Mindfulness-based Stress Reduction in Pregnancy: an App-Based Programme to Improve the Health of Mothers and Children (MINDFUL/PMI Study)

Achtsamkeitsbasierte Stressreduktion in der Schwangerschaft: ein App-basiertes Programm zur Verbesserung der Gesundheit von Müttern und Kindern (MINDFUL/PMI-Studie)

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ABSTRACT

Unfavourable intrauterine environmental factors increase the risk of delivery complications as well as postpartum developmental and behavioural problems in children and adolescents with ongoing effects into older age. Biomarker studies show that maternal stress and the use of alcohol and tobacco during pregnancy are associated with a higher intrauterine testosterone exposure of the child. The antenatal testosterone load, in turn, is a risk factor for lasting adverse health effects which extend into adulthood. A 15-week, mindfulness-oriented, app-based programme for the reduction of stress as well as for the reduction of alcohol and tobacco use in pregnant women is established. In the monocentre, prospective, controlled, and investigator-blinded MINDFUL/PMI (Maternal Health and Infant Development in the Follow-up after Pregnancy and a Mindfulness Intervention) study, pregnant women carry out the programme. Its effect on antenatal testosterone exposure of the child is examined by assessing the index/ring finger length ratio and other biomarkers in the 1-year-old children. In addition, the programme's effects on self-regulation, the developmental status and the mental health of the children at the age of one year will be investigated. Additional aspects of the course of the pregnancy and delivery represent exploratory study objectives. This longitudinal study project is

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intended to improve the understanding of the impact of intrauterine environmental factors on early childhood development and health. Maternal stress as well as alcohol and tobacco use during pregnancy are modifiable factors and represent potential preventive targets.

ZUSAMMENFASSUNG

Ungünstige intrauterine Umweltfaktoren erhöhen das Risiko für Geburtskomplikationen sowie postpartale Entwicklungs- und Verhaltensauffälligkeiten bei den Kindern und Jugendlichen mit permanenten Auswirkungen bis ins höhere Alter. Biomarkerstudien zeigen, dass mütterlicher Stress und Konsum von Alkohol und Tabak während der Schwangerschaft mit höherer intrauteriner Testosteronexposition des Kindes assoziiert sind. Die pränatale Testosteronlast ist wiederum ein Risikofaktor für anhaltende und bis ins Erwachsenenalter reichende Gesundheitsbeeinträchtigungen. Es wird ein 15-wöchiges, achtsamkeitsorientiertes, App-basiertes Programm zur Reduktion von Stress sowie zur Verminderung von Alko-

hol- und Tabakkonsum bei schwangeren Frauen etabliert. In der monozentrischen, prospektiven, kontrollierten und untersucherverblindeten MINDFUL/PMI (Maternal Health and Infant Development in the Follow-up after Pregnancy and a Mindfulness Intervention)-Studie führen schwangere Frauen das Programm durch. Dabei wird der Effekt auf die pränatale Testosteronexposition des Kindes untersucht, die mit dem Zeige-/Ringfingerlängenverhältnis und weiteren Biomarkern bei den 1-jährigen Kindern erhoben wird. Außerdem soll beforscht werden, wie sich das Programm auf die Selbstregulation, den Entwicklungsstand und die psychische Gesundheit der Kinder im Alter von einem Jahr auswirkt. Weitere Aspekte des Schwangerschafts- und Geburtsverlaufs stellen explorative Studienziele dar. Dieses longitudinale Studienprojekt soll das Verständnis der Bedeutung intrauteriner Umweltfaktoren für die frühe kindliche Entwicklung und Gesundheit verbessern. Mütterlicher Stress sowie Alkohol- und Tabakkonsum während der Schwangerschaft sind modifizierbare Faktoren und stellen potenzielle präventive Ansatzpunkte dar.

Background

Maternal behaviour and environmental influences during early childhood development have lifelong effects on individual health and disease risks. The antenatal phase is of particular interest. Maternal stress as well as alcohol and tobacco use during pregnancy negatively affect the delivery as well as the development of newborns and children. It is even assumed that these antenatal developmental factors have a permanent impact on health. A better understanding of the relevant modifiable maternal factors is necessary for the successful establishment of new prevention strategies.

Stress, alcohol and tobacco during pregnancy

Six out of ten pregnant women, thus a considerable percentage, complain of relevant stress. Stress during pregnancy negatively affects both the pregnant woman and the unborn child [1,2]. Pregnant women, who report subjective stress, who are exposed to objective stressors or who have higher cortisol values, more often deliver preterm infants [3] and children with a lower birth weight [4]. Children of pregnant women with a high stress level also more often show emotional disorders and cognitive impairments [5–9]. Mindfulness training reduces stress; it is therefore consistent that mindfulness-oriented meditation training in women during pregnancy exerts a positive effect on several postpartum behavioural characteristics of the infants [10]. It is also interesting that a higher level of mindfulness in women during pregnancy is associated with a better self-regulation in the children [11].

A rather considerable proportion of pregnant women consume alcohol and smoke tobacco with negative effects on childhood development. The children and adolescent survey (KIGGS), which is representative of Germany (2003–2006, 17 641 children and adolescents), shows that between 10 and 20% of pregnant women

occasionally smoke and/or drink alcohol. There was even more frequent and higher alcohol consumption in 9.2% of pregnant women [12]. Current epidemiological studies support these high prevalence rates [13]. In addition to the complete picture of foetal alcohol syndrome, antenatal alcohol use also leads to less apparent but still very relevant problems, such as irritability, reduced adaptability, disinhibition, attention problems and hyperactivity in infancy, toddlerhood and childhood as well as to mental health problems and disorders in adolescence [14–18]. An impairment of foetal growth due to maternal tobacco smoking during pregnancy is undisputed [17,19]. Intrauterine nicotine exposure increases the risk of miscarriage and stillbirth, preterm birth, low birth weight, impaired childhood pulmonary function and attention deficit/hyperactivity symptoms [20–23].

Long-term studies and antenatal testosterone exposure

Because of the long follow-up periods, there is only limited direct evidence to date as to which consequences for the child as a result of maternal stress, alcohol consumption and tobacco smoking during pregnancy persist into mid-adulthood and beyond. However, there are indirect indications that antenatal testosterone exposure is involved in lifelong health impairment due to maternal stress as well as alcohol and tobacco use during pregnancy. Biomarkers such as the index/ring finger length ratio (2D:4D ratio) are used to investigate the antenatal testosterone load. It is assumed that the 2D:4D ratio develops in utero and changes only little throughout the rest of life. A smaller 2D:4D ratio stands for a higher antenatal testosterone load and a larger 2D:4D ratio stands for a lower antenatal testosterone load [24–26].

Our own studies as well as reports from independent groups of researchers suggest that maternal stress as well as alcohol and tobacco use during pregnancy lead to an increased intrauterine testosterone load of the child [27–30]. At the same time, it is known

that elevated antenatal testosterone exposure is associated with illnesses throughout life. In the animal model, antenatal testosterone exposure causes brain changes which persist into adulthood and increases alcohol consumption [31, 32]. It is therefore not surprising that a high antenatal testosterone load (recorded in humans using biomarkers, such as the 2D:4D ratio, among others) is associated with a whole range of impairments throughout life. These include, for example, a worse overall state of health [33], behavioural problems in childhood [34], aggression-induced injuries [35, 36], attention deficit/hyperactivity disorder [37], video game addiction [38], addictive use of social networks [39], suicide [40–42], autism [43, 44], prostate carcinoma [45], primary brain tumours [46] as well as binge drinking and alcohol dependence [29, 47–49]. Finally, there are initial indications that a smaller 2D:4D ratio as a surrogate marker for a higher antenatal testosterone exposure is also associated with a shorter life expectancy [41, 49].

Model on the influence of maternal behaviour during pregnancy on the lifelong health of children

The associations described in the previous paragraphs indicate that maternal stress as well as alcohol and tobacco use during pregnancy increase testosterone exposure in children and thus influence the health of the children for life (► Fig. 1).

For this model, there is the above reported indirect evidence. However, it remains unclear whether this involves causal relationships which are actually suitable for establishing preventive approaches. In addition, possible effect sizes of corresponding interventions on later health can only be presumed to date. Therefore, it is intended to conduct the prospective and controlled app-based MINDFUL/PMI (Maternal Health and Infant Development in the Follow-up after Pregnancy and a Mindfulness Intervention) study on mindfulness-oriented reduction of stress and alcohol and tobacco use during pregnancy with the goal of improving the health of mothers and children.

Mindfulness in pregnancy

Mindfulness is an effective method for reducing stress and alcohol and tobacco use. Corresponding training methods promote a mindful attitude, that is, being intentional and nonjudgmental in the present moment, for example. Some studies have already shown that mindfulness training and related methods are suitable for reducing the level of stress and anxiety in pregnancy, also with lasting effects [50–53], and improving neonatal health [10, 54]. A high level of mindfulness also correlates with less alcohol and tobacco use [55] and mindfulness-based methods reduce heavy use [56]. There is evidence of a high level of adherence to mindfulness methods in pregnant women [53]. To increase the availability of the mindfulness programme and to support training at home and integration into daily life, the mindfulness intervention will be established in the form of an app and its effect will be validated.

Maternal health and “Foetal Programming”

“Foetal programming” refers to the imprinting of the foetus in the womb and in the perinatal period through various influences, resulting in the increased appearance of diseases in adolescence and

► Fig. 1 Research model on the influence of maternal behaviour during pregnancy on the lifelong health of children. 2D:4D ratio: index/ring finger length ratio.

adulthood, such as cardiovascular or metabolic diseases. There is some evidence that epigenetic mechanisms may play an important role here [57]. Children of mothers with preeclampsia have, for example, increased feeding problems, endocrine diseases and metabolic disorders [58]. Likewise, hyperemesis gravidarum can cause neurological developmental delays in the children [59]. In addition, illnesses during pregnancy also have a negative influence on the course of the delivery and post-delivery period. Depressive symptoms in the mother during pregnancy are associated, for example, with an increased rate of Caesarean sections and low birth weight [60]. The development of a hypertensive disease in pregnancy does not only present acute consequences during pregnancy for the mother and child. Following preeclampsia, mothers have an increased long-term risk for arterial hypertension, diabetes and cerebrovascular diseases [61].

Therefore, in addition to the expected effect of mindfulness on stress and alcohol and tobacco use as well as depressive symptoms in pregnant women, effects on pregnancy, delivery and on epigenetic patterns are also to be investigated in the MINDFUL/PMI study. The use of mindfulness during pregnancy could offer a preventive approach for reducing perinatal and long-term morbidity.

Issue and study objective

Within the scope of the MINDFUL/PMI research project, a mindfulness-oriented app-based programme to reduce stress as well as to reduce alcohol and tobacco use in pregnant women is to be established and the effect of this programme is to be validated using the childhood antenatal testosterone load. The antenatal testosterone exposure will be assessed using the 2D:4D ratio and additional biomarkers in the 1-year-old children. It will also be investi-

gated how the programme affects children's self-regulation, developmental status and mental health at the age of one year. Different aspects of the course of pregnancy and delivery represent additional exploratory study objectives.

This study is subproject 3 of the "IMAC-Mind" consortium supported by the Federal Ministry of Education and Research (BMBF) ("IMAC-Mind: Improving Mental Health and Reducing Addiction in Childhood and Adolescence through Mindfulness: Mechanisms, Prevention and Treatment, TP3: Reducing stress, alcohol and tobacco use in pregnant women to improve the children's later mental health"; BMBF funding code of subproject 01GL1745C). In accordance with the funding policy objectives of the BMBF initiative "Gesund – ein Leben lang" [Healthy – for life], in this study, a novel concept is being developed for use during the antenatal development phase with the intention of ongoing health promotion and prevention throughout life. Thus, the later risk of disease can already be decreased in the womb and the course can be set for a healthy life. This is an interdisciplinary project which extends over multiple phases of life.

MINDFUL/PMI Study: Summary of the Implementation of the Study

Study design

The MINDFUL/PMI study is a monocentre, prospective, controlled and investigator-blinded research project (▶ **Fig. 2**) at the Universitätsklinikum Erlangen (University Hospital Erlangen). It is planned that 312 pregnant women will participate. They will be randomised into the mindfulness-oriented experimental group or the pregnancy education control group; thus 156 pregnant women are planned for each group.

Study objective

The primary study objective is the comparison of the 2D:4D ratio in the children (as a marker for intrauterine testosterone exposure) between the two randomisation arms. In the women of the mindfulness-oriented experimental group, a larger 2D:4D ratio of the child at the age of 11–12 months (as the measured endpoint) is expected than in the pregnancy education control group.

► **Fig. 3** Sample screenshots of the app. **a** Login page of the app, **b** Information on data privacy, **c** Example for recording stress via selection of categories with the Perceived Stress Scale (PSS-10) [62], **d** Example of a query using a continuous scale, **e** Overview of the interventions and audio files to click on and open.

► **Table 1** shows an excerpt of secondary and exploratory study objectives.

Randomisation

The pregnant women are randomised 1:1 into the following groups upon inclusion in the study following stratification (nullipara versus $\geq$ primipara, high level of stress versus low level of stress (German version of the Perceived Stress Scale [PSS-10] [62]), high level of mindfulness versus low level of mindfulness (German version of the Mindful Attention and Awareness Scale [MAAS] [63]) and participate in a programme consisting of app contents (see sample screenshots of the app in ► **Fig. 3**) and direct contacts. ► **Table 2** shows the inclusion and exclusion criteria.

Mindfulness-oriented experimental group: The participants receive access to our own custom-made app which was adapted to the needs of pregnant women, with mindfulness exercises based on the Mindfulness-Based-Stress-Reduction (MBSR) programme developed by Jon Kabat-Zinn in the 1980s/90s in Worcester (USA) [64–66]. In three direct contacts, the study subjects are introduced to the topic of mindfulness and receive additional coaching. Via the app, they participate approximately twice per week in an app-based visit during which the mindfulness exercises are taught via audio recordings. These average 10 minutes in length and provide psychoeducation in mindfulness and stress. The audio recordings can be replayed and listened to again. There are various mindful movement meditations, mindful sitting meditations and two body scans of different lengths. The psychoeducation involves mindful attitude in everyday life, the distinction between physical sensations, emotions and thoughts, the tendency of the mind to lose itself in thought and the use of breathing to direct attention to the present moment. The participants

► **Table 1** Secondary and exploratory study objectives (excerpt).

Secondary study objectives	<p>In the mindfulness-oriented experimental group, in comparison to the pregnancy education control group, ...</p> <ul style="list-style-type: none"> ▪ there is a positive influence on self-regulation, developmental status and mental health of the 11–12-month-old infants. ▪ the anogenital distance is shortened in children and the strength of TEOAEs in children is increased. ▪ self-reported maternal stress, depressive symptoms, pregnancy-related anxieties and alcohol and tobacco use are reduced. ▪ cortisol, cotinine and ethyl glucuronide levels in maternal hair are reduced. ▪ the self-reported mindfulness of the mothers is increased. ▪ a positive influence on the course of pregnancy and delivery can be demonstrated.
Exploratory study objectives	<p>It shall be demonstrated that participation in the mindfulness-oriented experimental group, in comparison to the pregnancy education control group, ...</p> <ul style="list-style-type: none"> ▪ induces a change in the body mass index during pregnancy and in the first year after delivery. ▪ reduces the risk of hypertensive diseases of pregnancy, an excessively low birth weight, preterm birth and gestational diabetes. ▪ changes the course of biomarker and hormone levels in pregnancy and the post-delivery period. ▪ changes the immune status during pregnancy. ▪ has an effect on the immune cells of the mother and epigenetic patterns in the cells of the child.

TEOAEs: transient evoked otoacoustic emissions

► **Table 2** Inclusion and exclusion criteria.

Inclusion criteria	Pregnant women, <ul style="list-style-type: none"> ▪ who are between 8 + 0 to 14 + 0 weeks of pregnancy, ▪ who are at least 18 years old and a maximum of 50 years old, ▪ who have signed the informed consent, ▪ who agree to take part in the examinations (blood/urine testing, measurement of the 2D:4D ratio and heart rate variability, questionnaires, examination of the child, etc.), ▪ who agree to use the app, ▪ who have an unproblematic pregnancy at the time of inclusion.
Exclusion criteria	<ul style="list-style-type: none"> ▪ multiple pregnancy ▪ manifest comprehension problems during the introductory briefing ▪ prior severe psychiatric illness ▪ past history of adverse or missing effects of mindfulness exercises
2D:4D ratio: index/ring finger length ratio	

are to focus on the topic of mindfulness for 5–10 minutes, 2–7 times per week.

Pregnancy education control group: The participants in the pregnancy education control group receive also access to a custom-made app. This provides them with audio files with information on pregnancy, delivery, the post-delivery period and breastfeeding, at the same frequency and duration as well as with the same layout as in the mindfulness-oriented experimental group (audio recordings lasting an average of 10 minutes approximately twice per week). Three direct contacts also take place in the control group. General information on the development of the embryo and foetus at certain time points in the pregnancy as well as on the *Mutterpass* (pregnancy record), the regular examinations as part of antenatal care, on diseases of pregnancy and the additional possible examinations (such as first trimester screening, cfDNA, organ screening, oral glucose tolerance test, screening for Group B streptococci) is given. In addition, the topics of nutrition, sports and habits when travelling are addressed and the fields of mode of delivery and pain therapy during delivery are explained. Finally, information on breastfeeding and the post-delivery period is provided.

Entire duration of the study

The entire duration of the study comprises the preparation phase with a start in the first quarter of 2016, the active study phase with inclusion of pregnant women expected as of the fourth quarter of 2018 until the second quarter of 2020, the active study phase with the examination of the children from the first quarter of 2020 until the fourth quarter of 2021 and the data analysis, evaluation and post-processing in the fourth quarter of 2021 and the first quarter of 2022.

Individual course of the study and measurement methods

The study consists of a 15-week programme part with three direct visits during pregnancy and two postpartum direct visits to record the study endpoints. These are known as visits V1, V15, V29, V30 and V31 (► **Table 3**). In addition, the participants in the mindfulness-oriented experimental group are offered mindfulness exercises as part of the app approximately twice weekly. These are to be performed by the participants 2–7 times per week. The participants of the pregnancy education control group similarly receive information about pregnancy and delivery via the app approximately twice per week. The visits A2 to A14 and A16 to A28 provided via the app take place between V1 and V15 and between V15 and V29. The participants in the mindfulness-oriented experimental group are asked every week via the app how long they exercised mindfulness in the prior week. In addition, the heart rate variability is measured in a subgroup of the pregnant women each week using a smartphone camera app [67].

Statistical considerations and sample size calculation

The primary endpoint, the 2D:4D ratio, is evaluated using a multiple linear regression model with the predictors of study arm, sex of the child (female, male) and further predictors. The sex of the child is taken into account since differences between boys and girls are expected. Study participants with missing target variable values are excluded. Missing predictor values are imputed based on the available values of the other study participants. The analysis of the secondary study objectives is performed analogously. There are no interim analyses planned.

Assuming a standardised group difference of Cohen's $d = 0.35$ for the primary endpoint, the sample size estimate yields 260 study participants (significance level 0.05, power 0.80). A presumed failure rate of 15% yields a final sample size of 312 participants. It is expected that the mindfulness-oriented experimental group, in comparison to the pregnancy education control group, will reach a Cohen's $d = 0.40$ for self-regulation in children (secondary study objective). In this case, the statistical power for the secondary study objective is 89%.

Ethical aspects and trial registration

The study project has been approved by the Ethics Committee of the Friedrich-Alexander University Erlangen-Nürnberg (FAU) (application number: 58_18 B). The study is conducted in accordance with the principles of the Declaration of Helsinki (2013 in Fortaleza, Brazil, revised edition) and the ICH-GCP guidelines (German Register of Clinical Trials; www.drks.de; DRKS00014920).

► **Table 3** Study procedures (excerpt).

Visits	Screening	V1	V15	V29	V30	V31
Time		Day 1 (8th-14th WOP)	Day 53 ± 7 days	Day 105 ± 7 days	Delivery to + 14 days	11–12 months post partum
Inclusion/exclusion criteria	X	X				
Written informed consent		X				
Randomisation		X				
Recording of						
▪ General, gynaecological and obstetric past history		X				
▪ Stress as well as alcohol and tobacco use		X	X	X	X	X
▪ Mindfulness		X	X	X	X	X
▪ Depression		X	X	X	X	X
▪ Pregnancy-related anxieties		X		X		
▪ Heart rate variability		X	X	X		
Direct intervention		X	X	X		
Measurement of ethyl glucuronide in hair and meconium		X			X	
Blood sample – mother		X	X	X	X	X
Measurement of cotinine/cortisol in maternal hair		X			X	
Sampling of placental tissue and umbilical cord blood					X	
Oral mucosa swab in the child					X	X
Biomarker for prenatal testosterone exposure					X	X
Maternal microbiome (stool sample)					X	
Self-regulation, developmental status and emotional and behavioural problems of the child						X

The table shows the direct visits V1, V15, V29, V30 and V31 with an excerpt of the study procedures and the planned survey instruments.

Mother: Stress: German version of the Perceived Stress Scale (PSS-10) [62]; alcohol use: adapted version of the Alcohol Use Disorder Identification Test (AUDIT-C) [68] and nicotine use: adapted version of a smoking questionnaire from the Robert Koch Institute Berlin [69], in addition, Timeline Followback survey modified for pregnancy [70]; mindfulness: German version of the Mindful Attention and Awareness Scale (MAAS) [63]; depression: German version of the Edinburgh Postnatal Depression Scale (EPDS) [71, 72]; pregnancy-related anxieties: Pregnancy-Related Anxiety Questionnaire (PRAQ-R2) [73].

Child: Self-regulation: Infant Behavior Questionnaire Revised (IBQ-R) [74, 75]; developmental status: Bayley Scales of Infant and Toddler Development – Third Edition [76]; emotional and behavioural problems: Child-Behavior Checklist (CBCL 1.5–5.0) [77].

WOP: week of pregnancy

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Conflict of Interest

The authors quote some of their own publications on which this work and the idea of the study are based.

References

- [1] Stone SL, Diop H, Declercq E et al. Stressful events during pregnancy and postpartum depressive symptoms. *J Womens Health (Larchmt)* 2015; 24: 384–393
- [2] Stein A, Pearson RM, Goodman SH et al. Effects of perinatal mental disorders on the fetus and child. *Lancet* 2014; 384: 1800–1819
- [3] Lilliecreutz C, Larén J, Sydsjö G et al. Effect of maternal stress during pregnancy on the risk for preterm birth. *BMC Pregnancy Childbirth* 2016; 16: 5
- [4] Baibazarova E, van de Beek C, Cohen-Kettenis PT et al. Influence of prenatal maternal stress, maternal plasma cortisol and cortisol in the amniotic fluid on birth outcomes and child temperament at 3 months. *Psychoneuroendocrinology* 2013; 38: 907–915
- [5] Glover V. Prenatal stress and its effects on the fetus and the child: possible underlying biological mechanisms. *Adv Neurobiol* 2015; 10: 269–283
- [6] Talge NM, Neal C, Glover V et al. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry* 2007; 48: 245–261

- [7] Davis EP, Glynn LM, Schetter CD et al. Prenatal exposure to maternal depression and cortisol influences infant temperament. *J Am Acad Child Adolesc Psychiatry* 2007; 46: 737–746
- [8] Nolvi S, Karlsson L, Bridgett DJ et al. Maternal prenatal stress and infant emotional reactivity six months postpartum. *J Affect Disord* 2016; 199: 163–170
- [9] Huizink AC, de Medina PGR, Mulder EJJ et al. Psychological measures of prenatal stress as predictors of infant temperament. *J Am Acad Child Adolesc Psychiatry* 2002; 41: 1078–1085
- [10] Chan KP. Prenatal meditation influences infant behaviors. *Infant Behav Dev* 2014; 37: 556–561
- [11] van den Heuvel MI, Johannes MA, Henrichs J et al. Maternal mindfulness during pregnancy and infant socio-emotional development and temperament: the mediating role of maternal anxiety. *Early Hum Dev* 2015; 91: 103–108
- [12] Bergmann KE, Bergmann RL, Ellert U et al. Perinatale Einflussfaktoren auf die spätere Gesundheit. *Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz* 2007; 50: 670–676
- [13] Popova S, Lange S, Probst C et al. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. *Lancet Glob Health* 2017; 5: e290–e299
- [14] Alvik A, Torgersen AM, Aalen OO et al. Binge alcohol exposure once a week in early pregnancy predicts temperament and sleeping problems in the infant. *Early Hum Dev* 2011; 87: 827–833
- [15] Nulman I, Rovet J, Kennedy D et al. Binge alcohol consumption by non-alcohol-dependent women during pregnancy affects child behaviour, but not general intellectual functioning: a prospective controlled study. *Arch Womens Ment Health* 2004; 7: 173–181
- [16] Burger PH, Goecke TW, Fasching PA et al. [How does maternal alcohol consumption during pregnancy affect the development of attention deficit/hyperactivity syndrome in the child]. *Fortschr Neurol Psychiatr* 2011; 79: 500–506
- [17] Polańska K, Jurewicz J, Hanke W. Smoking and alcohol drinking during pregnancy as the risk factors for poor child neurodevelopment – a review of epidemiological studies. *Int J Occup Med Environ Health* 2015; 28: 419–443
- [18] Flak AL, Su S, Bertrand J et al. The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. *Alcohol Clin Exp Res* 2014; 38: 214–226
- [19] Abraham M, Alramadhan S, Iniguez C et al. A systematic review of maternal smoking during pregnancy and fetal measurements with meta-analysis. *PLoS One* 2017; 12: e0170946
- [20] McEvoy CT, Spindel ER. Pulmonary effects of maternal smoking on the fetus and child: effects on lung development, respiratory morbidities, and life long lung health. *Paediatr Respir Rev* 2017; 21: 27–33
- [21] Holz NE, Boecker R, Baumeister S et al. Effect of prenatal exposure to tobacco smoke on inhibitory control: neuroimaging results from a 25-year prospective study. *JAMA Psychiatry* 2014; 71: 786–796
- [22] Brook JS, Brook DW, Whiteman M. The influence of maternal smoking during pregnancy on the toddler's negativity. *Arch Pediatr Adolesc Med* 2000; 154: 381–385
- [23] Wiebe SA, Fang H, Johnson C et al. Determining the impact of prenatal tobacco exposure on self-regulation at 6 months. *Dev Psychol* 2014; 50: 1746–1756
- [24] Berenbaum SA, Bryk KK, Nowak N et al. Fingers as a marker of prenatal androgen exposure. *Endocrinology* 2009; 150: 5119–5124
- [25] Zheng Z, Cohn MJ. Developmental basis of sexually dimorphic digit ratios. *Proc Natl Acad Sci U S A* 2011; 108: 16289–16294
- [26] Talarovičová A, Kršková L, Blažeková J. Testosterone enhancement during pregnancy influences the 2D:4D ratio and open field motor activity of rat siblings in adulthood. *Horm Behav* 2009; 55: 235–239
- [27] Lilley T, Laaksonen T, Huitu O et al. Maternal corticosterone but not testosterone level is associated with the ratio of second-to-fourth digit length (2D:4D) in field vole offspring (*Microtus agrestis*). *Physiol Behav* 2010; 99: 433–437
- [28] Rizwan S, Manning JT, Brabin BJ. Maternal smoking during pregnancy and possible effects of in utero testosterone: evidence from the 2D:4D finger length ratio. *Early Hum Dev* 2007; 83: 87–90
- [29] Lenz B, Mühle C, Braun B et al. Prenatal and adult androgen activities in alcohol dependence. *Acta Psychiatr Scand* 2017; 136: 96–107
- [30] Barrett ES, Swan SH. Stress and androgen activity during fetal development. *Endocrinology* 2015; 156: 3435–3441
- [31] Huber SE, Zoicas I, Reichel M et al. Prenatal androgen receptor activation determines adult alcohol and water drinking in a sex-specific way. *Addict Biol* 2018; 23: 904–920
- [32] Brown ECZ, Steadman CJ, Lee TM et al. Sex differences and effects of prenatal exposure to excess testosterone on ventral tegmental area dopamine neurons in adult sheep. *Eur J Neurosci* 2015; 41: 1157–1166
- [33] Rapoza KA. Does life stress moderate/mediate the relationship between finger length ratio (2D4D), depression and physical health? *Pers Individ Differ* 2017; 113: 74–80
- [34] Eichler A, Heinrich H, Moll GH et al. Digit ratio (2D:4D) and behavioral symptoms in primary-school aged boys. *Early Hum Dev* 2018; 119: 1–7
- [35] Joyce CW, Kelly JC, Chan JC et al. Second to fourth digit ratio confirms aggressive tendencies in patients with boxers fractures. *Injury* 2013; 44: 1636–1639
- [36] O'Brian DE, Dawson PH, Kelly JC et al. Assessment of the 2D:4D ratio in aggression-related injuries in children attending a paediatric emergency department. *Ir J Med Sci* 2017; 186: 441–445
- [37] Martel MM, Gobrogge KL, Breedlove SM et al. Masculinized finger-length ratios of boys, but not girls, are associated with attention-deficit/hyperactivity disorder. *Behav Neurosci* 2008; 122: 273–281
- [38] Kornhuber J, Zenses EM, Lenz B et al. Low 2D:4D values are associated with video game addiction. *PLoS One* 2013; 8: e79539
- [39] Bouna-Pyrrou P, Mühle C, Kornhuber J et al. Internet gaming disorder, social network disorder and laterality: handedness relates to pathological use of social networks. *J Neural Transm (Vienna)* 2015; 122: 1187–1196
- [40] Lenz B, Thiem D, Bouna-Pyrrou P et al. Low digit ratio (2D:4D) in male suicide victims. *J Neural Transm (Vienna)* 2016; 123: 1499–1503
- [41] Lenz B, Kornhuber J. Cross-national gender variations of digit ratio (2D:4D) correlate with life expectancy, suicide rate, and other causes of death. *J Neural Transm (Vienna)* 2018; 125: 239–246
- [42] Lenz B, Röther M, Bouna-Pyrrou P et al. The androgen model of suicide completion. *Prog Neurobiol* 2018. doi:10.1016/j.pneurobio.2018.06.003
- [43] Masuya Y, Okamoto Y, Inohara K et al. Sex-different abnormalities in the right second to fourth digit ratio in Japanese individuals with autism spectrum disorders. *Mol Autism* 2015; 6: 34
- [44] Al-Zaid FS, Alhader AA, Al-Ayadi LY. The second to fourth digit ratio (2D:4D) in Saudi boys with autism: A potential screening tool. *Early Hum Dev* 2015; 91: 413–415
- [45] Mendes PHC, Martelli DRB, de Melo Costa S et al. Comparison of digit ratio (2D:4D) between Brazilian men with and without prostate cancer. *Prostate Cancer Prostatic Dis* 2016; 19: 107–110
- [46] Bunevicius A, Tamasauskas S, Deltuva VP et al. Digit ratio (2D:4D) in primary brain tumor patients: A case-control study. *Early Hum Dev* 2016; 103: 205–208
- [47] Han C, Bae H, Lee YS et al. The ratio of 2nd to 4th digit length in Korean alcohol-dependent patients. *Clin Psychopharmacol Neurosci* 2016; 14: 148–152
- [48] Kornhuber J, Erhard G, Lenz B et al. Low digit ratio 2D:4D in alcohol dependent patients. *PLoS One* 2011; 6: e19332

- [49] Lenz B, Bouna-Pyrrou P, Mühle C et al. Low digit ratio (2D:4D) and late pubertal onset indicate prenatal hyperandrogenization in alcohol binge drinking. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; 86: 370–378
- [50] Dunn C, Hanieh E, Roberts R et al. Mindful pregnancy and childbirth: effects of a mindfulness-based intervention on women's psychological distress and well-being in the perinatal period. *Arch Womens Ment Health* 2012; 15: 139–143
- [51] Muthukrishnan S, Jain R, Kohli S et al. Effect of mindfulness meditation on perceived stress scores and autonomic function tests of pregnant Indian women. *J Clin Diagn Res* 2016; 10: CC05–CC08
- [52] Guardino CM, Dunkel Schetter C, Bower JE et al. Randomised controlled pilot trial of mindfulness training for stress reduction during pregnancy. *Psychol Health* 2014; 29: 334–349
- [53] Goodman JH, Guarino A, Chenausky K et al. CALM Pregnancy: results of a pilot study of mindfulness-based cognitive therapy for perinatal anxiety. *Arch Womens Ment Health* 2014; 17: 373–387
- [54] Zilcha-Mano S, Langer E. Mindful attention to variability intervention and successful pregnancy outcomes. *J Clin Psychol* 2016; 72: 897–907
- [55] Karyadi KA, VanderVeen JD, Cyders MA. A meta-analysis of the relationship between trait mindfulness and substance use behaviors. *Drug Alcohol Depend* 2014; 143: 1–10
- [56] Cavicchioli M, Movalli M, Maffei C. The clinical efficacy of mindfulness-based treatments for alcohol and drugs use disorders: a meta-analytic review of randomized and nonrandomized controlled trials. *Eur Addict Res* 2018; 24: 137–162
- [57] Arabin B, Baschat AA. Pregnancy: an underutilized window of opportunity to improve long-term maternal and infant health—an appeal for continuous family care and interdisciplinary communication. *Front Pediatr* 2017; 5: 69
- [58] Wu CS, Nohr EA, Bech BH et al. Health of children born to mothers who had preeclampsia: a population-based cohort study. *Am J Obstet Gynecol* 2009; 201: 269.e1–269.e10
- [59] Fejzo MS, Magtira A, Schoenberg FP et al. Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol* 2015; 189: 79–84
- [60] Bartel S, Costa SD, Kropf S et al. Pregnancy outcomes in maternal neuropsychiatric illness and substance abuse. *Geburtsh Frauenheilk* 2017; 77: 1189–1199
- [61] Auger N, Fraser WD, Schnitzer M et al. Recurrent pre-eclampsia and subsequent cardiovascular risk. *Heart* 2017; 103: 235–243
- [62] Klein EM, Brähler E, Dreier M et al. The German version of the Perceived Stress Scale – psychometric characteristics in a representative German community sample. *BMC Psychiatry* 2016; 16: 159
- [63] Michalak J, Heidenreich T, Ströhle G et al. German version of the Mindful Attention and Awareness Scale (MAAS) – psychometric features of a mindfulness questionnaire. *Z Klin Psychol Psychother* 2008; 37: 200–208
- [64] Kabat-Zinn J. An outpatient program in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: theoretical considerations and preliminary results. *Gen Hosp Psychiatry* 1982; 4: 33–47
- [65] Kabat-Zinn J, Lipworth L, Burney R. The clinical use of mindfulness meditation for the self-regulation of chronic pain. *J Behav Med* 1985; 8: 163–190
- [66] Kabat-Zinn J, Massion AO, Kristeller J et al. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Am J Psychiatry* 1992; 149: 936–943
- [67] Plews DJ, Scott B, Altini M et al. Comparison of heart-rate-variability recording with smartphone photoplethysmography, polar H7 chest strap, and electrocardiography. *Int J Sports Physiol Perform* 2017; 12: 1324–1328
- [68] Bush K, Kivlahan DR, McDonell MB et al. for the Ambulatory Care Quality Improvement Project (ACQUIP). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Arch Intern Med* 1998; 158: 1789–1795
- [69] Latza U, Hoffmann E, Terschüren C et al. Erhebung, Quantifizierung und Analyse der Rauchexposition in epidemiologischen Studien. Berlin: Robert Koch-Institut; 2005
- [70] Sobell LC, Brown J, Leo GI et al. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug Alcohol Depend* 1996; 42: 49–54
- [71] Cox JL, Chapman G, Murray D et al. Validation of the Edinburgh postnatal depression scale (EPDS) in non-postnatal women. *J Affect Disord* 1996; 39: 185–189
- [72] Bergant AM, Nguyen T, Heim K et al. [German language version and validation of the Edinburgh postnatal depression scale]. *Dtsch Med Wochenschr* 1998; 123: 35–40
- [73] Huizink AC, Delforterie MJ, Scheinin NM et al. Adaption of pregnancy anxiety questionnaire-revised for all pregnant women regardless of parity: PRAQ-R2. *Arch Womens Ment Health* 2016; 19: 125–132
- [74] Gartstein MA, Rothbart MK. Studying infant temperament via the Revised Infant Behavior Questionnaire. *Infant Behav Dev* 2003; 26: 64–86
- [75] Vonderlin E, Ropeter A, Pauen S. Assessment of temperament with the Infant Behavior Questionnaire Revised (IBQ-R) – the psychometric properties of a German version. *Z Kinder-Jugendpsychiatr Psychother* 2012; 40: 307–314
- [76] Bayley N. Bayley Scales of Infant and Toddler Development – Third Edition. German adaptation: Reuner G, Rosenkranz J. Frankfurt a. M.: Pearson Assessment & Information GmbH; 2014
- [77] Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev* 2000; 21: 265–271