 71–73</sup> Therefore, we will test for potential effect-modifying variables on an exploratory level. Lastly, we intend to explore and analyse the participants' satisfaction, adherence, and acceptance of the intervention.

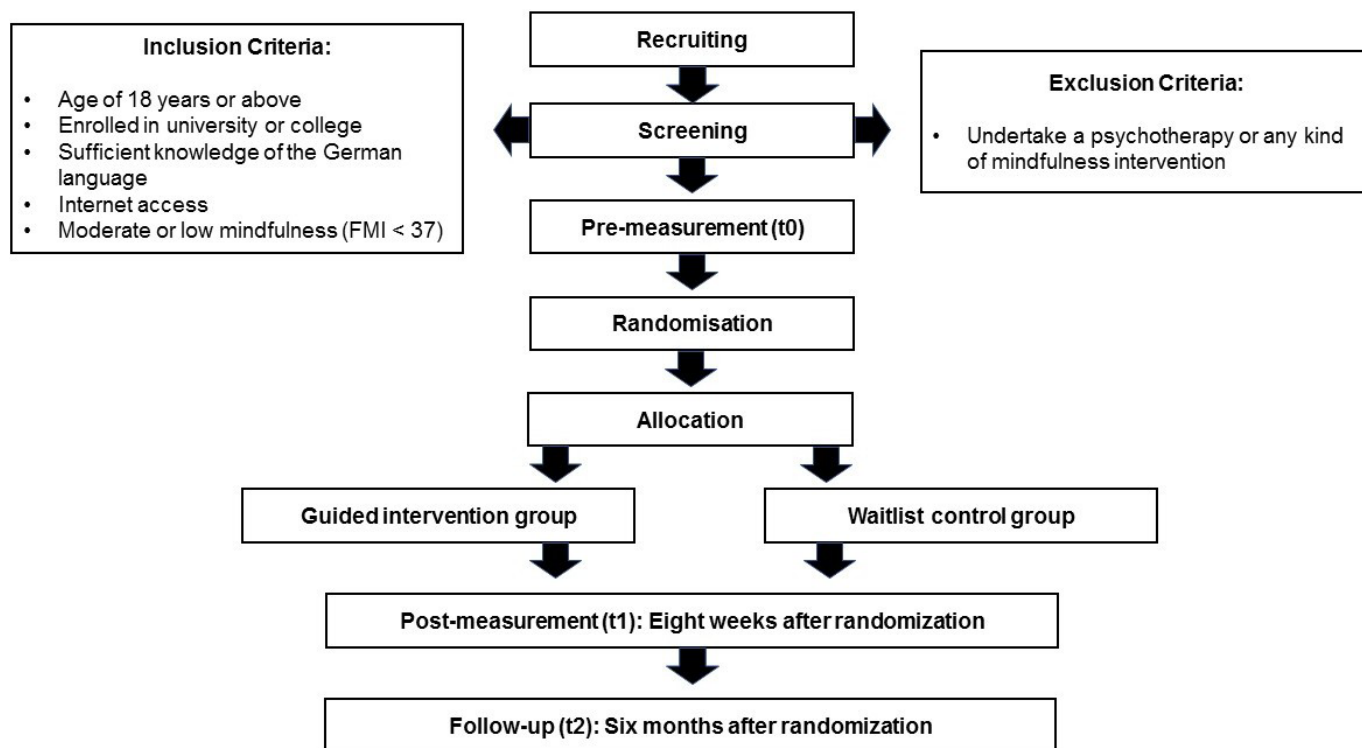
## METHODS

### Study design

This project is a two-armed randomised controlled trial with a parallel design comparing the effectiveness of a guided version of the online, preventive mindfulness intervention 'StudiCare Mindfulness' to a waitlist control group (see [figure 1](#) for flow chart). The research aims to examine the effectiveness of 'StudiCare Mindfulness' on different self-reported and psychobiological health-related parameters at three measurement points (before the intervention as well as eight weeks and six months after randomisation). Moreover, the individuals' adherence, acceptance, and satisfaction are measured to identify possibilities to improve the intervention. Participants of both the control and the intervention group have access to treatment as usual. Thus, participants can use other support or treatment options that will be monitored in order to control for potential confounding effects.

Two departments of the Ulm University are involved in the project, including the Department of Clinical and Health Psychology and the Department of Clinical Psychology and Psychotherapy. It should be noted that this is a cooperation project. Besides the presented study in this protocol, there is another parallel mindfulness trial, investigating the effectiveness of a 'guidance on demand' and an unguided version of 'StudiCare Mindfulness' in comparison to a waitlist control group.<sup>98</sup>

The present study is conducted and will be reported according to the Consolidated Standards of Reporting Trials 2010 Statement<sup>99</sup> and the guidelines for executing and reporting internet intervention research.<sup>100</sup> The study protocol complies with recommendations of the Standard Protocol Items: Recommendations for Interventional Trials 2013 Checklist for clinical trial protocols.<sup>101</sup>



**Figure 1** Flow chart of the study design. FMI, Freiburg Mindfulness Inventory.

The ‘StudiCare Mindfulness’ trial is carried out as part of the ‘StudiCare’ project funded by BARMER, a cooperation of the Universities of Erlangen-Nuremberg and Ulm. The overall project aims to improve college university students’ well-being by evaluating their mental health in longitudinal panel surveys as well as developing and offering a broad assortment of internet-based interventions for psychological and behavioural issues (such as procrastination, examination anxiety, physical activity). It is embedded in the ‘World Mental Health Survey International College Student’ project<sup>102</sup> and the ‘Caring Universities’ project.<sup>103</sup>

#### Patient involvement

University students as target end users of ‘StudiCare Mindfulness’ were involved in the development process of the intervention. They will also be involved in the conduct and the reporting of the research, however, not in their role as end users but in their role as scientists. The public will be informed about the results via several ways, among other publications, lectures and workshops.

#### Eligibility criteria

Participants providing written informed consent and fulfilling the following inclusion criteria for participation will be applied: (a) age of 18 or above, (b) enrolled at Universities (of Applied Sciences) in Ulm or Neu-Ulm, (c) sufficient knowledge of the German language, (d) internet access, (e) moderate to low mindfulness (Freiburg Mindfulness Inventory (FMI)<37); this cut-off was chosen as it represents the medium value of the FMI in subjects from the general population.<sup>104</sup> Participants

are excluded from the study if they currently undertake psychotherapy or any mindfulness intervention. To investigate if participants are eligible, they have to fill out a screening questionnaire.

#### Setting/recruitment

Recruitment has started in May 2018 and will continue until the target sample size of 120 participants will be reached. Participants are recruited from particular different universities in (Neu-)Ulm, including Ulm University, Ulm University of Applied Sciences and Neu-Ulm University of Applied Sciences because psychobiological parameters have to be assessed on site. The following recruiting channels are used: email, flyers and posters, social media, student unions, and student counselling services. University students get information about the ‘StudiCare’ offers and a link to the homepage ([www.studicare.com](http://www.studicare.com)), where they can get further information and register for the IMIs. Once registered, they receive an email with a link to the screening questionnaire. Depending on the location of their university, participants are either allocated to Kuechler *et al*’s trial<sup>98</sup> (all other cooperating universities in Germany, Austria and Switzerland) or to the present study (students from different universities (of Applied Sciences) in Ulm and Neu-Ulm), as psychobiological tests demand actual on-site attendance. Once the screening is completed, participants receive an email with further information on the study as well as an informed consent form which they are required to send back to the study staff via email. When written consent is obtained and the pretest completed, another email is sent to inform



participants about their group allocation (intervention or waitlist control group). If participants are part of the intervention group, they will also receive a link to the intervention. Participants are informed that ‘StudiCare Mindfulness’ cannot replace psychotherapy and are recommended to seek counselling/psychotherapy in case of distinctive mental health problems. Additionally, they are provided with alternative treatment options and contact details (this information is also given to participants who do not meet the selection criteria).

### Randomisation

After completing the baseline assessment, participants are randomly allocated to one of two study groups (guided intervention vs. waitlist control group) by an independent member of Ulm University not otherwise involved and therefore blinded to all processes of the study. Via an automated, online-based randomisation programme ([www.sealedenvelope.com](http://www.sealedenvelope.com)), permuted block randomisation is performed with an allocation ratio of 1:1 and variable block sizes of 2 and 4 (randomly arranged).

### Intervention

The online mindfulness-focused intervention consists of seven weekly, target-group-specific modules of approximately 60 min. each. Additionally, two booster sessions are activated four and twelve weeks after completion of the seventh module in order to enhance sustainability of the intervention effects. These booster sessions include a summary of the seven previous modules. Our aim was to give participants the possibility to collect a repertoire of useful methods. Beyond that, already completed sessions are accessible and can be repeated as often as participants wish to. All modules contain information on stress, well-being, and mindfulness with a weekly alternating focus on different topics such as interoception, dysfunctional and beneficial thinking, values, and goals. Whereas these contents are provided via texts, images, and interactive elements (such as quizzes or conditional content), the focus of the intervention lies on the regular practice of mindfulness exercises such as body scans, breathing meditations, or mindful yoga. Therefore, each module includes downloadable audio files as well as mindfulness diaries to be completed in weekly homework assignments. At the beginning of each module, participants are encouraged to reflect on their assignments and also on their most and least mindful moments of the week. The content of the intervention is mainly based on Acceptance and Commitment Therapy<sup>105</sup> as well as on mindfulness-based stress reduction<sup>106</sup> and also includes some elements of stress management<sup>107</sup> and cognitive-behavioural therapy. We summarised the different methods as one mindfulness-focused intervention.

The intervention’s primary goal is to increase the student participants’ mindfulness and psychological flexibility in order to enable them to manage their daily hassles flexibly. Furthermore, the intervention was mainly developed by the Department of Clinical Psychology and

Psychotherapy, Ulm University. Its efficacy has already been demonstrated in a randomised controlled trial.<sup>108</sup> Based on participants’ feedback, the different sessions were adapted and further refined in cooperation with the Department of Clinical and Health Psychology, Ulm University. Moreover, the two weekly sessions (‘Mindfulness body perception’ and ‘Body and sense’) were also extended. **Table 1** summarises the topics and contents of each module. The intervention is available for participants on the Minddistrict platform ([www.minddistrict.com](http://www.minddistrict.com)), a company specialised in the provision of internet-based health interventions. Participants can get access to the platform via their personal username and password on a 24/7 basis. All transferred data will be secured based on ISO27001 and guidelines NEN7510.

### Guidance and promotion of adherence

Participants randomised to the intervention will receive support by an e-coach. They can contact their e-coach in case of questions or if they wish to get feedback for any of their completed modules. E-coaches are trained and supervised psychologists (by HB, AMK) that give semi-standardised feedback within two working days after participants have finished their modules, following an e-coach manual. Whenever participants have questions or wish to get feedback on their module input, they can contact their personal e-coach via the Minddistrict platform’s message function. At the beginning of the intervention, each participant receives a welcoming message in which their e-coach introduces himself. Additionally, the first module explicitly highlights the possibility to contact the e-coach at any time. The feedback content is specific to the participants’ assignments in order to support treatment adherence. It also includes positive reinforcement to encourage and motivate the participants to continue the intervention. E-coaches are instructed to document any responses to questions or the given feedback. This will enable the evaluation of actual usage of a guided intervention by participants.

### Control condition

Participants in the waitlist control group have unrestricted access to any usual treatment options. They receive an information leaflet informing them about alternative support options such as university counselling services, psychotherapy or helplines as well as the advice to seek help in case their well-being declines. Six months after randomisation, participants of the control condition receive the unguided version of the intervention.

### Assessments and outcomes

Assessments take place before (t0; pre-measurement) as well as after eightweeks (t1; post-measurement) and six months (t2; follow-up) after randomisation. All self-report data are collected using the online survey platform ‘Unipark’ ([www.unipark.de](http://www.unipark.de)). Furthermore, participants come to the laboratory of the Department Clinical and Health Psychology to collect the psychobiological data

**Table 1** Overview of the different topics and contents of each module

Module	Aims and content	Examples of exercises and assignments
1. Being in the here and now	Introducing the concept of mindfulness	Reviewing most and least mindful moments of the day; practising body scan; taking mindful walks
2. Mindful body perception	Practising awareness of body signals	Testing one's heartbeat perception; practising 'heart meditation'; mindful eating and drinking
3. A new perspective on stress	Distancing oneself from stress-inducing thoughts	Identifying former ways of coping with stress; learning techniques to challenge automatic thoughts; meditation exercise
4. Developing beneficial thoughts	Getting to know alternative ways of thinking	Identifying one's 'stress patterns' and developing and internalising beneficial thoughts; practising breathing meditation
5. What makes your life valuable?	Identifying one's values and pursuing one's goals	Writing a speech for one's 70th birthday; setting and pursuing goals with the SMART technique; meditation exercise
6. Being mindful towards yourself	Learning how to accept one's personality traits appreciatively	Exercise to identify different personality traits and corresponding automatic reactions; learning to accept and appreciate all personality traits
7. Training your body and senses	Exercising the ability to enjoy and getting acquainted with the practice of yoga	Mindful chocolate eating exercise; mindful yoga exercises
Booster session 1 (four weeks after completion of module 7)	Repeating module 1 to 3 and different mindfulness exercises	Choosing favourite mindfulness exercises; setting goals for their implementation
Booster session 2 (twelve weeks after completion of module 7)	Repeating modules 4 to 7 and ensuring long-term integration of mindfulness into daily life	Reviewing pursuit of goals in the last two months; identifying potential barriers and developing solutions

(heartbeat perception task, hair samples for cortisol and DHEA as well as buccal cell swabs for the collection of DNA from buccal mucosa for genotyping FKBP5). Biological samples are processed in the Department of Clinical and Biological Psychology under the direct supervision of AK. See [table 2](#) to get an overview of the different outcome measures and assessment time points. Participants receive €20 or 3 course credits as compensation for the laboratory assessment. Importantly, they do not obtain any compensation for participation in the online intervention.

### Primary outcome: Mindfulness

The 14-item short version of the Freiburg Mindfulness Inventory (FMI)<sup>104 109</sup> is used to derive a mindfulness score. The FMI consists of a 4-point Likert scale ranging from 1='rarely' to 4='almost always'. The short version is sensitive to changes and appropriate for investigating subjects without meditation experience.<sup>104</sup> In a study by Heidenreich *et al*<sup>110</sup> a high internal consistency with a Cronbach's Alpha of 0.84 was shown.

### Secondary outcomes

#### Depressive symptoms

The depression module of the Patient Health Questionnaire (PHQ-9)<sup>111</sup> comprises nine items that are rated on a 4-point Likert scale (0='not at all' to 3='nearly every day'). The PHQ-9 is a widely used depression screening that has demonstrated validity and good diagnostic properties (sensitivity of 0.95 and specificity of 0.84) and internal consistency ( $\alpha=0.89$ ).<sup>112</sup>

#### Anxiety

The Generalized Anxiety Disorder Questionnaire (GAD-7)<sup>113</sup> consists of a 7-item anxiety scale ranging from 'not at all' (=0) to 'nearly every day' (=3) and is used to screen for generalised anxiety disorders. Evaluations of the questionnaire show a sensitivity of 0.89, specificity of 0.82 and a good test-retest reliability (intraclass correlation=0.83). The GAD-7 has been identified as a reliable and valid measure of anxiety in the general population with Cronbach's Alpha of 0.89.<sup>114</sup>

#### Stress

The Short Form Perceived Stress Scale (PSS-4), derived from the Perceived Stress Scale,<sup>115</sup> is used to measure the participant's perceived stress as the degree to which situations in one's life are rated as stressful (scale ranging from 0='never' to 4='very often'). The psychometric properties of the PSS-4 are acceptable and reliable across cultures, with Cronbach's Alpha of 0.77.<sup>116</sup>

#### Well-being

The well-established 5-item WHO Well-Being Index (WHO-5)<sup>117</sup> is used to assess subjective psychological well-being. The response scale refers to the frequency of relevant feelings over the past two weeks ranging from 'at no time' (=0) to 'all of the time' (=5). With a sensitivity of 0.86 and specificity of 0.81, WHO-5 is a screening tool for depression which has been demonstrated among several clinical studies. Applicability across study fields and clinical validity is very high.<sup>118</sup>

**Table 2** Summary of the outcome assessments and assessment time points

Variables	Measurement	Screening	T0	T1	T2
<b>Inclusion and exclusion criteria</b>					
Demographic variables	Eg, age, enrolled in a university, internet access, current participation in a mindfulness intervention	X			
Freiburg Mindfulness Inventory-short form	Mindfulness	X			
<b>Primary Outcome</b>					
Freiburg Mindfulness Inventory-short form	Mindfulness		X	X	X
<b>Secondary Outcomes</b>					
Patient Health Questionnaire	Depression		X	X	X
Generalized Anxiety Disorder Questionnaire	Anxiety		X	X	X
Perceived Stress Scale-short form	Stress		X	X	X
WHO Well-Being Index	Well-being		X	X	X
Body Perception Questionnaire	Interoceptive sensibility		X	X	X
Emotion Regulation Questionnaire	Reappraisal and suppression		X	X	X
Toronto Alexithymia Scale	Alexithymia		X	X	X
Heartbeat perception task	Interoceptive accuracy		X	X	X
Cortisol and DHEA	Psychobiological stress level		X	X	X
<b>Covariates</b>					
Demographic variables	Eg, weight, height, psychotherapy		X		
Previous experience with mindfulness, time spent practising mindfulness and use of additional treatment options	Self-reported mindfulness and treatment experience		X	X	X
Genotype FKBP5 (rs1360780)	Gen x environment interaction		X		
Client Expectancy Questionnaire	Treatment expectancy and rationale credibility		X		
Dropout	Intervention adherence		X	X	
Client Satisfaction Questionnaire	Intervention satisfaction			X*	
Inventory for the Assessment of Negative Effects	Potential adverse effect			X*	

\*Only for the intervention group.  
DHEA, dehydroepiandrosterone.

### Interoceptive sensibility

Interoceptive sensibility is assessed via the awareness subscale of the Body Perception Questionnaire (BPQ).<sup>119</sup> It includes 45 items of individual identifications of bodily signals on a 5-point Likert scale, ranging from 'never' (=1) to 'always' (=5). Calculated t scores reflect a standardised value according to a normal distribution based on a mean of 50 and a SD of 10. Previous reliability reports exist only for the short form of the BPQ,<sup>120</sup> showing a categorical omega coefficient between 0.68 and 0.97 and a high retest reliability.

### Emotion regulation

A German translation<sup>121</sup> of the Emotion Regulation Questionnaire (ERQ)<sup>122</sup> is used to assess individual

differences in the habitual use of two emotion regulation strategies, reappraisal and suppression. The questionnaire includes six items measuring reappraisal and four items measuring suppression. Participants are required to indicate whether they agree with each statement on a 7-point Likert scale ranging from 1 (= 'strongly disagree') to 7 (= 'strongly agree'). The ERQ demonstrates good scale score reliability for the suppression (Cronbach's Alpha=0.76) as well for the reappraisal factors (Cronbach's Alpha=0.74).<sup>121</sup>

### Alexithymia

The Toronto-Alexithymia Scale (TAS-20<sup>123</sup>; German adaptation by Kupfer *et al.*<sup>124</sup>) measures alexithymia. The questionnaire consists of 20 items rated on a 5-point Likert

scale (1='strongly disagree'; 5='strongly agree') with total scores ranging from 20 to 100, reflecting a three-factor scale: 'difficulty identifying feelings', 'difficulty describing feelings' and 'externally oriented thinking'. Higher scores on the different subscales indicate higher levels of alexithymia. The TAS-20 is a valid instrument with good internal consistency (Cronbach's Alpha of 0.85 to 0.86) and test-retest reliability.<sup>125</sup>

#### Subjective side effects and adverse events

In a survey with 195 former psychotherapy patients, 94% stated to have experienced negative effects during or after psychotherapy.<sup>126</sup> Consequently, Ladwig *et al*<sup>126</sup> developed the Inventory for the Assessment of Negative Effects which is included to assess any changes in the experiences during or after the treatment in the social and/or work environment and whether they are attributed to the psychotherapeutic intervention. The items cover potential adverse events in the personal, intrapersonal, and social context (eg, 'emotions', 'family and friends'). Four items are rated on a 7-point bipolar scale (-2='worse', +3='better'), the others are rated on a 4-point scale (0='no agreement', 3='full agreement'). The present trial uses an adapted 22-item version covering possible negative effects associated specifically with online training (eg, concerns about data protection). The original scale has demonstrated high internal consistency with a Cronbach's Alpha of 0.86.<sup>126</sup>

#### Intervention satisfaction and adherence

The Client Satisfaction Questionnaire (CSQ)<sup>127</sup> is a validated 8-item tool and is used in a German version adapted for the evaluation of IMIs (ZUF-8).<sup>128</sup> The ZUF-8 comprises eight items, each with a 4-point scale of specific response alternatives (eg, 1='quite unsatisfied', 4='very satisfied'). Good psychometric properties have been demonstrated including Cronbach's Alphas between 0.88 and 0.92.<sup>129</sup> Additionally, qualitative feedback is assessed via a self-developed questionnaire for further optimisation of the intervention. Adherence is operationalised by the number of modules participants complete during the "per protocol" intervention period of eight weeks.

#### Psychobiological outcomes

We also assess psychobiological variables including the heartbeat perception task (=interoceptive accuracy) as well as hair cortisol and DHEA at all three measurement points. The FKBP5 genotype dichotomous model (CC vs. CT/TT carriers) is only measured before the intervention and is used as a covariate in the analyses.

#### Heartbeat perception task

The heartbeat perception task by Schandry<sup>130</sup> assesses the sensitivity for cardiovascular signals, namely interoceptive accuracy. Therefore, participants are instructed to listen to their own heartbeats and count them silently during different intervals. We chose a training interval of 15s for participants to get familiar with the task followed by four test intervals (25, 35, 45 and 60s). Importantly,

participants do not get any information about the lengths of these intervals. They receive start and stop signals for each interval from the investigator. After every stop signal, they have to report their counted heartbeats as well as their confidence ratings (1='total guess/no heartbeat awareness' to 10='complete confidence/full perception of heartbeat'). Biopac MP 150 (sampling rate 1000 Hz) is used for recording the heartbeats.

#### Hair cortisol and DHEA

To assess the changes in the psychophysiology stress level across the time of intervention, cortisol and DHEA are used. Therefore, two strands (~3mm diameter) with a length of minimum 2 cm are obtained from the posterior vertex of each participant. Importantly, hair should be cut as close to the scalp as possible, using a fine medical scissor. The scalp hair is wrapped in aluminium foil and stored at -20°C in a dry, dark place until the analyses start.

#### Gene FKBP5

For the investigation of a possible gen x environment interaction, the FKBP5 genotype is included as another psychobiological variable in the study. Therefore, samples from the buccal mucosa are taken non-invasively using buccal mucosa collection swabs (Salimetrics, UK). DNA from buccal cells is isolated using commercially-available column-based purification techniques (Qiagen, Germany). DNA is tested for quality (260/280 nm absorption) and concentration (Qubit, Thermofisher, USA). TaqMan assays for FKBP5 genotyping at position rs1360780 (T/C-allele) are performed using qPCR technology on a QuantStudio6 machine (Thermofisher, USA).

#### Covariates

To investigate potential effect-modifying influences,<sup>131</sup> several sociodemographic variables are assessed: age, gender, nationality, marital status, study course and number of semesters, weight and height (for the calculation of the body mass index), previous experience with mindfulness, time spent practising mindfulness, psychotherapy experience, and use of additional treatment options (such as psychological counselling or psychotherapy). Regarding the hair analyses, we evaluate current hair colour and colouring, hair structure, and existence of permanent waves. To examine the influence of treatment expectations on outcomes, the ZUF-8 is used which has demonstrated high internal consistency ( $\alpha=0.84-0.85$ ; CEQ).<sup>132</sup> Higher scores represent positive expectations and credibility. Additionally, we collect data in the post-measurement of the online survey regarding the claim of other support (coaching, psychotherapy, psychiatry, family doctor, psychotropic drugs, mindfulness training, other health training or 'StudiCare' projects). Further, if subjects participate in another kind of mindfulness training, they are asked for the format (presence, online, book, coaching).



### Sample size estimation

The sample size estimation based on a calculation of G\*Power V. 3.1.9.2, assuming a small effect size of  $f=0.15$  (consistent with  $d=0.3$ ) in a repeated measurement model and a comparison of two groups. Based on an  $\alpha$ -level of 0.05 and a power of 0.90, the total sample should consist of 120 participants including 60 for the guided intervention group and 60 for the waitlist control group. The assumed effect size of  $d=0.3$  is based on the meta-analysis of Jayewardene *et al*<sup>65</sup> and Spijkerman *et al*<sup>64</sup> regarding online mindfulness-based interventions.

### Dissemination and data processing

The trial was registered prior to the recruitment at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS; ID: DRKS00014701). Participants received written information on study conditions, data security, participation being voluntary and the right to leave the study at any time. To confirm understanding, written consent is obtained from all participants prior to study entry. Data collection is pseudonymised and only accessed by authorised study personnel obliged to secrecy. After data collection is completed, personalised information will be deleted and all data will be completely anonymised. The results will be published in peer-reviewed journals and presented on international conferences.

### Statistical analyses

All statistical analyses will be conducted according to the intention-to-treat principle. Procedures of imputation will be chosen based on patterns and mechanism of missingness (eg, by multiple imputations). Additionally, per protocol analyses will be performed to examine the impact of dropouts on the study results. The significance level for all analyses will be  $p \leq 0.05$  and will be adjusted for multiple comparisons using the Holm-Bonferroni correction method.

Standardised mean differences with 95% CIs will be calculated post-treatment and follow-up to analyse between-group effect sizes. Regression analyses will be performed as a primary method, using linear regression for dichotomous outcomes. Based on the data structure, regression analysis will be adjusted accordingly (eg, use of robust estimation or use of multilevel regression analysis in case of substantial intra-class correlation). Analysed variables will include the covariates (eg, age, gender, gene FKBP5) using path modelling.

## DISCUSSION

This study protocol describes the study design of a randomised controlled trial that investigates psychological health-related variables in addition to the commonly used self-report data of a guided online mindfulness-focused intervention in a student sample. We assume that individuals who participate in the guided intervention will show decreased depression, anxiety, and

stress levels as well as reduced alexithymia in comparison to the waitlist control group. Furthermore, we hypothesise an increase of well-being, interoceptive sensibility, and emotion regulation in the intervention group compared to the waitlist control group. Focusing on different psychobiological variables (interoceptive accuracy, hair cortisol, and DHEA), we expect similar positive effects. In order to find out more about the covariates, we also include sociodemographic data, the gene FKBP5, and expectations regarding the intervention in our analyses. Our study focuses on some aspects discussed in previous studies, aiming at combining these points here. Consequently, this study has several strengths:

### Combination of self-report and psychobiological measurements

In comparison to earlier studies, our investigation includes self-report and psychobiological markers. Consequently, we use subjective as well as objective parameters to emphasise our results, meaning that especially psychobiological markers are less biased compared to the self-report measurements. This is especially based on the research so far, showing that a combination of both is suitable to include advantages and disadvantage of both approaches.<sup>66 67 133</sup> Furthermore, the hair stress markers represent longitudinal markers from the last weeks or even months.<sup>79</sup> In contrast, cortisol measurements such as salivary, plasma, or urine are time-limited and depend on changes associated with circadian rhythm regulation.

### Procedures to improve the adherence level

Our proposed intervention includes different opportunities to improve adherence. This is based on the high dropout rates of 40% to 70% in different online or smartphone interventions.<sup>60 134 135</sup> Firstly, we only include participants with low or moderate mindfulness in our intervention. One reason for choosing this level is a potential higher motivation and interest from participants, resulting in an assumed lower dropout rate in the intervention. However, it should be mentioned that it is only a hypothesis which is not measured in the study. Secondly, we use different modes of delivery in order to increase the adherence level of our online intervention. These modes include text, audio files, self-reflection, homework, instructions, and tips for implementing and transferring intervention components into daily life. Following the main seven intervention modules, participants also get two booster sessions which summarise and repeat the other modules before. Thus, a moderate to long-term intervention effect is obtained, and the adherence level is expected to be high. Thirdly and importantly, we include e-coaching in our training. A current study by Kvillemo *et al*<sup>60</sup> reported that a higher contact level decreases the dropout rate and is an important option that increases the adherence level of participants. The e-coach has the task to give the participants feedback concerning the completed modules and remind them if they do not attend. Additionally, participants get the opportunity to

contact the e-coach via the messenger system of Minddistrict. Lastly, the online mindfulness-focused intervention is tailored to the particular needs of students, which will raise the adherence level and likely enhance the effectiveness of the online intervention.

### Adherence level

To explore the reasons for different adherence levels, participants answer quantitative and qualitative questions regarding the content of modules and their motivation. These responses will help us to adapt and improve the online intervention and accordingly enhance adherence.

### Follow-up measurements six months after randomisation

Several studies reported no follow-up measurements.<sup>60 62 63 136</sup> Other studies used different intervals for the follow-up measurement after the intervention, ranging from two weeks up to six months.<sup>28 43 61 134 137</sup> To focus on the longitudinal effects of our intervention, we examine participants again six months after randomisation.

### Conclusion

Assuming positive results of the present online mindfulness-focused intervention, it could be a helpful opportunity for universities to establish a time- and cost-effective healthcare service. Given the high stress rate in the student population, the present intervention will contribute information and practices to decrease individual's stress levels as well as to improve mental health in general. Another advantage is the prevention of other upcoming mental health problems, resulting from a high stress level. Thus, this stand-alone intervention can provide advantages for users and the healthcare system. Moreover, results will have implications for researchers, healthcare providers, and public health policymakers.

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**Contributors** DS, AMK, DDE, HB and OP initiated this study. AMK, DS, HB and OP contributed to the design of this study. DS, AMK, CS and FW adapted the intervention content and the assessment. DS and AMK are responsible for the recruitment. AK is responsible for the analysis of the biological marker. DS wrote the draft of the manuscript. All authors contributed to the further writing of the manuscript and approved the final version of the manuscript.

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**Competing interests** DS, AMK, DDE, HB and OP were involved in the development of 'StudiCare Mindfulness' or its predecessor versions. AK has received fees for lectures/workshops from chambers of psychotherapists and health insurance companies. HB reports having received consultancy fees and fees for lectures/workshops from chambers of psychotherapists and training institutes for psychotherapists in the e-mental-health context. DDE reports having received consultancy fees/served in the scientific advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and German health insurance companies. He is a stakeholder of the Institute for health training online (GET.ON)

which aims to implement scientific findings related to digital health interventions into routine care.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not required.

**Ethics approval** All study procedures were approved by the Ethics Committee of Ulm University (application No. 48/18).

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**Data availability statement** No data are available. At the moment, this is only a study protocol. Consequently, there are no data that are integrated into the manuscript.

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