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From Laboratory Stress to Everyday Life: A Multimodal Twin-Family Study of Risk and Resilience Factors for Mental Health

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Abstract

Background

Mental illnesses are on the rise, highlighting the urgent need for preventive measures. However, preventive programmes show slow to moderate effects that diminish over time, potentially due to limited knowledge of mechanisms underlying resilience. Despite growing evidence on risk and resilience factors for the development of mental illness, their relative importance and dynamic interplay under real-time conditions, such as acute stress, remain unclear.

Method

This study investigates biological and psychological risk and resilience factors for the development of mental illness, focusing on individuals' capacity to cope with stress, using an innovative mixed-methods twin-family design. Analyses will integrate the mixed-methods and twin-family structure and will primarily be exploratory and hypothesis-generating, given the expected sample size. The study will include *N* = 50 monozygotic and dizygotic twin pairs and, where available, their non-twin siblings aged 16 years and older. It comprises two complementary parts: (1) a *laboratory assessment* including self-report questionnaires, an experimental stress task, physiological monitoring, and biological sampling; and (2) a one-week *intensive longitudinal ambulatory assessment* including repeated measures of emotional states and perceived stress, audio diaries, nocturnal ECG recordings, and saliva samples. Biological factors (epigenetic markers, stress reactivity), psychological factors (childhood experiences, emotion regulation, perceived stress), social factors (social networks, family support), and background factors (parental health, socioeconomic status) will be assessed across both parts. Laboratory and ambulatory data will be integrated to examine trait-level risk and resilience factors and state-level dynamic processes. Comparisons between monozygotic and dizygotic twins and non-twin siblings will allow estimation of genetic and environmental contributions to stress coping and mental health outcomes.

Discussion

The study will provide novel insights into interactions between biological, psychological, and social risk and resilience factors in shaping mental health. By combining laboratory-based stress assessment, real-time ambulatory data, and a twin-family design, it aims to advance understanding of stress-related and transgenerational mechanisms.

Trial registration

The study was approved by the ethics committee of the University and University Hospital of Tübingen (No. 737/2023BO1) and was conducted in accordance with the ICH-GCP guidelines, the Declaration of

Helsinki, and applicable legal requirements. The study was retrospectively registered in the German Clinical Trials Register (DRKS; DRKS00033660) on July 14, 2026 (https://www.drks.de/DRKS00033660).

1. Background

Psychological resilience is an important factor in successful adaptation and the maintenance of psychological functioning across diverse life domains. It is increasingly understood as a dynamic, multi-level process that enables individuals to adapt to adversity, recover from stress, and maintain or regain mental health despite challenging circumstances [1; 2; 3]. Importantly, resilience encompasses not only recovery following discrete adverse events but also the ability to sustain well-being under chronic or cumulative stress through the mobilization of personal, social, and environmental resources [4]. Consistent with this conceptualization, higher levels of resilience have been associated with better mental health, enhanced quality of life, stronger social functioning, and lower levels of psychological distress [5; 6]. A recent meta-analysis by Chuang et al. [7] confirmed a robust positive association between resilience and quality of life among individuals with mental illness. Similarly, Hu et al. [8] demonstrated that trait resilience is negatively associated with symptoms of depression and anxiety and positively related to indicators of well-being such as life satisfaction and positive affect. Conversely, individuals characterized by low resilience, elevated familial risk, and difficulties in emotion regulation are at increased risk of developing psychiatric disorders, including depression and anxiety [9]. This vulnerability is of particular relevance given the high prevalence and substantial societal burden of mental disorders worldwide [10; 11].

One particularly important context in which resilience processes become relevant is the intergenerational transmission of psychopathology. Children of parents with depression constitute a high-risk population, showing a three- to sixfold increased likelihood of developing depressive disorders themselves [13]. This elevated vulnerability is thought to arise from the interaction of multiple risk pathways associated with parental psychopathology, including genetic and epigenetic influences, chronic environmental stressors (e.g., marital conflict and financial hardship), maladaptive coping strategies, negative cognitive styles, and impaired parent–child interactions [14]. Influential theoretical models proposed by Goodman and Gotlib [15] and later extended by Hosman et al. [14] conceptualize these intergenerational processes by integrating biological, psychological, and social risk and resilience factors, together with relevant mediating and moderating mechanisms (see Fig. 1).

Recent empirical findings support these theoretical frameworks. For example, Xerxa et al. [16] found that social support factors may buffer the intergenerational transmission of psychopathology, while Reese et al. [17] identified family health as an important mediator of intergenerational trauma transmission. Despite their elevated risk, approximately 25% of children of parents with depression show resilient developmental trajectories [19]. However, despite the identification of numerous risk and resilience factors, the mechanisms through which resilience develops and exerts its protective effects remain insufficiently understood. A better understanding of these processes is crucial for identifying biological and psychosocial markers of vulnerability and protection and may contribute to the development of

personalized, biomarker-informed prevention and intervention approaches within the emerging framework of precision psychiatry and psychotherapy.

Building on these theoretical and empirical foundations, the following sections review key risk and resilience factors associated with the development and intergenerational transmission of psychopathology. Given the large body of predominantly cross-sectional research in this field, particular emphasis is placed on evidence derived from longitudinal studies, meta-analyses, and systematic reviews whenever available, including most recent findings. Specifically, we summarize current evidence regarding scientific consensus on biological, parent-related, child-related, parent–child interaction, and broader social factors that contribute to vulnerability and resilience across development. Although these factors are closely interrelated and conceptual overlap is therefore unavoidable, we distinguish them analytically to provide a clear overview of the most relevant risk and resilience factors.

1.1 Biological factors

Biological factors provide an important foundation for children's mental health development by shaping how environmental influences and psychological processes affect vulnerability and resilience. Rather than acting in isolation, genetic variants involved in stress regulation, emotion processing, and neuroplasticity interact with environmental experiences, such that the same genotype may confer either risk or resilience depending on exposure to factors such as parenting quality, maltreatment, or chronic stress [19]. Consistent with this perspective, genetic studies of resilience have shown that specific variants and polygenic profiles are associated with more adaptive stress responses and better maintenance of functioning despite adversity [20; 21]. These findings suggest that resilience is partly influenced by genetic factors that shape the impact of attachment patterns, personality traits, and stress reactivity on later psychopathology.

Prenatal factors are primarily maternal in origin and may influence offspring development through both biological and behavioural pathways. Meta-analyses have demonstrated that prenatal depression is associated with adverse birth outcomes, including low birth weight and preterm birth [22; 23; 24; 25], potentially through mechanisms such as altered placental functioning in response to prenatal stress [26]. Substance use during pregnancy, which is associated with postpartum depression [27], may disrupt fetal development. Prenatal tobacco and alcohol exposure have been linked to greater negative affect, neurocognitive impairments, and structural alterations in brain regions involved in learning, executive functioning, reward processing, and emotion regulation [28; 29]. Prenatal alcohol and tobacco exposure may have lasting effects through epigenetic modifications that alter gene expression involved in brain development, stress responsivity, neuronal growth, and neurotransmission. These changes may contribute to later cognitive, emotional, and behavioural difficulties in offspring [30; 31]. Parental stress during pregnancy is also associated with adverse outcomes in the offspring including mental disorders such as depression and anxiety, but also ADHD. Transgenerational transmission of epigenetic marks, but also newly acquired epigenetic signatures link parental stress status and psychopathology to stress reactivity and mental health of the offspring [32]. Research thus far is mainly based on candidate genes

and provides evidence of a potential role of *NR3C1*, SCL6A4 and *BDNF* [33], whereas a recent review of EWAS results in only small overlaps between study findings and generally rather small effect sizes indicating that multiple, interacting factors contribute to the transgenerational transmission of risk and resilience [34].

Importantly, disentangling genetic and environmental contributions to resilience and psychopathology requires genetically informative study designs. The inclusion of monozygotic and dizygotic twin pairs alongside their non-twin siblings allows genetic variance to be modeled explicitly, as monozygotic twins share almost 100% of their segregating genetic material, whereas dizygotic twins and non-twin siblings share, on average, approximately 50%. By leveraging these differences in genetic relatedness while accounting for the shared family environment, the design facilitates a more precise differentiation between genetic and environmental influences and improves estimation of their relative contributions to the outcomes of interest.

Sleep is a fundamental biological process supporting brain maturation, emotional regulation, memory consolidation, and stress-system functioning, making sleep disturbances particularly consequential during childhood and adolescence [35; 36; 37]. Longitudinal and meta-analytic evidence indicates that insomnia and insufficient sleep prospectively increase the risk of depression and anxiety, rather than merely occurring as symptoms of existing disorders [37; 38]. Sleep should therefore be considered a central and potentially modifiable biological risk and resilience factor in the development of mental health problems.

1.2 Parents

Parents shape child development through genetic transmission and the caregiving, psychological, health-related, and socio-demographic environments they provide. Parent-related characteristics therefore represent a key domain of developmental risk and resilience, including the socio-economic, cultural, and linguistic contexts in which children grow up [39; 40]. Research suggests that adverse developmental outcomes are rarely attributable to a single risk factor; rather, the accumulation of multiple (parental) risk factors appears to be particularly detrimental [41; 42]. Socio-economic stressors, such as financial hardship, unemployment, and reliance on social welfare benefits, often co-occur with psychosocial stressors including family conflict, early parenthood, single parenthood, migration-related challenges, and domestic violence. Using a cluster-analytic approach, Lorenz et al. [42] demonstrated that families exposed to three or four concurrent risk factors already showed moderate levels of burden, whereas families experiencing more than eight risk factors were classified as severely burdened. These cumulative stressors affect not only parental well-being but may also influence child development through spillover processes operating within the family system.

One important consequence of elevated parental burden is an increased risk of parental psychopathology, which has consistently been associated with adverse outcomes in offspring [44; 13; 44; 45]. Difficulties in emotion regulation, which are common across both clinical and subclinical forms of psychopathology, have been linked to more negative parenting behaviours, with particularly

pronounced effects observed in depressive disorders, borderline personality disorders, and substance use disorders [46]. Previous research has identified several moderating and mediating factors, including parental and child age, child gender, characteristics of the disorder (e.g., duration, severity, timing, and chronicity), parent-child-interaction and the presence and support of a second caregiver [15; 14; 48]. However, the specific effects of parental psychopathology on child outcomes are highly heterogeneous, and it remains unclear which offspring develop adverse outcomes, under what conditions, and through which mechanisms, while others remain resilient [18].

1.3 Child

Among numerous vulnerability factors, cognitive factors [48], emotion regulation capacities [49], low self-esteem [50], biological vulnerabilities [51] (see above) and the exposure to negative life events [52; 53] were consistently shown to play a key role for increasing negative coping with stress and hence, the risk for mental disorders in individuals. Such factors were shown to be shaped by parental mental health substantially (e.g. 54; 55; 56; 13] and are summarized shortly in the following.

Firstly, cognitive style, including habitual thought patterns, beliefs, and information-processing tendencies, substantially influences vulnerability to mental disorders. Maladaptive cognitive styles characterized by negative interpretations, rumination, and cognitive biases are consistently associated with depression and anxiety disorders [57]. Individuals who habitually interpret experiences negatively are especially vulnerable to emotional distress and persistent psychopathology [58]. These maladaptive cognitive processes may intensify negative emotional states and contribute to the maintenance and severity of mental health problems. More specifically, cognitive coping processes are strongly influenced by subjective stress appraisal. Individuals' perceptions regarding the severity and controllability of stressors shape their vulnerability to adverse psychological outcomes. Those who consistently perceive stressors as overwhelming and uncontrollable are more likely to experience chronic stress, which may disrupt emotional well-being and contribute to the emergence of mental health problems [48]. Moreover, perceived stress and negative emotions may reciprocally reinforce one another, resulting in a cognitive–emotional downward spiral [48]. From a transgenerational perspective, offspring of parents with depression have been shown to exhibit less cognitive flexibility [55] and a less positive attributional style [54].

Secondly, emotion regulation has increasingly been recognized as a central resilience factor in coping with stress. Extensive evidence indicates that mental health is closely associated with competencies in emotional expression, emotional regulation, and emotional understanding [59; 60]. Consequently, deficits in emotion regulation constitute an important vulnerability factor for mental illness. Individuals who struggle to effectively regulate their emotions are at increased risk for disorders such as anxiety, depression, and borderline personality disorder [61]. Impaired emotion regulation may result in persistent and overwhelming negative affect, thereby exacerbating or prolonging psychological distress. In contrast, adaptive emotion regulation, particularly in combination with good sleep quality, has been shown to foster resilience to depression and anxiety under conditions of chronic stress [62]. Offspring of parents with depression were characterized with deficits in adaptive emotion regulation strategies, a

positive attributional style and, simultaneously, had more psychopathology symptoms than the population-based comparison group [63].

In addition to cognitive and emotional factors, social competencies represent another important determinant of mental health. Poor social skills can impair the formation and maintenance of supportive interpersonal relationships, thereby increasing feelings of loneliness and social isolation, both of which constitute established risk factors for mental illness [64]. Furthermore, impaired social functioning may amplify the adverse effects of stress and life adversities [65].

Low self-esteem and low self-efficacy constitute closely related yet distinct dimensions of self-perception and have both been identified as transdiagnostic risk factors for mental health problems and reduced quality of life [50]. Low self-esteem, characterized by a negative self-image and persistent feelings of inadequacy or self-doubt, has been associated with feelings of worthlessness and the development of affective disorders [66; 67]. In contrast, low self-efficacy refers to diminished confidence in one's ability to successfully perform tasks or achieve goals [68]. Individuals with low self-efficacy are more likely to avoid challenging situations and may become increasingly vulnerable to stress and anxiety due to impaired problem-solving [69], decision-making, and coping abilities [70]. Importantly, low self-esteem and low self-efficacy may interact bidirectionally with mental illness. As psychological symptoms intensify, individuals may experience a further decline in self-worth and perceived competence, resulting in a self-reinforcing negative feedback cycle [50; 71].

Finally, negative life events such as trauma, loss, or chronic stress represent significant environmental risk factors for the onset of mental illness, particularly in individuals with an underlying predisposition [52; 53]. Such experiences may overwhelm existing coping capacities, disrupt emotional functioning, and lead to persistent psychological distress. Moreover, negative life events often interact with additional vulnerability factors, including genetic predispositions and maladaptive coping strategies, thereby further increasing the likelihood of developing mental health problems, especially when stressors occur repeatedly or cumulatively [52]. Again, negative life events such as adverse childhood experiences (ACE) were shown to increase the likelihood of post-partum depression, which fully mediated the mother-infant bonding [56; 72, see below more details on parent-child interaction].

As indicated in Fig. 1, such factors converge in coping with stressor and an individual's stress reactivity, defined as the manner in which individuals respond and cope with stressors [73]. Heightened stress reactivity, characterized by intensified physiological and emotional responses to stress, has been associated with an increased susceptibility to anxiety disorders, depression, and post-traumatic stress disorder, while also exacerbating the severity of existing psychopathology [73]. Prolonged exposure to chronic stress may further contribute to dysregulation of the body's stress response systems (Russel & Lightman, 2019), thereby triggering or aggravating mental health symptoms [74; 75; 76]. In addition, stress-induced alterations have been linked to multifaceted pathophysiological processes affecting cognitive appraisal and executive functioning [77]. Deficits in cognitive abilities such as problem-solving,

self-regulation, and decision-making can impair adaptive coping with everyday challenges and increase vulnerability to disorders including depression, anxiety, eating disorders, and substance abuse [78; 79].

1.4 Parent–Child Interaction and Relationship

The parent–child relationship represents a central mechanism through which parental and child characteristics influence one another. Evidence suggests that parental psychopathology is associated with impaired attachment relationships [80; 81; 82], reduced parental enjoyment in interactions with the child [83], and more negative perceptions of child behaviour [84]. At the same time, child characteristics contribute to these transactional processes. Difficult child temperament may challenge parental caregiving, while insecure attachment has also been linked to the development of more difficult temperament characteristics, indicating a bidirectional relationship between child temperament and parent–child attachment [85; 86; 87].

At the extreme end of the risk continuum, the parent–child relationship may be disrupted by abuse and neglect. Such experiences have been associated with reduced parental sensitivity, greater frustration and anger during parent–child interactions, and lower levels of positive engagement [88]. Children exposed to abuse or neglect are more likely to develop insecure-avoidant or disorganized attachment patterns, display withdrawn behaviour and heightened negative affect, exhibit increased aggression, and show broader difficulties in emotional regulation [89]. In addition, childhood maltreatment (CM) has been linked to alterations in brain development and neurobiological functioning [12; 90; 91]. Hence, CM constitutes one of the strongest environmental risk factors for the development of psychopathology. A representative German study estimated that approximately one in seven children experiences severe abuse or neglect at least once during childhood [92]. Individuals exposed to CM are roughly twice as likely to develop mental disorders that persist into adolescence and adulthood [93]. Consistent with these findings, accumulating evidence indicates that CM alters psychological and neurobiological development in ways that increase vulnerability to a broad range of psychiatric disorders [94; 95; 96; 44]. McLaughlin et al. [97] proposed a transdiagnostic framework in which alterations in emotional processing, social information processing, and accelerated biological aging represent key mechanisms linking childhood trauma to later psychopathology.

Recent evidence further suggests that the consequences of CM may extend into the transition to parenthood. Vogel et al. [56; 72] demonstrated that childhood maltreatment, particularly emotional abuse and neglect, was strongly associated with postpartum depressive symptoms in mothers, with emotion regulation difficulties emerging as a key mediating mechanism. Similar associations were observed in fathers, for whom maladaptive emotion regulation was linked to greater postpartum depression severity, although these findings should be interpreted cautiously given the limited sample size.

Emerging evidence indicates that CM is associated with enduring epigenetic alterations, particularly in DNA methylation, which may contribute to heightened vulnerability to later psychopathology. Studies from our own group in adults with social anxiety disorder demonstrated that early life adversity, including

maltreatment, was associated with differential DNA methylation in genes involved in stress regulation and emotional functioning, as well as altered immune-related transcriptional pathways [98; 99]. These findings suggest that early adversity may induce persistent molecular alterations that influence stress responsivity and mental health risk across the lifespan. Consistent with this interpretation, studies in maltreated children and adolescents identified maltreatment-related methylation differences in genes involved in neural development, tissue development, mitochondrial function, and stress regulation [100; 101; 102; 103], supporting epigenetic embedding as a central mechanism through which childhood maltreatment may affect brain development and emotional functioning.

1.5 Social factors

The family environment is a key context for child development and can act as both a risk and protective factor. Family discord, poor relationship quality, single parenthood, parental depression, and marital conflict have been linked to poorer child mental health and family functioning, whereas supportive family relationships, coparenting, and the involvement of a second caregiver may promote socio-emotional adjustment and buffer stress [104; 105; 106; 107; 108; 109]. Beyond the immediate family, broader social networks, including relatives, friends, professional support services, and increasingly peers during adolescence, represent important resilience factors for parental and child well-being [110; 111; 112; 113; 114; 115].

However, much of the literature examines isolated predictors, often cross-sectionally, and thus provides limited insight into the interaction of biological, psychological, social, and contextual factors over time. Addressing this gap, Löchner et al. [116] investigated multiple risk and resilience factors in a secondary analysis of 8,063 families with children aged 0–3 years and showed that predictors of parental mental health and child well-being differed across baseline and two-year follow-up assessments. While the study's large representative sample and comprehensive assessment are major strengths, it did not include biological markers such as genetics or epigenetics, captured only limited dynamic psychological and biological processes, and focused on families with infants, a developmental period shaped by the specific challenges of early parenthood.

1.6 Summary

Taken together, the reviewed literature suggests that risk and resilience emerge from complex interactions among biological, psychological, familial, and social factors across development. Although substantial evidence exists for individual predictors of mental health outcomes, relatively few studies have integrated these domains within a longitudinal framework while simultaneously accounting for genetic relatedness. Evidence from experimental stress coping tasks is further limited. Furthermore, novel assessment approaches allow following participants in their everyday lives and assess their individual stress coping abilities in ecological momentary assessment (EMA), overcoming psychometric shortcomings as memory biases, but capture their daily behavior [118]. In addition, audio data can be used to enrich classic psychometric data with open format reports, which can be analyzed using machine learning approaches [118].

The present twin-sibling study addresses these gaps by examining the joint and interactive contributions of biological, psychological, and environmental risk and resilience factors to the development of psychopathology combining multimodal data of a laboratory stress task and real-time assessment, including traditional psychometrical and EMA, biological data (saliva, blood) and audio diary data. In specific, the study exploratorily investigates i) the importance and interaction of various risk and resilience factors in relation with stress coping (cognitive attitude, emotion regulation, self-esteem, sleep) in the development of mental disorders within a twin cohort and ii) their role within the transmission of psychopathology in a laboratory and ambulatory assessment setting to explore interactive patterns and standardized and real-time conditions.

Research Questions:

1. Which risk and resilience factors most robustly predict psychopathology, and to what extent do their effects differ across monozygotic twins, dizygotic twins, and non-twin siblings?
2. Does parental psychopathology moderate risk and resilience factors (coping with stress, cognitive attitude, emotion regulation, self-esteem, sleep) and offspring psychopathology, and how do these pathways vary by genetic relatedness (monozygotic twins, dizygotic twins, and non-twin siblings)?
3. How do risk and resilience factors dynamically interact across controlled laboratory and real-world conditions, and how are these interaction patterns moderated by genetic relatedness?

We hypothesize that greater cumulative exposure to biological, psychological, social, and familial risk factors will be associated with higher levels of psychopathology, whereas resilience factors will attenuate these associations. In particular, maladaptive cognitive appraisal, emotion-regulation difficulties, low self-esteem, ineffective coping, and disturbed sleep are expected to predict stronger subjective and biological stress responses under laboratory conditions and greater negative affect and stress reactivity in everyday life. We further expect that these dynamic stress-response patterns will mediate, at least partly, the association between stable risk factors and mental-health problems. Finally, concordance in risk profiles and psychopathology is expected to be greater among monozygotic twins than among dizygotic twins and non-twin siblings, while differences within genetically related pairs will provide evidence for the contribution of modifiable environmental and psychosocial factors.

2. Methods

2.1 Study design

This study employs a mixed-methods design, combining cross-sectional and time-series approaches to investigate the development and transmission of mental disorders in a twin cohort. The study integrates both laboratory-based assessments and real-time EMA, capturing both state and trait factors related to stress coping (see Fig. 2).

By utilizing a combination of experimental methods, ambulatory data collection, and real-time monitoring, the study provides a comprehensive understanding of how various risk and resilience factors

interact in the context of mental health. The study was approved by the ethics committee of the University and University Hospital of Tübingen (No. 737/2023BO1) and was conducted in accordance with the ICH-GCP guidelines, the Declaration of Helsinki, and applicable legal requirements. The study was retrospectively registered in the German Clinical Trials Register (DRKS; DRKS00033660) on July 14, 2026 (https://www.drks.de/DRKS00033660).

2.2 Sample and recruitment

The target population of the study comprises twin pairs aged 16 years and older, as well as their non-twin siblings and parents. Inclusion in the study requires the willingness of both twins to participate, parental consent in case of underaged participants and sufficient proficiency in the German language. Furthermore, participants should have a daily routine compatible with the ambulatory assessment schedule of the EMA week (e.g. no working hours at night) and possess a smartphone suitable for completing brief online questionnaires and voice recordings. Exclusion criteria include current pregnancy, engagement in shift or night work, and refusal to participate in any of the study's assessment components. Recruitment is conducted via the existing TwinHealth cohort at the University Hospital Tübingen, internal mailing lists of the University and University Hospital Tübingen, physical notice boards, and personal networks. An initial invitation letter provides basic information about the study procedure and the contact details of the study coordinators. Individuals who express interest are invited to a low-threshold informational and screening session, conducted either via telephone or through a data protection–compliant video platform. These sessions may be attended by both twins or the entire family together. During this initial meeting, participants receive detailed information about the study, and a preliminary screening of inclusion and exclusion criteria is conducted. Only families who meet the study requirements are invited to attend the on-site baseline appointment. Study information sheets and informed consent documents are sent to all potential participants in advance via email for review.

2.3 Procedure

Twin pairs and, if available, their non-twin siblings are invited to a laboratory appointment. This session is scheduled within a fixed time window (between 13:00 and 17:00) and is carried out by trained study personnel following a standardized protocol (see Fig. 3). Each session is conducted by at least three research staff members: two who administer the parallel stress tasks and one who is responsible for collecting biological samples. The staff members are trained and supervised to conduct all procedures. At the beginning of each session, any remaining questions are addressed and signed informed consent forms are collected. Twin participants are then escorted to two separate laboratory rooms, where they complete the self-report questionnaire battery simultaneously (see Questionnaires below). Afterwards, the Montreal Imaging Stress Task (MIST) will be conducted to test each participant's physiological stress reactivity. During this stress test, heart rate will be collected via an ECG and saliva samples (before and after) will be collected for cortisol determination. At the end of the visit, a blood draw and hair sample are obtained and further detailed instructions for the home setting week are provided, e.g., on the use of the study-related apps and technical equipment.

After successful completion of the laboratory assessment, the participating twins and non-twin siblings begin a one-week ambulatory assessment comprising daily ecological momentary assessments, saliva samples, audio diaries, and the collection of an overnight sleep ECG.

Montreal Imaging Stress Task (MIST)

To induce acute psychosocial stress under standardized laboratory conditions, participants complete the MIST, a computer-based stress paradigm adapted from the Trier Mental Challenge Test [119]. Participants are initially informed that they will complete a "cognitive performance test," which serves as a cover story for the stress induction procedure. During the MIST, participants are exposed to a series of arithmetic tasks presented on a computer display. In the experimental condition, psychosocial stress is induced through a combination of time constraints, adaptive task difficulty, and standardized negative feedback. The software dynamically adjusts the difficulty level and response time limits to each participant's performance, setting the time limit approximately 10% below the participant's average response time and adjusting task difficulty so that only 20–45% of responses can be answered correctly. To contrast it with the control condition, a red rectangle surrounds the presentation area and the feedback to the arithmetic tasks includes the comment 'recorded'. In addition, a fictitious comparison with an expected performance is displayed on top, showing the individual performance on a color bar with red, yellow and green sections. While the own performance moves from green to red over the course of the run, the average performance indicated by a second arrow remains in green or yellow. In addition, in between the runs, the experimenter expresses concern about the performance being substantially below expectations and encourages the subject to improve subsequently. Participants complete two MIST runs, each lasting nine minutes (The procedure followed the protocol described by Dedovic [120]). For the current project, only the experimental condition was employed. After completion of the MIST, participants undergo a 20-minute recovery period, during which they are instructed to remain seated, refrain from speaking, and avoid using their smartphone. Cardiac activity is assessed as a physiological marker of acute and chronic stress responses. For this purpose, participants wear a Movesense Sensor HR+ attached to the chest using a Movesense belt with two electrodes. The sensor records single-channel ECG data, which are transmitted via Bluetooth to the eHealth Studio app, developed by the cooperation partner for secure physiological data acquisition in compliance with data protection regulations. Heart rate and heart rate variability are assessed based on the recorded cardiac data. Further, five saliva samples are collected via passive drool: one before the MIST as a baseline measure, one between the two MIST runs, one immediately after the second run, and two additional samples 10 and 20 minutes after the MIST during recovery. To ensure standardized cortisol sampling conditions, participants are instructed to avoid eating for at least one hour and physical activity prior to the assessment. Upon arrival, participants complete the study questionnaires before saliva collection. Sampling is conducted within a standardized time window to account for cortisol's circadian rhythm. Before the first sample, participants rinse their mouths with water and swallow it. After the final saliva sample, participants are fully debriefed about the purpose of the MIST and asked to provide retrospective informed consent for the use of the stress-task data.

Blood and hair samples

Peripheral venous blood will be drawn in Ethylenediaminetetraacetic tubes (EDTA, BD, Franklin Lakes, NJ, USA) from all participants at the baseline assessment and stored at – 80°C. Genomic DNA will be isolated from whole blood using the QIAamp DNA Blood maxi Kit (Qiagen, Hilden, Germany) following the manufacturer's protocol. DNA yield and quality will be assessed using a Qubit™ 2.0 Fluorometer (Life Technologies, Carlsbad, CA, USA). 500 ng genomic DNA will be bisulfite converted using the EpiTect Fast Bisulfite Kit (Qiagen) according to the manufacturer's instructions. Bisulfite-converted DNA will be eluted in 20 µl elution buffer and stored at -20°C until further analysis. Region-specific PCRs (e.g., FKBP5, OXTR, SLC6A) will be conducted using the PyroMark PCR Kit (Qiagen) according to the manufacturer's protocol. Successful amplification and specificity of the PCR products will be verified and visualized via agarose gel electrophoresis. DNA methylation levels will be further analyzed by pyrosequencing using the PyroMark Q24 system (Qiagen). Each sample will be amplified twice and both amplicons will be sequenced as technical replicates. The mean percentage will be used for further analysis. However, replicates revealing a relative deviation of ≥ 3% of the respective DNA methylation level will be repeated. To detect disparate amplification of unmethylated DNA fragments a titration assay using standardized bisulfite-converted control DNA samples (EpiTect Control DNA, Qiagen) with established DNA methylation levels of 0%, 25%, 50%, 75% and 100% will be performed.

To obtain hair samples, it has been recommended to use hair from the occipital protuberance. The hair is cut off directly above the scalp, wrapped in aluminum foil to protect it until analysis. Due to the sample collection, no visible areas remain on the head and there are no other impairments on the subjects. Ceratinized cortisol will be measured in hair samples to determine its long-term levels and chronic stress burden [121; 122].

Questionnaires

Demographic questions will be captured with a self-generated questionnaire including age, gender, family information, socio-economic status, cultural background.

Mental health: Mental health is assessed using the Symptom Checklist-90 (SCL-90) [123; 124], which measures subjectively perceived impairment by physical and psychological symptoms within the last 7 days. The questionnaire consists of 90 items assigned to nine symptom dimensions. Items are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). In addition to the subscales, a Global Severity Index (GSI) is calculated to reflect overall psychological distress. Internal consistency ranges from Cronbach's α = .76 to .92 for the subscales and reaches α = .97 in adults and α = .98 in adolescents for the GSI. The SCL-90 demonstrates good item discrimination and is considered a valid instrument.

Well-being: The overall well-being will be assessed with the 5-item World Health Organization Well-Being Index (WHO-5) [125]. The WHO-5 consists of five items rated on a 6-point-Likert scale ranging from '1' (all of the time) to '6' (at no time). The WHO-5 shows overall good psychometric properties with an internal consistency of Cronbach's alpha = 0.920 [125].

Emotion regulation: Emotion regulation is assessed using the short form of the Difficulties in Emotion Regulation Scale (DERS-18) [126]. The questionnaire consists of 18 items across six subscales, each represented by three items. Items are rated on a 5-point Likert scale ranging from 1 (almost never) to 5 (almost always), with higher scores indicating greater difficulties in emotion regulation. Three items of the Awareness subscale are reverse-coded. The DERS-18 demonstrates good psychometric properties, with item-total correlations ranging from r = .53 to .83 and internal consistency ranging from Cronbach's α = .89 to .91.

Childhood Maltreatment: Childhood maltreatment is retrospectively assessed using the Childhood Trauma Questionnaire (CTQ) [127; 128]. The CTQ consists of 28 items covering five types of maltreatment, items are rated on a 5-point Likert scale ranging from 1 (never true) to 5 (very often true). Subscale scores and a total score can be calculated, with higher scores indicating greater exposure to maltreatment. The CTQ demonstrates good psychometric properties. For the German version, internal consistency is high for most subscales (Cronbach's α ≥ .80), whereas the physical neglect subscale shows weaker reliability and should be interpreted with caution. Construct validity is supported by positive associations with anxiety and depression and negative associations with life satisfaction [128].

Attachment: Attachment is assessed using a modified version of the Relationship-Specific Attachment Scales for Adults (BBE) [129], based on Bartholomew's model of adult attachment. The instrument measures attachment along the dimensions secure–anxious and dependent–independent. In the present study, items on attachment to the mother were replaced by questions on social relationships and friendships, including open-ended items on number of friendships and contact frequency. Additional sections assess partnership status, attachment-related statements, and prototypical attachment descriptions, all rated on 5-point Likert scales (1 = not at all to 5 = completely). The BBE shows satisfactory psychometric properties, with internal consistencies between α = .71 and .87 and 6-month test–retest reliabilities between r = .70 and .84. Validity is supported by expected associations with attachment prototypes, relationship quality, contact frequency, and partnership satisfaction. No normative data is available.

Cognitive Attitude: Cognitive attitudes are assessed using the Dysfunctional Attitude Scale – Short Form (DAS-18) [130]. The scale consists of 18 items measuring dysfunctional beliefs associated with depression, particularly in the domains of performance evaluation and need for approval. Items are rated on a 7-point Likert scale ranging from 1 (total disagreement) to 7 (total agreement). Higher scores indicate more dysfunctional attitudes. The DAS-18 shows good internal consistency (Cronbach's α = .80–.89). Evidence for validity is supported by positive correlations with depressive symptoms (e.g., BDI-II) and negative correlations with related cognitive constructs.

Depressive symptoms: Depressive symptoms are assessed using the Beck Depression Inventory-II (BDI-II) [131; 132]. The BDI-II is a 21-item self-report questionnaire measuring depressive symptom severity over the past two weeks. Each item is rated on a 4-point Likert scale ranging from 0 to 3, with total scores ranging from 0 to 63. Higher scores indicate greater symptom severity. The BDI-II shows excellent

psychometric properties, including high internal consistency (Cronbach's α = .89–.92) and good test–retest reliability (r_{tt} ≈ .73–.96).

Self-esteem and self-efficacy: Self-efficacy is assessed using the General Self-Efficacy Scale (SWE/GSE-10) [133]. The scale consists of 10 items measuring general perceived self-efficacy across various life domains. Items are rated on a 4-point Likert scale ranging from 1 (not true) to 4 (exactly true), with higher scores indicating higher self-efficacy. The SWE demonstrates good psychometric properties, with internal consistency ranging from Cronbach's α = .71 to .89 and moderate test–retest reliability over one year (r_{tt} = .54–.57), indicating acceptable temporal stability. Construct validity is supported by correlations with related psychological constructs.

Sleep quality: Sleep quality is assessed using the Pittsburgh Sleep Quality Index (PSQI) [134]. It consists of 19 self-rated items that are used to calculate seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Each component is scored from 0 to 3, resulting in a global score ranging from 0 to 21, with higher scores indicating poorer sleep quality. A global score above 5 is commonly used to indicate poor sleep quality. The PSQI demonstrates good psychometric properties, including satisfactory internal consistency, test–retest reliability, and validity in distinguishing good from poor sleepers. The German version has also shown acceptable reliability and validity in clinical and community samples [135; 136].

Ambulatory assessment

During the one-week ambulatory assessment, participants complete repeated EMA to capture fluctuations in mood, perceived stress, and contextual factors in daily life. Short online questionnaires are administered six times per day, beginning at 10:00 and continuing every two hours until 20:00. Participants receive individualized survey links and are instructed during the initial laboratory visit to set smartphone reminders for each assessment time point. The first daily EMA assessment differed slightly from subsequent assessments by including additional questions on sleep during the previous night. Current mood was assessed using the Multidimensional Mood Questionnaire (MDBF; 12-item short form), capturing good–bad mood, alertness–tiredness, and calmness–restlessness. The subscales show substantial intercorrelations (r = .70–.75, $p < .001$) and good internal consistency (α = .78–.86; total score α = .92), with factorial validity supported [137; 138]. Perceived stress was assessed using the 4-item version of the Perceived Stress Scale (PSS-4), adapted for ambulatory assessment [139]. The scale measures perceived unpredictability, uncontrollability, and overload over the past month, with items rated on a 5-point scale. The PSS-4 has demonstrated acceptable reliability and validity in German samples [140] and showed good internal consistency (Cronbach's α = .84). Further, at each EMA time point, participants also answer brief contextual questions relevant to the interpretation of saliva-based biomarkers. These include questions on physical activity, caffeine and alcohol consumption, food intake, sleep, and other recent behaviours that may influence salivary measures. These variables will be considered as covariates in analyses of biological stress responses. As part of the final EMA

assessment each day at 8:00 p.m., participants are asked to record a brief audio diary of approximately two minutes. In this diary, they are instructed to describe emotionally relevant events of the day, including positive and negative experiences, as well as their personal highs and lows. Audio recordings are transmitted via Famedly [141], a GDPR-compliant messenger approved for secure communication in healthcare settings. The audio diaries provide additional contextual information about participants' daily experiences and will be analysed using automatic speech recognition and natural language processing methods. Analyses will focus on both the semantic content of the recordings and paralinguistic vocal features. Previous research suggests that speech data can provide information about emotional states, fatigue, cognitive or physical load, and depressive symptom severity [142; 143]. In the present study, audio diary data will support the interpretation of EMA responses and biological stress markers by providing richer contextual information about daily stressors and emotional experiences.

2.4 Data analysis

Analyses will follow the mixed-methods and twin-family design of the study. Given the expected sample size of approximately 50 twin pairs plus available siblings and parents, analyses will be primarily exploratory and hypothesis-generating. Results will therefore be interpreted mainly in terms of effect sizes, confidence intervals, and consistency across data sources. First, descriptive statistics will be calculated for all questionnaires, biological, physiological, EMA, and audio-derived variables. Data will be inspected for missingness, outliers, and distributional properties. Biological markers such as salivary cortisol, hair cortisol, and DNA methylation values will be transformed or standardized where appropriate. EMA compliance and technical data quality for ECG, saliva, and audio recordings will be reported. The primary outcome will be psychological distress, assessed with the Global Severity Index of the SCL-90. Secondary outcomes will include depressive symptoms, well-being, stress reactivity, perceived stress, mood, and biological stress markers. Main predictors will include parental psychopathology, childhood maltreatment, emotion regulation, dysfunctional attitudes, self-efficacy, attachment-related variables, perceived stress, sleep-related variables, social support, and biological stress markers. Cross-sectional baseline data will be analyzed using linear mixed-effects models with individuals nested within families. Family will be included as a random intercept to account for dependency between twins and siblings. Age, sex/gender, socioeconomic indicators, medication use, smoking, and other relevant health variables will be considered as covariates. Zygosity or sibling status will be included as a grouping variable and tested exploratorily as a moderator. Laboratory stress reactivity during the MIST will be analyzed using repeated-measures mixed-effects models. Heart rate, heart rate variability, and salivary cortisol will be modelled across baseline, stress, and recovery phases. Summary indices, such as cortisol area under the curve and physiological reactivity or recovery scores, will be calculated where appropriate and examined in relation to SCL-90 scores and psychological risk or resilience factors. EMA data will be analyzed using multilevel models with repeated assessments nested within days, days nested within individuals, and individuals nested within families. These models will examine within-person associations between momentary stress, mood, sleep, contextual factors, and daily experiences. Time of day, day of assessment, physical activity, food intake, caffeine, alcohol, and sleep will be considered as time-varying covariates. Exploratory lagged models will test whether stress

predicts later mood or whether negative mood predicts later perceived stress. Laboratory and ambulatory data will be integrated by examining whether stress reactivity during the MIST predicts daily-life stress levels, affective stress reactivity, recovery, or nocturnal ECG-derived stress markers. Audio diaries will be transcribed and analyzed using natural language processing and acoustic feature extraction. Linguistic and vocal features will be linked to same-day EMA responses and biological stress markers to contextualize daily stress and coping processes. Familial similarity will be examined using intraclass and cross-sibling correlations separately for monozygotic twins, dizygotic twins, and non-twin siblings. Formal ACE (additive genetic [A], shared environmental [C], and non-shared environmental [E] components) models will only be conducted for selected outcomes if data completeness and model stability are sufficient; otherwise, genetically informed analyses will focus on similarity patterns and zygosity moderation. Intergenerational transmission will be examined by testing associations between parental psychopathology and SCL-90 scores, including potential mediating or buffering effects of stress regulation, social support, and biological markers.

3. Discussion

This study aims to advance understanding of how risk and resilience factors related to stress coping interact in the development and intergenerational transmission of mental health problems [1; 2; 3]. By applying a multimodal design that combines a standardized laboratory stress task with ambulatory assessment in everyday life, the study integrates psychometric measures, EMA, biological markers derived from saliva and blood, and audio-diary data. This approach is intended to enable the investigation of both stable characteristics and dynamic stress-related processes, including cognitive appraisal, emotion regulation, self-esteem, coping, and sleep. The primary aim is to implement the study design and to obtain initial exploratory findings.

This study addresses important gaps in understanding the development and intergenerational transmission of psychopathology by examining the joint and interactive contributions of biological, psychological, familial, and broader environmental risk and resilience factors [15; 14]. The study specifically examines which risk and resilience factors most robustly predict psychopathology, whether these associations differ between monozygotic twins, dizygotic twins, and non-twin siblings, and which mechanisms contribute to the intergenerational transmission of parental psychopathology. In addition, it investigates how these factors interact under controlled laboratory conditions and in real-world contexts, and whether these patterns vary as a function of genetic relatedness. Together, these analyses aim to provide a more integrated account of how genetic vulnerability, modifiable psychosocial factors, and context-dependent stress responses jointly shape mental-health outcomes.

We hypothesize that greater cumulative exposure to biological, psychological, social, and familial risk factors will be associated with higher levels of psychopathology, whereas resilience factors will buffer these associations. Specifically, maladaptive cognitive appraisals, difficulties in emotion regulation, low self-esteem, ineffective coping strategies, and poor sleep are expected to predict heightened subjective and biological stress responses during laboratory assessments, as well as greater negative affect and

stress reactivity in daily life. We further hypothesize that these dynamic patterns of stress responding will partially mediate the relationship between stable risk factors and mental-health problems. Finally, we expect greater similarity in risk profiles and psychopathology among monozygotic twins than among dizygotic twins and non-twin siblings. At the same time, differences observed within genetically related pairs are expected to highlight the contribution of modifiable environmental and psychosocial influences.

A key strength of the study is the inclusion of monozygotic twins, dizygotic twins, non-twin siblings, and parents, which allows exploratory differentiation between genetic, shared environmental, and non-shared environmental influences. Although the sample size limits formal behavioural genetic modelling, comparing similarity patterns across monozygotic and dizygotic twin pairs can provide important preliminary evidence on the relative contribution of genetic relatedness to stress coping, psychopathological symptoms, and biological stress markers. The inclusion of parents further enables investigation of intergenerational pathways, including whether parental psychopathology is associated with offspring mental health for example through biological stress regulation, emotion regulation, or childhood adversity. Another major strength is the integration of standardized laboratory assessment with real-world ambulatory data enabling a much broader picture, which is potentially less-biased and assessed under standardised conditions but also including individualised daily stressors [116]. The MIST provides a controlled context for examining acute physiological and endocrine stress reactivity, while the one-week ambulatory assessment captures fluctuations in mood, perceived stress, sleep, contextual factors, and daily emotional experiences [119; 144]. This combination allows the study to examine whether laboratory-based stress responses correspond to stress processes in everyday life. Audio diaries add an additional qualitative and digital layer by providing contextual information on daily stressors and emotional experiences, while also enabling exploratory analyses of linguistic and vocal markers of affective states.

The study also has important limitations. The sample size is small, and analyses will therefore be exploratory and hypothesis-generating. The cross-sectional baseline design prevents conclusions about causality or developmental change. In addition, retrospective assessment of childhood adversity and family experiences may be affected by recall bias. The ambulatory assessment period of one week provides rich real-time data but may not fully represent longer-term stress patterns or seasonal and developmental variation. Developmental stages that may have substantial impact on the current mental health state are not considered. Despite the relevance of other important risk and resilience factors (e.g. alcohol exposure in pregnancy, social support, educational environment), we only included such factors with the highest impact based on our literature review, based on an update of the theoretical framework of Goodman & Gotlib [15] and Hosman et al. [14]. Finally, the relatively demanding study protocol may lead to selection effects, as families with higher motivation, fewer current burdens, or greater interest in mental health research may be more likely to participate.

Future research should include larger samples to enable robust analyses, ideally extend recruitment to infants, adopt a longitudinal design, and use the most suitable psychometric methods. The present study

can help identify which assessment tools provide the greatest scientific value while minimising participant burden.

The clinical implications lie in identifying modifiable risk and resilience factors and understanding how they fluctuate in everyday life, thereby informing more targeted and potentially more effective prevention strategies. Clinicians may also benefit from a prioritised overview of these factors and their interplay to support more precise case formulation and therapeutic decision-making.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Medical Faculty of the Eberhard Karls University and University Hospital Tübingen (No. 737/2023BO1) and was conducted in accordance with the ICH-GCP guidelines, the Declaration of Helsinki, and applicable legal requirements. The study was retrospectively registered in the German Clinical Trials Register (DRKS) under registration number DRKS00033660 on July 14, 2026 (https://www.drks.de/DRKS00033660). Prior to participation, all participants were informed orally about the study procedures and provided written informed consent in person no later than before the first study visit. For participants under 18 years of age, written informed consent was obtained from their legal guardians, and assent was obtained from the adolescent participants.

Consent for publication

Not applicable. This study protocol does not report individual participant data.

Availability of data and materials

Data collection and laboratory analyses are ongoing. The datasets generated and analysed during the study are not currently publicly available. Data are stored securely at the University Hospital Tübingen in accordance with applicable data protection regulations. Due to the sensitive nature of the collected data, access to individual-level data will be subject to applicable ethical, legal, and data protection requirements and the terms of informed consent. Where possible and compatible with the protection of participants' rights and privacy, data and/or study materials may be made available for scientific purposes through appropriate repositories or upon reasonable request to the corresponding author. Access to sensitive data may be restricted to authorised researchers and may be subject to appropriate data use agreements and, where required, ethical approval.

Competing interests

The authors declare that they have no competing interests.

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AP coordinated the overall study and was responsible for project administration and day-to-day study coordination. AP drafted the manuscript. LS contributed to the conceptualization and design of the study, provided scientific and methodological input, was responsible for the saliva and hair sample components and the statistical analysis, and contributed substantially to writing and revising the manuscript. VN contributed to the conceptualization and design of the study, supervised the study as Principal Investigator, was primarily responsible for the epigenetics component, and supported the financial and administrative coordination of the project. SE contributed to the conceptualization and design of the study, provided scientific input, contributed to the epigenetics component, and critically revised the manuscript. GMB provided scientific and methodological input regarding the ECG and sleep-ECG components. NNS provided scientific input and critically revised the manuscript. SM provided scientific input and critically revised the manuscript. BS provided scientific and methodological input regarding the voice recording component. AC provided scientific input and critically revised the manuscript. TJR contributed to the conceptualization of the study and provided scientific and institutional supervision within the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy at the University Hospital Tübingen. JCP provided the MIST developed by his research group, provided training and methodological advice regarding its administration, and contributed to the

corresponding section of the study protocol. SF provided scientific input and critically revised the manuscript. RR provided scientific input and critically revised the manuscript, including the first draft. JL contributed to the conceptualization and overall design of the study, provided close scientific supervision throughout the project, and assumed overall responsibility for the study design and manuscript. All authors read and approved the final manuscript.

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Figures

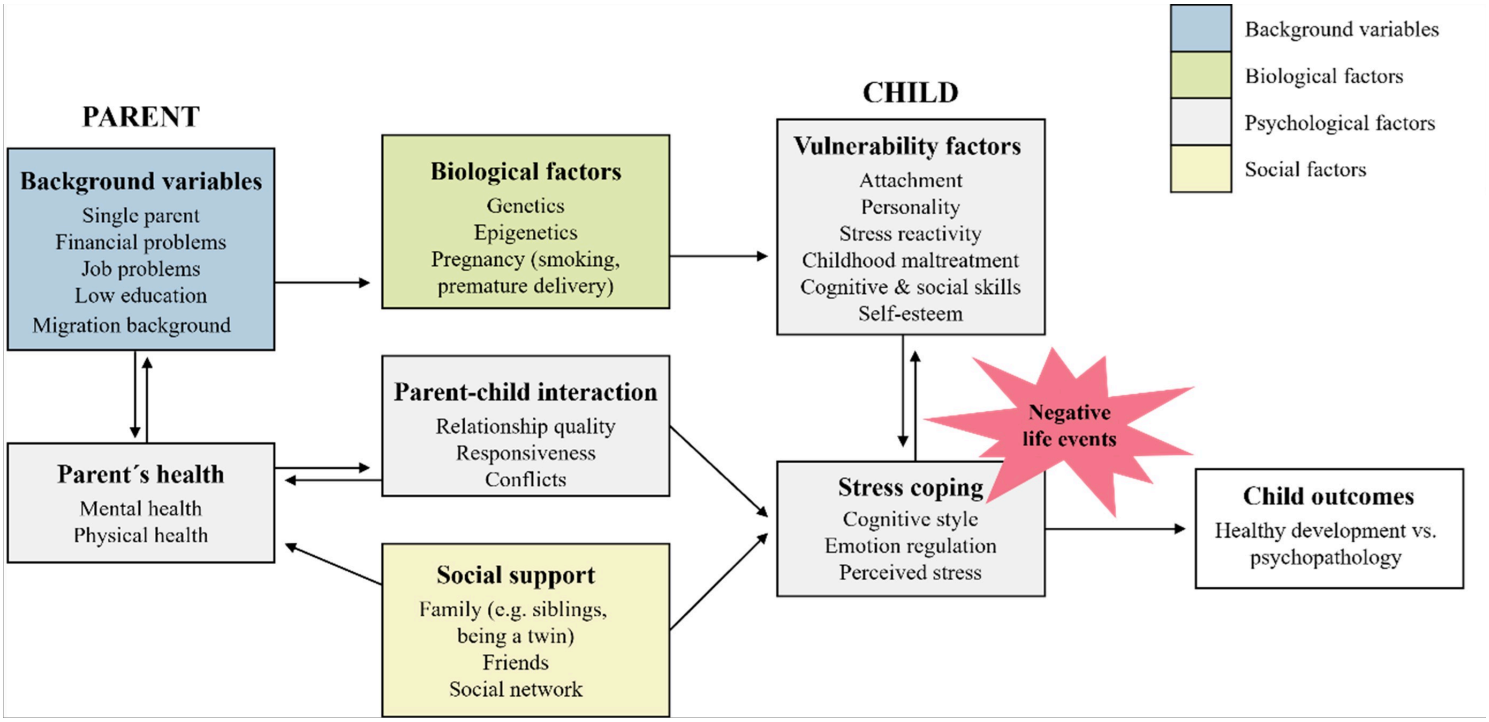


Figure 1

Risk and resilience factors for psychopathology, adapted from Hosman et al., 2009

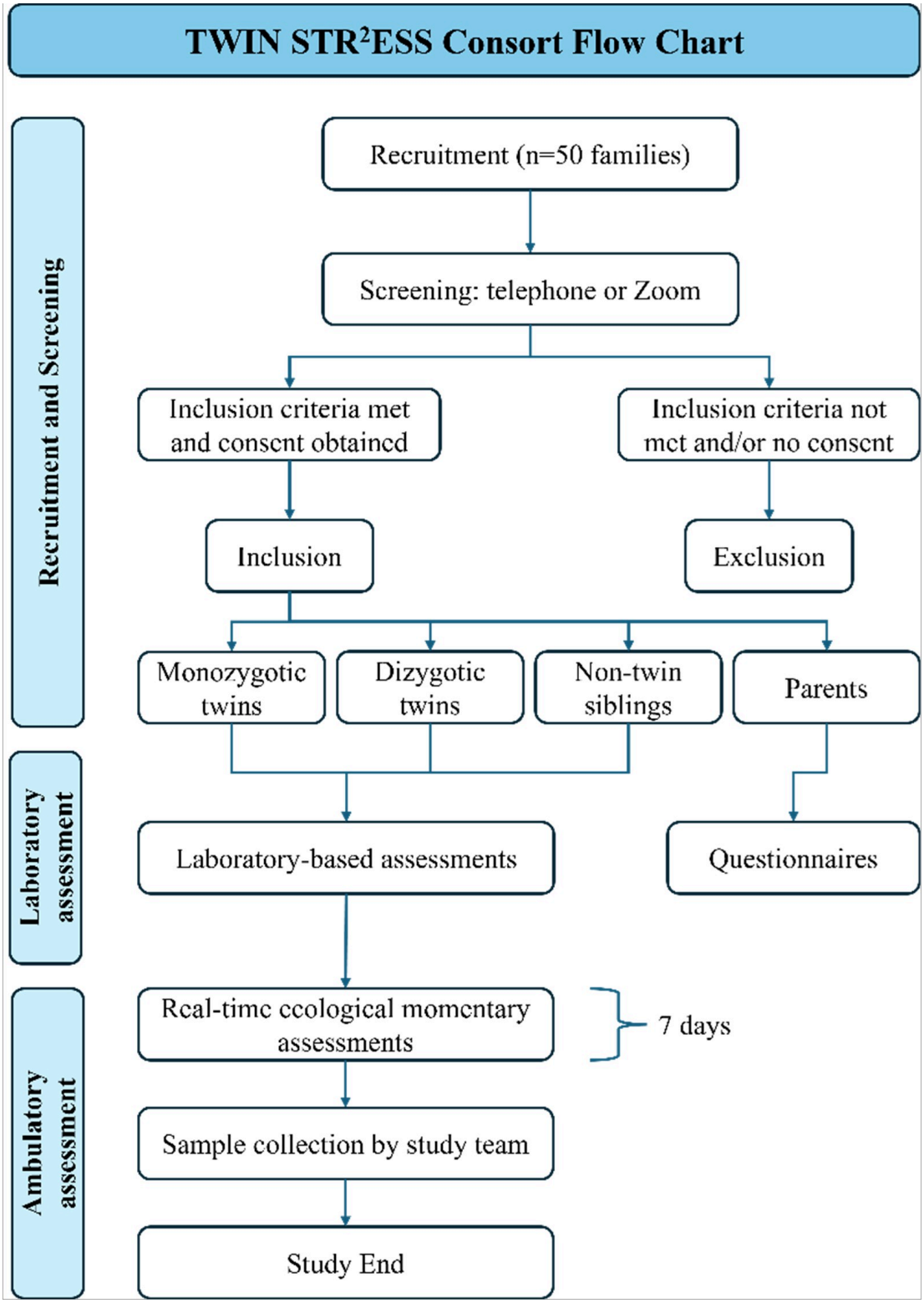


Figure 2

TWIN STR²ESS Consort flow chart of recruitment, laboratory and ambulatory assessment

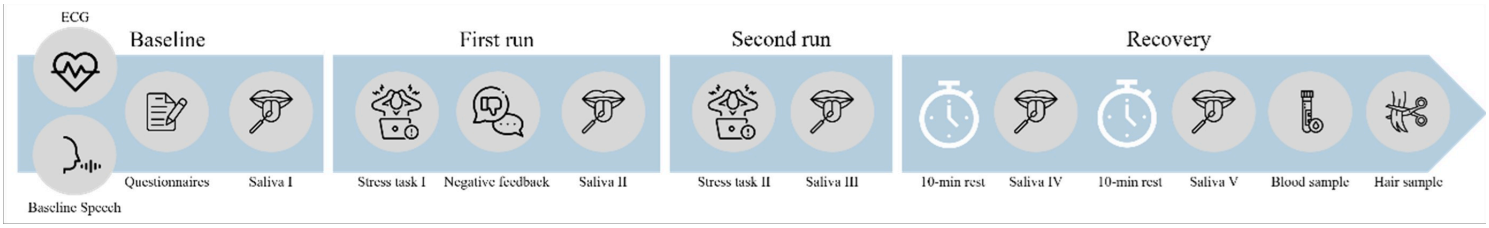


Figure 3

Schematic overview of the laboratory visit procedure. Icons from Microsoft PowerPoint