


# BMJ Open Vulnerability for alcohol use disorder after adverse childhood experiences (AUDACE): protocol for a longitudinal fMRI study assessing neuropsychobiological risk factors for relapse

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## ABSTRACT

**Background** Adverse childhood experiences (ACE) are common and may predispose affected individuals to various health problems, including alcohol use disorder (AUD). Although a relationship between ACE and AUD has been well-established, potential mechanisms that may underlie this relationship remain to be elucidated. The importance of these mechanisms with respect to relapse risk is of particular interest, given the clinical relevance of relapse in addictions. Thus, the aim of this study is to longitudinally assess the role of clinically relevant variables in the relationship between ACE and AUD, namely stress sensitivity, emotion processing, cue reactivity and cognitive functioning (response inhibition and working memory), in relation to relapse risk.

**Methods and analysis** In this observational, longitudinal case-control study, 36 patients with AUD and heavy drinkers with varying degrees of ACE from a previous project (NCT03758053) as well as newly recruited participants from the same study population will be assessed. Besides measuring long-term relapse in AUD by re-examining these 36 previous participants after 2–2.5 years, factors contributing to short-term relapse will be examined by reassessing all participants on a 3-month follow-up. Furthermore, participants with no or mild ACE will be compared with participants with moderate to severe ACE to assess between-subject differences in risk factors for AUD. Questionnaires and interviews will thus be used to cover individuals' drinking behaviour and ACE. Emotion processing, stress sensitivity, cue reactivity and cognitive functioning will be assessed using task-based functional MRI (fMRI). Additionally, saliva cortisol and blood samples will be taken to measure hormonal stress response and to perform genome wide association analyses, respectively. The general linear model will be applied on the first level fMRI analyses, whereas for the second level analyses and analyses of behavioural data, t-tests, regression analyses, repeated-measures and one-way analysis of variances will be used.

**Ethics and dissemination** This study has been approved by the ethics committee of the Medical Faculty Mannheim

## Strengths and limitations of this study

- ⇒ This study will employ a wide range of methods (questionnaires, interviews, functional MRI, saliva and blood samples), providing several lines of evidence at the behavioural, neuroimaging, genetic and physiological level.
- ⇒ The longitudinal design will enable us to look at changes with respect to the variables of interest over time and relate these changes to long-term relapse risk.
- ⇒ Given the longitudinal nature of this study (follow-up after 2–2.5 years), participants may drop out for various reasons, which could threaten the validity of the results.
- ⇒ Participants cannot be randomly assigned to groups, given that allocation will be based on a preexisting attribute (degree of adverse childhood experiences), which may lead to notably uneven group sizes.
- ⇒ The observational nature of this study merely allows for correlational inferences.

of Heidelberg University (ethics approval number: 2018-560N-MA with amendment from 29 June 2021). The findings of this study will be presented at conferences and published in peer-reviewed journals.

**Trial registration number** NCT05048758; Pre-results, [clinicaltrials.gov](https://clinicaltrials.gov).

## INTRODUCTION

Adverse childhood experiences (ACE) are common across different populations and represent a major public health problem.<sup>1,2</sup> ACE are defined as 'potentially traumatic events that occur in childhood (0–17 years)'.<sup>3</sup> It is important to note that ACE can manifest themselves in different forms, including emotional, sexual and

physical abuse, physical and emotional neglect as well as household challenges (eg, substance abuse in the family).<sup>4</sup> According to the World Health Organization (WHO),<sup>5</sup> it is estimated that around 300 million children are maltreated psychologically or physically between the ages of 2 and 4. There is a large body of evidence indicating that ACE have long lasting consequences on the developing brain as well as physical and mental health.<sup>6</sup> In fact, a multitude of psychiatric disorders can result from ACE such as depression, post-traumatic stress disorder and, of particular interest to the aim of our study, substance use disorders (SUD).<sup>4</sup>

SUD have the highest mortality among all psychiatric disorders.<sup>7</sup> The investigation of the relationship between ACE and SUD has increasingly gained attention in recent years, whereby most studies on this topic were published between the years 2016 and 2020.<sup>8</sup> A recent review by Leza *et al*<sup>8</sup> have found consistent evidence for an association between ACE and a later diagnosis of SUD. The same authors have also found a higher prevalence of ACE among individuals treated for SUD relative to the general population.<sup>8</sup> ACE seem to have a cumulative effect on the risk of SUD development with sexual and physical abuse being more strongly associated with SUD than witnessing domestic violence during childhood.<sup>9</sup> In addition, parental substance abuse is associated with a higher risk of developing SUD in later life, suggesting that specific types of ACE may have a greater clinical significance.<sup>10</sup>

Among SUD, alcohol use disorder (AUD) has been indicated as one of the most prevalent and comorbid disorders.<sup>11–13</sup> AUD is a disabling condition that greatly contributes to morbidity and mortality globally.<sup>14</sup> ACE are often a precursor to AUD, whereby the odds of developing AUD have been found to increase as the number of ACE increases.<sup>15</sup> Importantly, early adolescence is suggested to be a critical period with respect to AUD development, which underlines the clinical relevance of the developmental transition from childhood to adolescence, particularly for individuals who have been exposed to ACE.<sup>12</sup>

Although a relationship between ACE and SUD has been well established,<sup>8 16</sup> there is a lack of empirical findings on the mechanisms underlying this relationship. In addition, it remains unclear how these mechanisms relate to relapse, which is a major problem in SUD. Thus, it is important to identify and elucidate the role of potential mechanisms and their involvement in relapse to gain an insight into the development and maintenance of SUD after ACE, which may provide a fruitful basis for improving prevention and intervention efforts for this subgroup of patients. Given that AUD is one of the most prevalent SUD, this project aims to focus on AUD as an SUD subtype. In the following, SUD will be frequently used as an umbrella term to emphasise that some of the empirical findings are not applicable only to AUD but to SUD in general.

## Current state of knowledge and gaps

Cognitive functioning is increasingly recognised as a key domain that is affected in both ACE and SUD.<sup>17 18</sup> In fact, cognitive deficits, such as memory deficits, may emerge during development as a result of ACE and persist into adulthood.<sup>19</sup> These deficits are also an important characteristic of SUD, which is consistent with the structural finding that both ACE and SUD are associated with a reduced hippocampal volume.<sup>20 21</sup> Edalati and Krank<sup>22</sup> have proposed a model of cognitive pathways, in which impairments in cognitive functions such as behavioural inhibition and working memory are suggested to mediate the relationship between ACE and SUD. Specifically, it is suggested that cognitive impairments may lead to impaired reasoning, which could cause an irrational response to stressful situations, ultimately leading to the development of SUD. This line of reasoning is consistent with the self-medication model of SUD, indicating that substances are used to cope with stress or negative emotions.<sup>23</sup> With respect to relapse, response disinhibition has been found to be a strong predictor in alcohol-dependent patients.<sup>24</sup>

Next to cognitive functioning, emotion regulation is clinically relevant to the development of SUD.<sup>25 26</sup> Evidence suggests that childhood maltreatment is capable of disrupting the development of healthy emotion regulation, which may facilitate what has been referred to as ‘emotion dysregulation’.<sup>27</sup> Emotion dysregulation is a key concept in the development of psychopathology.<sup>28</sup> Wolff *et al*<sup>29</sup> have conducted a study on the role of emotion dysregulation in the relationship between childhood maltreatment and SUD and found that emotion dysregulation could be a mediator in this relationship.<sup>29</sup> At a neural level, ACE have been associated with adaptations in the amygdala, whereby a hyperreactivity to emotional faces has been indicated.<sup>30</sup> A similar result has been found for adolescents at high risk of SUD development,<sup>31</sup> indicating that changes in neural substrates associated with emotional regulation, which may be in part influenced by ACE, could predispose individuals to SUD development.

Stress sensitivity is another important factor in ACE and SUD. A significant dysregulation in the hypothalamic–pituitary–adrenal (HPA) axis has been observed in both ACE and SUD.<sup>32 33</sup> Using the example of AUD, it has been shown that alcohol-induced HPA axis dysregulation contributes to sensitised dopaminergic reward pathways which, in turn, may influence craving and the development of AUD.<sup>32</sup> It is important to note that both stress and drugs such as alcohol activate overlapping pathways, particularly within the reward system.<sup>34</sup> Another important aspect is that chronic alcohol consumption may lead to a decreased influence of prefrontal executive control over stress and reward systems, leading to craving and a greater susceptibility to relapse.<sup>35</sup>

Craving, which is a predictor of relapse, is associated with cue reactivity; that is, neural reactivity can be provoked by alcohol-related cues such as images of alcoholic beverages.<sup>36 37</sup> Vollstädt-Klein *et al*<sup>38</sup> have demonstrated that

neural cue reactivity in response to images of alcohol primarily takes place in the mesocorticolimbic reward system and is associated with an attentional bias, which is consistent with the role of the dopaminergic system in attributing motivational salience.<sup>39</sup> Other findings show that social drinkers, relative to heavy drinkers, exhibit increased prefrontal activation and thus more cognitive control, while heavy drinkers show higher activation in the dorsal striatum associated with alcohol craving.<sup>40</sup>

Taken together, cognitive functioning, emotion regulation, stress sensitivity and cue reactivity play an important role in both ACE and SUD. It is important to look at these mechanisms in relation to one another, rather than in isolation. The ways in which both constructs influence each other need to be further examined. In addition, it is important to consider the timing and severity of ACE in the development of SUD.<sup>6</sup> Lastly, it is crucial to further elucidate relapse risk associated with these mechanisms.

### Relevance of the subject

Given the high prevalence of ACE and the high prevalence and mortality rate of AUD relative to other psychiatric disorders,<sup>7</sup> it is of great importance to study ACE and their consequences in affected individuals such as their influence on the pathogenesis of AUD. This study seeks to improve our understanding of potential mechanisms involved in the relationship between ACE and AUD, particularly with respect to relapse, which is a central issue in SUD. The clinical implications of these findings may provide a fruitful basis for improving prevention and intervention efforts that target the mechanisms of interest.

### Objectives

The aim of this study is to investigate the modulating impact of ACE on neural activity in specific brain regions associated with emotion processing, stress sensitivity, cue reactivity and cognitive functioning (response inhibition and working memory) in individuals with AUD. Specifically, we are interested in how these mechanisms relate to relapse and abstinence at a behavioural, neurobiological and physiological level.

As this is a follow-up project, which reassesses patients from a previous project (see <https://clinicaltrials.gov/ct2/show/NCT03758053>; in the following referred to as 'project 1'), the aim is to assess the effects of ACE on emotion processing, stress sensitivity and cue reactivity in relation to relapse in patients with AUD within a time period of 2–2.5 years. Additionally, we aim to examine (short-term) relapse by performing a follow-up screening after 3 months of completing the current project to relate it to neural, clinical and behavioural parameters. Given that neural correlates of cognitive functioning have not been measured in project 1, we can only look at their correlation with short-term (and not long-term (2–2.5 years)) relapse. In the hypotheses below, 'T1' refers to project 1, while 'T2' refers to the current project.

The hypotheses are as follows:

#### Hypothesis 1

ACE severity modulates activation in the hippocampus during a working memory task (n-back task) and in prefrontal regions during a response inhibition task (stop-signal task).

#### Hypothesis 2

ACE severity modulates performance on the cognitive tasks from hypothesis 1.

#### Hypothesis 3

ACE severity is associated with alcohol-related measures (eg, craving, alcohol consumption) before the assessment (T1 and T2, respectively).

#### Hypothesis 4

Alcohol-related measures (eg, craving, alcohol consumption) as measured at T1 are associated with relapse risk (in the 2–2.5 years period).

#### Hypothesis 5

Neural measures at T1 (emotion processing, stress sensitivity and cue reactivity) are associated with relapse risk (in the 2–2.5 years period).

#### Hypothesis 6

Deficits in response inhibition and working memory (T2) are associated with (short-term) relapse risk.

#### Hypothesis 7

Neural measures at T2 are associated with (short-term) relapse risk.

#### Hypothesis 8

ACE severity modulates cortisol levels during the stress task (ScanSTRESS task).

## METHODS

### Study sample

Our non-probability sample will be drawn from residents of Mannheim and Heidelberg, Germany. A total of 36 participants (excluding healthy controls) from project 1 will be recontacted for reassessment after 2–2.5 years of participation in project 1. As it is unclear how many participants from the first study will participate in this follow-up study, new participants from the same study population will be recruited internally via the Department of Addictive Behaviour and Addiction Medicine and Addiction Day Unit at the Central Institute of Mental Health in Mannheim, Germany, and externally via advertisements on websites and flyers. Recruitment is planned to start in September 2021 and expected to end in December 2023.

The inclusion criteria for this study will be as follows: (1) all participants must be sufficiently able to communicate with the investigator, more precisely sufficiently fluent in German, to understand instructions and provide written informed and fully informed consent before participating in the study, and to answer questions in



oral and written form, (2) age between 18 and 65 years, (3) normal or correctable eyesight and (4) diagnosis of AUD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or heavy drinking (alcohol intake on more than 5 days/week and >40 g/day (women) or >60 g/day (men) with or without ACE.

Exclusion criteria will be as follows: (1) withdrawal of the declaration of consent, (2) met exclusion criteria for an MRI scan (pregnancy, metal implants etc), (3) severe internal, neurological and psychiatric comorbidities, (4) pharmacotherapy with psychoactive substances within the last 14 days (except treatment with selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) for at least 28 days), (5) axis-I disorder according to the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and DSM-5 (except tobacco and AUD, substance abuse with less than 2 (11) criteria according to DSM-5, mild depressive episode, adaptation disorder and specific phobia within the last 12 months), (6) positive urine drug screening (cannabis, amphetamine, opiates, benzodiazepines, cocaine), (7) withdrawal symptoms (Clinical Institute Withdrawal Assessment for Alcohol-Revised<sup>41</sup> > 7), (8) intoxication at the time of investigation (breathalyser > 0.3% o) and (9) suicidal tendency or potential danger for others.

### Sample size calculation

G\*Power<sup>342</sup> was used to determine the required sample size for this study. Based on previous work done in our research group, we used an effect size of  $f=0.40$ . Combined with a power of 90% and an alpha error of 0.05, a sample of 19 participants from project 1 would be sufficient for the longitudinal analyses (repeated measures analysis of variances (ANOVAs) with two measurements). Using the same input parameters, 68 participants are sufficient for examining group differences (no or mild ACE vs moderate to severe ACE) on the variables of interest.

### Study design

The study design will be that of an observational functional MRI (fMRI) study with two factors: AUD and ACE. The dependent variables of interest are neural correlates of emotion processing, stress sensitivity, cue reactivity and cognitive functioning. Depending on ACE severity, participants in the experimental group will be divided into two groups, namely one group with no or mild ACE (group 1) and a second group with moderate to severe ACE (group 2). This will allow for the analysis of between-subject differences on the dependent variables between these two groups. Reassessment of the participants from project 1 will allow us to investigate within-subject changes in emotion processing, stress sensitivity and cue reactivity in the context of relapse and abstinence at a longitudinal level.

**Table 1** Overview of measurements

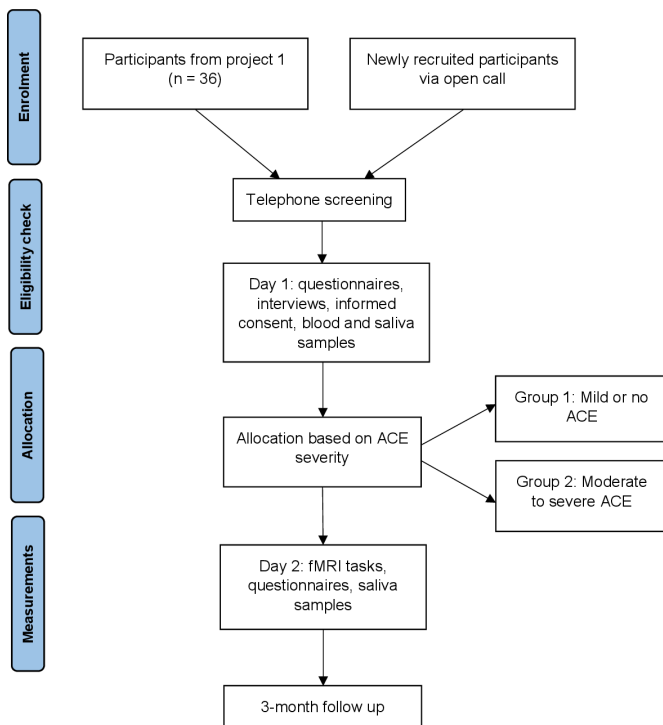
Instrument(s)	Measured variable
Questionnaires and interviews	
Lifetime Drinking History <sup>43</sup>	Long-term relapse
Maltreatment and Abuse Chronology of Exposure <sup>45 46</sup>	ACE type and severity
Form 90 <sup>44</sup>	Short-term relapse
fMRI tasks	
ScanSTRESS task <sup>47</sup>	Stress sensitivity
Emotional face-matching task <sup>48</sup>	Emotion processing
Alcohol cue reactivity task <sup>40</sup>	Cue reactivity
Stop signal task <sup>49</sup>	Response inhibition
N-back task <sup>50</sup>	Working memory
Biological markers	
Salivary cortisol level	Hormonal stress response
Blood sample	Genetic markers of AUD
ACE, adverse childhood experiences; AUD, alcohol use disorder; fMRI, functional MRI.	

### Paradigms and questionnaires

See table 1 for an overview of the key instruments. Primary outcome measures will be as follows: as long-term follow-up of project 1 to explore the mechanisms of long-term relapse, the Lifetime Drinking History diagnostic interview (LDH)<sup>43</sup> assessing self-reports of long-term alcohol consumption over the last 2–2.5 years will be used. As short-term follow-up of the current study, self-reports of short-term alcohol consumption will be taken from the whole sample measured with the Form 90 interview<sup>44</sup> 3 months after the second day of measurement to investigate factors involved in short-term relapse in AUD. The German version of the Maltreatment and Abuse Chronology of Exposure Scale (MACE)<sup>45 46</sup> will be administered to assess the type and timing of ACE.

Participants will be asked to complete several fMRI paradigms to assess group (effects of ACE severity) and within-subjects (longitudinal changes) differences in task specific brain activation patterns. Stress sensitivity will be measured using the ScanSTRESS task,<sup>47</sup> an Imaging Stress Task to assess neural activation patterns during mental arithmetic tasks with negative feedback and a social evaluative component by means of a live video transmission of the investigators that the participant can see. Emotion processing will be assessed with the Emotional Face-matching Task.<sup>48</sup> Cue reactivity will be measured with the alcohol cue reactivity task,<sup>40</sup> whereby participants are shown pictures of alcoholic beverages and neutral images. Participants' response inhibition will be assessed with the stop signal task<sup>49</sup> and working memory will be measured with the N-back task.<sup>50</sup>

As secondary outcome measures, several biological markers will be taken from all participants: hormonal stress response will be measured using salivary cortisol



**Figure 1** Study flow diagram. ACE, adverse childhood experiences; fMRI, functional MRI.

levels. The collection of saliva will be conducted on a subject's regular week-day for the individual's normal cortisol awakening response and circadian rhythm (basal HPA function). Cortisol awakening reaction, area under the curve and slope will therefore be calculated (nmol/L). Salivary cortisol levels will also be measured on the day of the fMRI experiment. The course of salivary cortisol level, area under the curve and slope will be calculated (nmol/L). Additionally, a sample of 40 mL EDTA-blood for genotyping will be taken from each participant to perform genome-wide association analyses. Glutamatergic, serotonergic and single-nucleotide polymorphisms will be analysed for genetic markers of AUD and possible gene-environment interactions (G×E) as part of an initial, explorative data analysis. These data will be added to a bigger pool of available data for further investigations.

### Study procedure

See [figure 1](#) for an overview of the study procedure. All participants will undergo a telephone screening to broadly assess if they are eligible to participate in the study. This is followed by the baseline assessments on study day 1 consisting of different questionnaires (sociodemographic data, handedness, etc), interviews (LDH, Form 90 and MACE) and a diagnostic screening to assess psychiatric comorbidities (next to AUD/ heavy drinking). The LDH will be administered only to participants from project 1 to obtain data on long-term relapse (differences in drinking behaviours from the time point of study completion of project 1 to study day 1 of project 2). Blood samples will also be taken on study day 1, provided that participants

consent to having their blood drawn by us (unlike saliva samples, blood samples are not mandatory to participate in the study). If participants meet the eligibility criteria, they will be asked to fill in online questionnaires (mood, alcohol use, trauma, etc) on REDCap (<https://www.project-redcap.org>), which may be completed from home. They will also be asked to collect four saliva samples on a regular week-day 0, 0.5, 8 and 14 hours after waking up. Participants will take the saliva samples themselves before midday after waking up at a 'regular time' (between 8 and 9 o'clock after 7–9 hours of sleep). They will receive verbal and written instructions on how to collect the saliva samples after the baseline assessments. The research team may be contacted in case of questions or problems regarding the self-collection of saliva samples. Participants will be asked to bring the saliva samples to study day 2 where the fMRI experiment takes place. Next to administering questionnaires assessing alcohol craving, mood and stress, salivary cortisol levels will be measured on the day of the fMRI experiment at 110, 85, 65 and 25 min before the the onset of stress reactions induced by the ScanSTRESS task during the fMRI measurement and at 30, 45, 60 and 75 min after the onset of stress reactions. For this, eight saliva samples will be taken under the supervision of the research team. The study will be concluded by a follow-up measurement consisting of the Form 90 interview 3 months after study day 2 (either on site or by phone).

### Data analysis

All behavioural data will be analysed using the statistical software IBM SPSS Statistics (Version 27.0, IBM Corp.). To analyse the data of the variables which were already assessed in the previous project (emotion processing, stress sensitivity and cue reactivity), repeated-measures ANOVA will be used (longitudinal design, T1 vs T2). One-way ANOVAs will be used to analyse the data of the new variables, namely response inhibition and working memory (cross-sectional design, T2). Regression analyses, t-tests and correlation analyses will be used to assess group differences on questionnaire data.

With respect to fMRI data analysis, the general linear model will be applied on the first level analyses using the software Statistical Parametric Mapping, V.12 within the MATLAB platform (The MathWorks, Natick, Massachusetts, USA). t-Tests, regression analyses, repeated-measures and one-way ANOVAs will be used for second level analyses. Prior to data analysis, a preprocessing will be performed. The preprocessing step will include procedures such as motion correction of head movements, deletion of non-brain tissue as well as spatial smoothing and normalisation.

### DISCUSSION

Because the study design includes no experimental manipulation of the observed variables, the results will be merely correlational. The participants can also not be



randomly assigned to the groups of the ACE and AUD factors because they already have developed certain values on these variables and experimental manipulation of those would be unethical. Uncontrolled third variables could thereby have unmeasured impact on the relationship between ACE and AUD. Therefore, a causal interpretation of statistical associations between ACE, AUD and the hypothesised mediating processes would not be fully justified.

As this is a prospective follow-up study due to the repeated recruitment of participants from project 1, it is uncertain how many participants will participate again. Indeed, participants may drop out for various reasons such as loss of interest, non-response, change of location or selective mortality. Due to such practically uncontrollable factors, the interpretation of a dropout-analysis would be problematic. Teague *et al*<sup>51</sup> have found that retention strategies that reduce participant burden (eg, offering flexibility or avoiding lengthy surveys) appear to be most effective in mitigating attrition. Thus, these strategies will be employed to minimise the dropout rate. Additional participants may be recruited to mitigate sample attrition from project 1 and to achieve the desired sample size for between-subjects analyses.

In combination with the results from project 1, this longitudinal follow-up allows for the analysis of within-subject changes over time on all variables investigated in project 1, namely stress sensitivity, emotion processing and cue reactivity. The results of these repeated measures will be truly comparable because both studies implement the same test instruments. The inclusion of cognitive functioning as an additional variable will further provide neuropsychological insights into the relationship between ACE and AUD. Given the breadth of clinically relevant variables being investigated, this study will provide a fruitful basis for elucidating potential mechanisms underlying the development of AUD after ACE and for individualising treatment plans for AUD patients with ACE.

### Risks associated with participation

As this study is of purely observational character and applies well-established methods such as questionnaires, interviews or fMRI, there is no notable risk involved in participation. Participants will be asked sensitive questions regarding ACE and alcohol consumption, which may cause emotional discomfort in some participants. To mitigate this potential issue, the research team will regularly check if participants wish to take breaks, to skip questions or to stop the interview. Qualified clinicians may be contacted to cope with cases of severe emotional discomfort. Given that participants are required to come on two separate days for a fairly prolonged period of time (approximately 3 hours per day), it is crucial to make sure that participants have the required time commitment. Due to its duration, assessment might be slightly exhausting for some participants. Thus, we will offer participants the option to fill in most of the questionnaires from home. This will provide flexibility and reduce

time pressure for the participants, as they can save their progress and return to the survey at a later time point. Additionally, we offer participants who cannot come to the hospital for the baseline measurements the option to complete study day 1 from home via a secure online video conferencing platform.

### ETHICS AND DISSEMINATION

This study has been approved by the Ethics Committee of the Medical Faculty Mannheim of Heidelberg University (ethics approval number: 2018-560N-MA with amendment from 29 June 2021) and conforms to the requirements of the World Medical Association's Declaration of Helsinki.<sup>52</sup> All informed consents of participants will be obtained prior to participation in the study. The findings of this study will be presented at conferences and published in peer-reviewed journals.

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