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Alcohol and Nicotine Consumption during Pregnancy:

Prevalence, Predictors and Effects on Early Child Development

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Abstract

Background and Aim Prenatal exposure to alcohol and nicotine poses one of the highest risks for a healthy child development. The aim of this dissertation was to analyse current literature on effects of high- and low to moderate prenatal exposure on early child development. Consumption prevalence during all stages of pregnancy and factors that may predict the consumption were estimated based on a dataset.

Methods To analyse the effects of consumption on early child development, a comprehensive and systematic literature review was conducted, using the electronic databases Pubmed, Science Direct and Web of Science (publication I and II). The analysis of consumption prevalence and predictors (publication III) was realized with a dataset of 260 pregnant women participating in the Bremen initiative to strengthen early childhood development (BRISE) in Germany.

Results Literature reviews showed that besides high consumption amounts even exposure of low to moderate amounts poses a risk for healthy child development. BRISE-data indicated that women consumed alcohol and nicotine during all stages of pregnancy but primarily until confirmation of pregnancy. Social support, age, Islamic cultural background and pregnancy planning seemed to predict the consumption of alcohol. Education and pregnancy planning appeared to predict the consumption of nicotine during pregnancy.

Conclusions When discussing prenatal alcohol and nicotine exposure, alongside effects on early child development, it is essential to address aspects like consumption prevalence and predictive factors. By sharing such scientifically and socio-politically relevant findings to experts in the social and health system, prevention and education measures can be made more effective.

Zusammenfassung

Hintergrund und Ziel Pränatale Alkohol- und Nikotinexposition birgt eines der höchsten Risiken für eine gesunde kindliche Entwicklung. Ziel dieser Dissertation war es einen Überblick über die aktuelle Literatur zu den Auswirkungen hoher und geringer bis moderater Konsummengen auf die frühkindliche Entwicklung zu generieren. Konsumprävalenzen während der Schwangerschaft, sowie weitere Faktoren, die den Konsum vorhersagen könnten, wurden anhand eines Datensatzes untersucht.

Methoden Zur Untersuchung von Effekten des Konsums auf die frühkindliche Entwicklung wurde eine umfassende Literaturrecherche unter Verwendung der elektronischen Datenbanken Pubmed, Science Direct und Web of Science (Publikation I und II) durchgeführt. Die Analyse der Konsumprävalenz und der weiteren Einflussfaktoren (Publikation III), wurde mit einem Datensatz von 260 schwangeren Frauen durchgeführt, die an der Bremer Initiative zur Stärkung frühkindlicher Entwicklung (BRISE) in Deutschland teilnehmen.

Ergebnisse Scheinbar können auch pränatale Expositionen in geringen bis moderaten Mengen ein Risiko für die frühkindliche Entwicklung darstellen. Die Analyse der BRISE-Daten zeigte, dass Frauen in allen Stadien der Schwangerschaft Alkohol und Nikotin konsumierten, jedoch hauptsächlich bis zur Bestätigung der Schwangerschaft. Die Art der sozialen Unterstützung, das Alter, islamisch-kultureller Hintergrund und die Schwangerschaftsplanung können den Alkoholkonsum vorhersagen. Nikotinkonsum hingegen scheint durch das Bildungsniveau und die Schwangerschaftsplanung vorhergesagt zu werden.

Schlussfolgerungen Bei der Diskussion zu pränataler Alkohol- und Nikotinexposition müssen, neben den Auswirkungen auf die frühkindliche Entwicklung, auch andere entscheidende Aspekte wie die Konsumprävalenz und mögliche Prädiktoren berücksichtigt werden. Durch die Weitergabe von solchen wissenschaftlich und gesellschaftspolitisch relevanten Erkenntnissen an Experten des Sozial- und Gesundheitssystems kann Präventions- und Aufklärungsarbeit effektiver gestaltet werden.

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ADHD	Attention Deficit Hyperactivity Disorder
BRISE	Bremer Initiative zur Stärkung frühkindlicher Entwicklung; engl.: Bremen initiative to strengthen early childhood development
CO	Carbon Monoxid
COHb	Carboxyhemoglobin
EEG	Electroencephalography
EKG	Electrocardiogram
C_2H_6O	Ethanol
FAS	Foetal Alcohol Syndrome
FASD	Foetal Alcohol Spectrum Disorders
FTS	Foetal Tobacco Syndrome
$C_{10}H_{14}N_2$	Nicotine
nAChR	Nicotinergic Acetylcholine Receptors

List of publications

Three scientific articles, published in peer-reviewed journals, are propounded within the scope of this dissertation. A list of these three publications is presented in Table 1.

Table 1: List of publications relevant to the present dissertation

Publication I	Römer P, Reinelt T, Petermann F, Teickner C. Alcohol consumption during pregnancy-which effects on early child development are known? Alkoholkonsum während der Schwangerschaft-Welche Auswirkungen auf die frühkindliche Entwicklung sind bekannt? *Kindheit und Entwicklung,* 2019, 28 (1) 6-18.
Publication II	Römer P, Mathes B, Reinelt T, Stoyanova P, Petermann F, Zierul C. Systematic review showed that low and moderate prenatal alcohol and nicotine exposure affected early child development. *Acta Paediatrica*. 2020, 109 (12) 2491-2501.
Publication III	Römer P, Kemmerich R, Petermann F, Mathes B, Zierul C. Alcohol and nicotine consumption during pregnancy: Prevalence and predictors among women in Bremen, Germany. *Sucht*. 2023, 69 (3), 99-111.

Further publications in peer-reviewed journals and contributions to scientific conferences that were worked on during the doctorate are listed below.

Further publications:

Römer P, Gómez Putzer A, Kemmerich R, Mathes B. Effects of Prenatal
Electronic Cigarette Exposure On Foetal Development: a Review of the
Literature. *Geburtshilfe und Frauenheilkunde*, 2021;11:1224-1237.

Stoyanova P, Wienke A.S, Römer P, Mathes B. (in preparation).
Neurophysiological markers of parental depression and anxiety in
infants, children and adolescents.

Contributions to conferences:

Römer P, Kemmerich R, Petermann F, Zierul C (2019). Alcohol and nicotine
consumption during pregnancy: Prevalence and additional risc factors.
Poster presentation on the congress of developmental and pedagogical
psychology (PaePsy) in Leipzig, Germany.

Römer P, Kemmerich R, Petermann F, Mathes B, Zierul C (2019). Prevalence
of alcohol and nicotine consumption in the first trimester of pregnancy
and additional risk factors. Poster presentation on the first BRISE-
conference on early childhood development in Berlin, Germany.

Römer P, Mathes B, Reinelt T, Stoyanova P, Petermann F, Zierul C (2020).
Effects of prenatal alcohol and nicotine exposure on early child
development. Poster presentation on the scientific advisory committee in
Bremen, Germany.

Stoyanova P, Wienke A.S, Römer P, Petertmann F, Mathes B. (2019).
Neurophysiological markers of parental depression and anxiety in infants,
children and adolescents. Poster presentation on the congress of
developmental and padagogical psychology (PaePsy) in Leipzig,
Germany.

Scientific field of activity and research during the doctorate

The doctoral project was implemented as part of the Bremen initiative to foster early childhood development (German: Bremer Initiative zur Stärkung frühkindlicher Entwicklung (BRISE) at the University of Bremen. The project has started in 2017 and is currently funded until 2025. The longitudinal project aims to investigate the effects of early childhood intervention strategies from pregnancy to the first year at school and to support educational equality.

The main focus of the dissertation included literature and empirical research on alcohol and nicotine consumption during pregnancy regarding consumption prevalence, additional factors that may predict the consumption as well as effects on early child development. The literature research established the basis for the empirical part. It included extensive and systematic literature reviews on the effects of high levels of prenatal alcohol exposure and low to moderate levels of prenatal alcohol and nicotine exposure on early child development, comprising the first two years of life. Since the BRISE-sample is a non-clinical population, the majority of women who consumed alcohol or nicotine during pregnancy were expected to primarily consume low to moderate amounts. The empirical research and its focus arose from relevant gaps in current research, detected trough the literature reviews. These comprised a lack of knowledge about consumption prevalence, especially regarding low to moderate amounts during any stage of a pregnancy. Coherent definitions for different consumption amounts are missing as well as the inclusion of factors that may influence the consumption behaviour during pregnancy as potential predictors. The current study is based on data collected in the first data wave of the BRISE project (i.e., the measurement time point during pregnancy (T0) or within the first weeks postpartum (T0post)). The research question of the empirical part focused on

the consumption prevalence of alcohol and nicotine during pregnancy and additional factors such as the pregnant women's social environment or their level of education. These factors may be seen as predictors of consumption behaviour during pregnancy. Besides the systematic literature reviews, the empirical part of this dissertation was based on scientific work with practical aspects. This means, part of this dissertation was to work in the field, recruiting participants and collecting data but also to foster the relationship with participating families, organizing and conducting home and lab visits, using different test formats, for example surveys and (neuro-) developmental test-batteries. In addition to the T0 and T0post measurement time-points, which were relevant to the research questions of the doctorate, the data collection during the doctoral phase also included the implementation and piloting of new surveys and tests for further measurement time points. Measurement time points were divided into eight different time-points between the last third of pregnancy and the child's school enrolment. In order to map the women's behaviour and early childhood development on different dimensions, the program includes not only extensive surveys but also observational measures, tests and development diagnostics. For this purpose, extensive training and further education took place. A corresponding infrastructure for research regarding electroencephalography (EEG), electrocardiogram (EKG), eye tracking and time-synchronized video recordings from different perspectives were provided and established for the measurement procedures in the BRISE research laboratory. Funded by the Jacobs Foundation, it comprised paradigms for three different measurement times corresponding future data waves to test early child development. A more detailed methodology on the dissertation project is described in section 4.1.1. and publication III (Appendix C).

Introduction

Starting with fertilization, children are particularly sensitive to environmental factors, because of their high developmental plasticity (Nigg, 2016; Römer et al., 2020; Ulrich & Petermann, 2016). The embryogenesis, the foetal period and the first years of life represent a period in which remarkable qualitative and quantitative growth and shaping processes in various functional areas take place (Dawson et al., 2000). Toxic substances are among the most influential factors for the development of the offspring (Bolte et al., 2022; Forray, 2016). Alcohol, nicotine and their metabolites are able to reach the foetal blood stream through the maternal placenta (Nulman et al., 2018). Thus, they are causing toxic effects on essential developmental processes like cell proliferation and migration (Nulman et al., 2018). Children in their early development are especially vulnerable to toxins, as detoxification processes are significantly delayed in the biochemically immature organisms (Spohr, 2005). Hence, prenatal exposure to alcohol and nicotine is one of the highest risks for the course of a healthy pregnancy. This does not only apply to high quantities but also to low and moderate amounts of alcohol and nicotine consumed during pregnancy (King et al., 2018; Nulman et al., 2018). Prenatal exposure to alcohol and nicotine can cause long term consequences, such as behavioural, cognitive and morphological deficits in affected children (King et al., 2018; Subramoney et al., 2018; Ulrich & Petermann, 2016). Apart from well-known effects of high-level consumption that are documented comprehensively in the literature, the influence of low and moderate levels of alcohol and nicotine on perinatal outcomes is still not well understood and needs further investigation. For a comprehensive analysis of the effects of prenatal alcohol and nicotine exposure on early child development, further aspects must be included. This involves a

continuous and global assessment of consumption prevalence with adequate underlying definitions of different consumption amounts like high, moderate and low. Furthermore, it is essential to include factors that may predict the consumption behaviour of toxic substances during pregnancy. Thus, a comprehensive knowledge about environmental and socioeconomic circumstances that may predict the consumption during pregnancy could lead to the establishment of adequate preventive measures.

1   Theoretical background

The theoretical background relevant to the present dissertation includes the following aspects: (i) Prevalence of alcohol and nicotine consumption and definitions of consumption amounts, (ii) prevalence of alcohol and nicotine consumption during pregnancy, (iii) transmission of alcohol and nicotine to the foetus during pregnancy, (iiii) their effects on early child development and (iiiii) additional factors that may predict the consumption during pregnancy. Finally, gaps in current research and resulting topics and research questions addressed in this dissertation as well as related publications are described.

1.1   Prevalence of alcohol and nicotine consumption

Although the general consumption prevalence of alcohol and especially of nicotine decreased in Germany during the last decades (Deutsche Hauptstelle für Suchtfragen e.V. (DHS), 2022), both substances are among those toxic substances most frequently consumed by women in childbearing age (Forray, 2016; Rauschert et al., 2021). Despite their known harmfulness to health, the consumption of alcohol and nicotine appears to take place all across the world, even during pregnancy (Forray, 2016; Popova et al., 2017).

1.1.1   Definitions of different consumption amounts

To gather representative data on the prevalence of different consumption amounts like high, moderate and low, precise definitions for these amounts are decisive. In current literature, definitions of alcohol and nicotine consumption generally differ in terms of (i) the variety of what is measured to define consumption patterns (e.g., the amount, frequency, and timeframe of consumption) and (ii) the different definitions of these measured aspects (e.g.,

how many grams of alcohol/nicotine are contained in one drink/one cigarette (Clifford et al., 2012; Kuntsche et al., 2017).

Definitions for alcohol consumption pattern are usually given in drinks per week or drinks per occasion. Definitions for high amounts contradict strongly, given as two or more drinks (Myers et al., 2018) but also seven or more drinks per week (Muggli et al., 2016; O'Leary et al., 2010). Definitions for moderate amounts range between five and eight drinks per week (Falgreen-Eriksen et al., 2012) which partly overlaps with definitions for high amounts. Furthermore, seven or less drinks per week are classified as both, moderate (Muggli et al., 2016; O'Leary et al., 2009, 2010), and low consumption (McCormack et al., 2017; Muggli et al., 2016; O'Leary et al., 2009, 2010). In addition, one to four drinks per week are used to define low consumption (Falgreen-Eriksen et al., 2012), whereas the similar amount of up to six drinks per week is reported as moderate amounts (Flak et al., 2014). Definitions describing the consumption in occasions seem to be more consistent. High amounts are defined as three or more (Nulman et al., 2018) and five to six drinks per occasion (Popova et al., 2017). Moderate amounts are defined as more than two but less than five drinks (Muggli et al., 2016; O'Leary et al., 2009, 2010) and low amounts are defined as less than two drinks per occasion (McCormack et al., 2017; Muggli et al., 2016; O'Leary et al., 2009, 2010). Recent studies used definitions that were already established previously by O´Leary et al., 2010 (e.g., Hutchinson et al., 2019).

As the amount of alcohol is mostly classified by the number of consumed alcoholic drinks (e.g., Falgreen-Eriksen *et al.*, 2012; Esper and Furtado, 2014; Popova *et al.*, 2017, 2018; Myers *et al.*, 2018), it lacks a coherent definition of one alcoholic drink. The type of drink (e.g., beer, white wine, red wine, spirits), its exact quantity in litres or centilitres and its consequent pure ethanol content

in milligram needs to be indicated consistently to delimit exact definitions (Kuntsche et al., 2017). Additionally, most studies include a timeframe in which alcoholic drinks are consumed, like one week (Falgreen-Eriksen et al., 2012; Flak et al., 2014; Myers et al., 2018), one day (Flak et al., 2014; Popova et al., 2017) or one occasion (Falgreen-Eriksen et al., 2012; Flak et al., 2014; Iversen et al., 2015; Nulman et al., 2018; Popova et al., 2017, 2018) to define a level or pattern of alcohol consumption. Furthermore, gender specific differences are frequently given, with lower amounts of alcohol per timespan for women than for men to define the same level or pattern of alcohol consumption (Kuntsche et al., 2017; Lenz et al., 2018; Raspe, 2012).

Definitions for nicotine consumption levels are not contemporary given in literature and even less differentiated than those for alcohol. High-level nicotine consumption is considered as smoking 10 or more cigarettes per day by some studies (D'Onofrio et al., 2009; Lundberg et al., 2010) and as smoking 20 or more cigarettes by others (Clifford et al., 2012; Cornelius & Day, 2009; S. Lange et al., 2018). The definitions for moderate consumptions pattern range from less than nine cigarettes per day (D'Onofrio et al., 2009; Lundberg et al., 2010) or to between 10 and 19 cigarettes per day (Cornelius & Day, 2009). Exact definitions of low levels are rarely given as for example, more than 0 and less than 10 cigarettes per day (Cornelius & Day, 2009). Declarations of exact amounts of nicotine in one cigarette and information about differences across countries are not given in literature. Timeframes, in which a specific amount of nicotine is consumed, are primary restricted to a period of one day (Clifford et al., 2012; Cornelius & Day, 2009), and gender-specific differences are not considered. Most studies focused on distinguishing between smokers and non-smokers (Magnus et al., 2018) or different amounts of smoked cigarettes

without an exact definition of high, moderate or low levels of nicotine (Braun et al., 2009).

According aforementioned definitions of consumption amounts in current literature, the following definitions were established and used in this dissertation: Less than four to six alcoholic drinks per occasion, less than seven drinks per week and no binge drinking (≥ 5 drinks per occasion) on more than one occasion indicated low to moderate alcohol consumption and less than 20 cigarettes a day indicated low to moderate nicotine consumption. Amounts consumed beyond were defined as high. The establishment of definitions enabled to distinguish between consumption amounts when focusing on effects on child development and to detect possible predictive factors for a non-clinical and social accepted consumption behaviour.

1.1.2 Global prevalence of consumption during pregnancy

Current data on consumption prevalence have indicated that women consume high, moderate and low levels of alcohol and nicotine during pregnancy across the world (Forray, 2016; Mulat et al., 2022; Popova et al., 2017). Nevertheless, data are only represented for certain countries and regions from the last decades based on heterogeneous methods. This exacerbates global comparisons. In addition to incoherently defined consumption amounts, the majority of studies reported data on prevalence, without including the period between conception and confirmation of pregnancy. Consequently, prevalence may be underestimated. Particularly for low and moderate consumption amounts. Similar to the definitions of different consumption amounts, data on prevalence for alcohol consumption were presented more often and more precisely described than prevalence for nicotine consumption.

Data on intercontinental consumption prevalence of alcohol indicated that 22.8 % of women in the Sub-Sahara in Africa (Mulat et al., 2022) and 13.5 % in the United States of America (Gosdin et al., 2022) consumed any amount of alcohol during pregnancy. Binge drinking during pregnancy was reported by 3.1 % of women in Africa, 2.8 % in America and 1.8 % in Western Pacific (Popova et al., 2018). In Australia, 3.6 % consumed moderate amounts in trimester two and three (Muggli et al., 2016). In South Africa and the Northern Plains, 24.9 % of women consumed moderate amounts during the first trimester (Dukes et al., 2017). Low consumption amounts during trimester one were reported for 31.9 %, of Australian women, during trimester two by 35.5 % and during trimester three by 39.0 % (O'Leary et al., 2009). Popova et al., (2017), summarized that 10 % of women of the global population consumed alcohol during pregnancy. The highest rate of consumption is reported for the European region (Popova et al., 2017).

Data for intercontinental prevalence of nicotine consumption were for example reported for the USA, where 7.1 % of the women consumed high or low amounts during trimester one, 6.1% during trimester two and 5.7 % during trimester three (Kondracki, 2019). Further studies represented that 18.1 % of women from the Northern Plains, the USA and South Africa consumed moderate amounts continuously and 7.5 % during trimester one and two (Dukes et al., 2017). Data on low consumption amounts indicated that 9.6 % of women from the Northern Plains, the USA and South Africa (Dukes et al., 2017) and 3 % from Singapore (Taal et al., 2011) consumed continuously during pregnancy. In African-American populations, 23.9 % consumed low amounts during trimester one and 36.9 % during trimester three (Cornelius & Day, 2009). Lange et al. (2018) summarized data of 104 countries worldwide, reporting that 13,5 %

of analysed women consumed high amounts, 34,8 % moderate amounts and 51,8 % low amounts of nicotine during pregnancy (S. Lange et al., 2018).

Data regarding current prevalence of alcohol and nicotine consumption during pregnancy in Germany are scarce and not contemporary. The German Health Update Study from 2012 indicated that in a non-clinical population, almost a third of the sample (103 of 374 pregnant women) stated to have consumed alcohol during pregnancy (C. Lange et al., 2015). Data of the German Health Interview and Examination Survey for Children and Adolescents revealed that 12,1 % of women consumed nicotine during pregnancy (Robert Koch Institute, 2016).

1.2   Effects of prenatal alcohol and nicotine exposure

The following sections give an overview on the transmission of alcohol and nicotine to the foetus during pregnancy and resulting effects on early child development.

1.2.1   Transmission of alcohol and nicotine to the foetus

To understand the effects of prenatal alcohol and nicotine exposure on early child development, knowledge on some biological principles is required.

Alcohol, or ethanol (C_2H_6O), is a psychoactive molecule that acts cytotoxic. It enters the blood circulation within minutes after consumption and distributes quickly through the human organism (Levy, 2012; Nulman et al., 2018). Nicotine ($C_{10}H_{14}N_2$) and carbon monoxide (CO) are two main derivatives of tobacco. Nicotine is a neurotoxin and exposure to it interferes with normal neurotransmitter function. The CO that is inhaled when smoking, results in the formation of carboxyhemoglobin (COHb), which adversely affects the human

organism, since it reduces the oxygen carrying capacity of the blood cells (Diamanti et al., 2019).

The structures that separate maternal and foetal blood are grouped together as the placental barrier. It has to be permeated during the exchange of substances and its structure changes during the progress of pregnancy. Towards the end of pregnancy, maternal and foetal blood are approximately 4 µm apart (Schiebler & Korf, 2007). The individual structures serve as a filter membrane that regulates maternal and foetal blood and the passage of various substances contained in the blood. These include, for example, oxygen, glucose and immunoglobulins. Various active and passive transport mechanisms occur. Compared to the blood-brain barrier, the placental barrier is less dense (Ulfig & Brand-Saberi, 2017). This signifies that all drugs and stimulants that circulate in the mother's organism reach the foetus. If the mother consumes alcohol or nicotine, the foetus can also develop an addiction (Moore et al., 2013). It is well known that both substances cross the placenta, and distribute into the foetal organism. Furthermore, both substances are eliminated slowly by the foetus, leading to greater exposure, compared to the mother (Heller & Burd, 2014). In addition, several characteristics make the foetus more fragile to alterations in the oxidative metabolism. In consequence, teratogenic effects of alcohol lead to mitochondrial damage, brain lipid peroxidation, and a decrease in endogenous antioxidant levels, to disrupted neuron-neuron adhesion, placenta vasoconstriction, and inhibition of cofactors required for foetal growth and development (Gupta et al., 2016). When the nicotine reaches the foetus, it binds to the nicotinergic acetylcholine receptors (nAChR). The nAChR are ionotropic acetylcholinergic receptors that are found in the central nervous system (CNS), in regions of the autonomic nervous system and on the motor-end plates of the

skeletal muscles and the heart muscles. The nAChR are used for neuromuscular signal transmission and the regulation of inflammatory processes in the immune system (Dellas, 2018). Normally acetylcholine binds to the nAChR. However, if the foetus consumes nicotine, it can imitate acetylcholine and bind to the nAChR. This leads to a change in the signal transmission causing pathological effects, depending on the region (Speckmann et al., 2008).

1.2.2 Effects of prenatal alcohol exposure on child development

The consumption of high amounts of alcohol during pregnancy has the most harmful effects on foetal health outcomes (Pop-Jordanova & Demerdzieva, 2022). Consumed during pregnancy, ethanol is responsible for multiple congenital anomalies comprising growth restriction, CNS impairments, and malformations (Nulman et al., 2018). It has also been associated with a range of negative birth outcomes, including increased risks of miscarriage (Armstrong et al., 1992), stillbirth and infant mortality (O'Leary et al., 2012), low birthweight, reduced gestational age, preterm delivery, and being small-for-gestational age (Forray, 2016; Whitehead & Lipscomb, 2003). Further, prenatal alcohol exposure is associated with the development of the foetal alcohol syndrome (FAS) and the foetal alcohol spectrum disorders (FASD (Le Daré et al., 2019; Nulman et al., 2018)). In addition, prenatal drinking is known to cause long-term effects in affected children, such as problems with cognition and behaviour (Bakoyiannis et al., 2014), adverse speech and language outcomes, executive functioning deficits (Fuglestad et al., 2015), and psychosocial consequences in adolescent and adulthood (Rangmar et al., 2015). Apart from extensive research on long-term effects of heavy prenatal alcohol exposure on the

development of affected children, adolescents and adults, the exact pathology remains unexplained. Especially, knowledge on the effects of low to moderate consumption amounts during pregnancy is sparse.

While the effects of high alcohol consumption on fertility, the course of pregnancy and birth outcomes are well described, there is a lack of research addressing the effects on early child development comprising the first two years of life.

1.2.3 Effects of prenatal nicotine exposure on child development

Nicotine is one of the leading causes for a broad spectrum of negative and pathological birth outcomes, when consumed during pregnancy (Diamanti et al., 2019). Effects of high consumption amounts on early child development are comprehensively described in literature.

Specifically, maternal smoking is associated with an increased risk of adverse obstetric effects like miscarriage, ectopic pregnancy and stillbirth (Mendelsohn et al., 2014) or gestation diabetes mellitus (Aulinas et al., 2016).

Pathological effects on the foetus comprise small-for-gestational-age, low birth weight and Intra-Uterine Growth Retardation (Mendelsohn et al., 2014).

Adverse effects on birth outcomes can appear for example in form of preterm birth and limb reduction defects (Aulinas et al., 2016; Mendelsohn et al., 2014), a cleft lip or palate and club foots (Diamanti et al., 2019; Mendelsohn et al., 2014). Furthermore, it can come to a lack of the eye system, smallness or only rudimentary development of one or both eyeballs (Diamanti et al., 2019; Mendelsohn et al., 2014), or heart defects (Diamanti et al., 2019). In addition, known effects are premature ossification of one or more skull sutures, malformations of the abdominal wall, malformations of the rectum, gaps in the

area of the abdominal wall, and the absence of one or both testes from the scrotum (Diamanti et al., 2019; Horak et al., 2012; Mendelsohn et al., 2014).

Pathological effects on new-borns and children comprise a significantly increased risk of sudden infant death syndrome, obesity, type 2 diabetes (Holbrook, 2016; Mendelsohn et al., 2014), reduction in male reproduction ability (Fowler et al., 2011) and earlier menarche for girls (Holbrook, 2016). The consumption of nicotine during pregnancy influences various physiological parameters in pregnant women, resulting in a lack of oxygen and a reduction of the supply of nutrients in the foetus (Spohr, 2005). In consequence, a broad spectrum of respiratory effects like upper respiratory tract infections, bronchitis or asthma can appear (Holbrook, 2016; Mendelsohn et al., 2014). Further evidence for pathological outcomes is described in form of deficits in neurodevelopment. Trough crossing the placental barrier, nicotine influences neuronal development via the neurotransmitter system (Spohr, 2005). Nicotine consumption causes abnormal cell proliferation and premature cell differentiation and is involved in the development of various neurotransmitter systems (Dwyer et al., 2009; Smith et al., 2010). This leads to a dysregulation of neurotransmitters like serotonin or catecholamine that are involved in processing basic cognitive processes such as learning, memory and attention (Bublitz & Stroud, 2012).

Further outcomes that can occur during later developmental stages comprise behavioural outcomes like a lower global intelligence and academic performance (Holbrook, 2016), Attention Deficit Hyperactivity Disorder (ADHD), externalizing behaviours, or antisocial behaviour (Button et al., 2005; Holbrook, 2016). In addition, prenatal exposure to nicotine may result in nicotine dependence and an abuse of further substances in affected offspring (Holbrook,

2016; Mendelsohn et al., 2014), as well as in psychiatric disorders in early adulthood (Ekblad et al., 2017). Deficits caused by prenatal nicotine exposure are clinically termed by the Foetal Tobacco Syndrome (FTS (Horak et al., 2012)).

In addition to research on how prenatal alcohol and nicotine consumption influences early child development, current research has also addressed epigenetic processes (Schmidt et al., 2012). Gene activity is altered by environmental influences via endocrine, immunological and molecular processes. It is not modifying the genome itself, but rather the genome's function. The DNA sequence remains unchanged (For an overeview see: Schmidt et al., 2012). When exposed to during pregnancy, chemical substances can cause epigenetic effects in the offspring, developing in the womb (Chatterton et al., 2017; Loke et al., 2018; Schmidt et al., 2012). Studies on epigenetic effects caused by prenatal nicotine exposure gave evidence for DNA methylation in offspring, which is associated with foetal growth attenuation. Epigenome-wide placental DNA methylation and gene expression were found (Suter et al., 2012), revealing signature pathways that are associated with smoking-mediated foetal growth attenuation. These results were confirmed by another study (Chatterton et al., 2017) which yielded altered global DNA methylation and gene expression and its association with reduced mature neuronal content, which may lead to disruptions in neuronal-and further early child development. Another study reported effects on DNA methylation in foetal lung and placental tissues associated with chronic diseases and persistent wheezing and asthma in children (Chhabra et al., 2014). Specific developmental outcomes in affected children and whether the found alterations in DNA

methylation are biologically or clinically relevant, needs to be further explored (Markunas et al., 2014).

As the majority of current research focused on effects caused trough high consumption amounts, results for low to moderate amounts during pregnancy remains poorly understood.

1.3 Predictive factors

A variety of factors influencing the drinking and smoking behavior of pregnant women have been described in literature (Hauge et al., 2012; Melchior et al., 2015; Mulat et al., 2022; Powers et al., 2013). It is important to derive these factors, as they can be functioning as possible predictors for consumption during pregnancy in further research. This enables differentiated analysis of resulting effects on early child development and the establishment of adequate preventive measures.

Correlations are documented for alcohol/nicotine consumption during pregnancy and socio-demographic factors, such as, the level of education of the consumer. Prenatal alcohol consumption, particularly in low to moderate amounts, is seemingly associated with a higher education (> high school degree) of pregnant women (Melchior et al., 2015; Pfinder et al., 2013). In contrast, nicotine consumption seems to correlate with lower education of pregnant women (Almeida et al., 2022; Baron et al., 2013; Melchior et al., 2015; Schmidt et al., 2012).

Additionally, the social environment correlates with prenatal alcohol and nicotine consumption. For both substances, studies represented that if pregnant women are lacking social support from their environment, the probability of drinking and smoking increases (El-Khoury et al., 2016; Powers et al., 2013; Skagerstróm et al., 2011). The experience of burdens like violence (in partnership) or critical life

events (e.g., fatalities) are also among the predictors of alcohol and nicotine consumption prior and during pregnancy (El-Khoury et al., 2016; Hauge et al., 2012; Powers et al., 2013).

A higher age (≥ 25 years) is associated with prenatal alcohol consumption, especially in low to moderate amounts whereas a lower age (<25 years) of women is associated with nicotine consumption during pregnancy (Melchior et al., 2015; Mulat et al., 2022; Murphy et al., 2013).

Furthermore, it was found that women who consumed alcohol or nicotine during pregnancy were less likely to have actively planned their pregnancy in comparison to women that abstained from alcohol (Baron et al., 2013; El-Khoury et al., 2016; Murphy et al., 2013).

The origin or cultural ackground of pregnant women also seems to correlate with the consumption of alcohol and nicotine (Melchior et al., 2015; Mulat et al., 2022). Previous findings indicated that European and African women that had a cultural background of no or low alcohol and nicotine consumption (e.g., Islamic regions like North Africa), consumed less alcohol and nicotine during pregnancy than women without this background (Melchior et al., 2015; Mulat et al., 2022).

A lack of access to supportive measures, like sessions with midwifes or antenatal classes, also appears to increase the likelihood of prenatal substance consumption (Nulman et al., 2018). It was found that especially the consumption of high- but not low to moderate amounts was believed to pose a risk for the offspring (Popova et al., 2022). Additionally, poly drug use and pre-pregnancy substance consumption is associated with alcohol and nicotine consumption during pregnancy (Baron et al., 2013; Nulman et al., 2018; Skagerström et al., 2013).

To comprehensively analyse effects of toxic substances on developmental processes in affected children, it seems to be important to include these additional factors that may predict the consumption.

2   Gaps in current literature and research questions of the dissertation

Currently, there is no fixed limit in literature to the amount of alcohol and nicotine that can be consumed during pregnancy without any harmful effect on the unborn child (Deutsche Gesellschaft für Ernährung, 2014; Nulman et al., 2018). There is evidence on a linear relationship between consumption amounts and the severity of developmental disorders in affected children. Nevertheless, the exact pathogenesis is still not fully understood, despite high numbers of animal and human studies (for an overview, see Nulman et al., 2018). To comprehensively analyse the effects of prenatal alcohol and nicotine exposure, it is important to understand the pathogenesis caused by high consumption amounts. In comparison to controversial results of low to moderate levels (Römer et al., 2020), high amounts of alcohol and nicotine exposure are known to result in considerable pathological outcomes. Nevertheless, especially for alcohol, studies on effects of consumption on early child development concerning the first two years of life are rare and mostly focused on later developmental stages (Mukherjee et al., 2019).

While the majority of research primarily focused on effects of high amounts of prenatal substance use, the influence of low and moderate levels of alcohol and nicotine is still scarcely understood (Halliday et al., 2017; Römer et al., 2020; Todorow et al., 2010). Reported effects remain unclear and controversially, especially concerning the first two years of life. As the identification of pregnant women that consume low to moderate amounts keeps more challenging in

comparison to clearly defined clinical samples, research on effects of low to moderate consumption amounts is rare.

To address effects of alcohol and nicotine exposure on early child development, various aspects such as the determination of exact prevalence and consequently, coherent underlying definitions of consumption amounts, has to be considered in advance. It needs to be taken into account that both substances, depending on dose and timing of the consumption during pregnancy, can influence different developmental stages, from fertilization to postnatal periods (Chahal et al., 2017; Forray, 2016; Nulman et al., 2018; Subramoney et al., 2018). As described in section 1.1.1, current research lacks coherent definitions for different consumption amounts as well as representative data on consumption prevalence. Additionally, the number of studies addressing the period between fertilization and recognition of pregnancy and the prevalence of drinking and smoking during this sensitive period for development of the offspring is low. Consequently, it lacks adequate preventive measures that address the consumption of alcohol and nicotine while intending to become pregnant. Additionally, the majority of current studies overlooked to include factors, described in section 1.3., that influence drinking and smoking behaviour during pregnancy as potential predictors.

Through gaps in current research, five main research questions concerning three central topics were developed and are presented in the following sections:

2.1 Topic 1: Effects of high prenatal alcohol exposure

The first topic provides an overview of current literature studying the effects of high-level consumption amounts of alcohol during pregnancy on child development. In order to consider current gaps in literature, it is primarily

focused on effects on early child development concerning the first two years that have not been adequately addressed in previous studies. With the special focus on early stages of child development it provides a general basis for further research such as the analyses of the BRISE-sample. Gained knowledge could be used to compare findings from analyses of the first measurement time points of the BRISE-data concerning early developmental stages, with evidence of current literature.

Research question I: How does high level alcohol exposure affect early child development during pregnancy and the first two years of life? (Publication I)

2.2 Topic 2: Effects of low to moderate prenatal alcohol and nicotine exposure

The second topic primarily entails a systematic review of current literature on effects of low and moderate amounts of prenatal alcohol and nicotine exposure. It concerns current gaps in literature that focused primarily effects of high consumption amounts. The focus of the second topic provides a basis for further research regarding consumption in low to moderate amounts and specifically for the analyses of the BRISE-sample. As the BRISE-sample is non-clinical, the analysis of studies concerning low to moderate consumption amounts serves as a basis to understand the need of further investigations comprising coherent measures and aspects like data on prevalence and additional risk factors that should be included.

Research question II: How does low to moderate alcohol and nicotine exposure affect early child development during pregnancy and the first two years of life? (Publication II)

2.3 Topic 3: Consumption prevalence and predictive factors

Concerning current gaps in literature on prenatal alcohol and nicotine exposure described in previous sections and as an expansion of topic 1 and topic 2, the third topic concerns data of the first and second wave of the BRISE-sample. This analysis is focused on the consumption prevalence during pregnancy, including factors predicting the consumption behaviour. Concerning a non-clinical BRISE-sample, it was possible to determine consumption prevalence and predictive factors for low to moderate consumption amounts. A main focus was set on the moment when pregnant women stop consuming alcohol and nicotine. There is evidence that many women do not stop or restrict consumption until pregnancy is medically confirmed, although both substances can have negative effects on sensitive developmental processes in the first trimester of pregnancy (McCormack et al., 2017). The influence of further factors, such as the socioeconomic status or social support, was also taken into account. Factors that correlate with the consumption of alcohol and nicotine during pregnancy are important to know but often not considered in previous research and thus, when planning preventive measures. Consequently, the current analyses focussed on the consumption prevalence during pregnancy and on environmental and social factors that could be detected as predictors of prenatal alcohol and nicotine exposure.

Research question III: How is the consumption prevalence during pregnancy in the BRISE-sample? (Publication III)

Research question IV: How is this consumption prevalence distributed concerning different subgroups that consumed (i) at any time point during

pregnancy, (ii) pre-confirmation of pregnancy or (iii) continued consumption post-confirmation of pregnancy? (Publication III)

Research question V: Which kind of factors may predict the consumption of alcohol and nicotine during pregnancy? (Publication III).

Beside the scientific relevance, the research questions of this dissertation are focused on an issue that is of a high socio-political relevance not only in Germany but worldwide, as a large number of pregnancies are still alcohol- and/or nicotine-related (Cornelius & Day, 2009; Dukes et al., 2017; Popova et al., 2018). The combination of addressed research questions will ensure a comprehensive overview of a coherent subject area and form the basis for further analyses.

3   Literature research

The following sections include the description of the methodological procedure and an overview of the results regarding the two literature reviews (publication I and II). The literature reviews comprise a comprehensive search of current literature concerning the research questions of topic 1 and 2 as a basis for the empirical research with the BRISE-data.

3.1   Topic 1: Effects of high prenatal alcohol exposure

The first literature review concerns topic 1 and the research question I, on how high-level prenatal alcohol exposure affects early child development during pregnancy and in the first two years of life (publication I).

3.1.1   Methods of topic 1

An extensive but non-systematic literature review was carried out using different databases and appropriate keywords. The collected literature on this topic was then summarized in publication I (see appendix A). The non-systematic review is characterized by a targeted search for literature in bibliographic databases and provides an overview of existing knowledge (Sutton et al., 2019). After defining the research question, an adequate search strategy was applied. This included the use of appropriate keywords and combinations of these keywords, specified inclusion and exclusion criteria and a screening and selection of generated literature through different authors. The concrete methodological approach, including search strategies and data identification is described in publication I. Results are described in section 3.1.2. in addition.

As topic 1 covers a broad subject area that should be reviewed and summarized in a coherent way that is understandable for a broad spectrum of readership in a moderate length, a non-systematic approach was applied. The

literature review was carried out, to gain a considerable overview of the research field of interest and to detect current gaps in literature. Consequently, it serves as a base for specifying further research questions, concerning the literature review of topic 2 and the empirical research of topic 3.

3.1.2 Results of topic 1

The results of topic 1 are presented in publication I and give an overview of current literature studying the effects of high-level prenatal alcohol exposure on early stages of child development. They comprise effects on embryogenesis, the foetal period and especially, the first two years of life.

Effects on embryogenesis and the foetal period revealed that there are sensitive time windows during pregnancy that are associated with different effects (see Figure 1, publication I). Consumption of alcohol during this time may lead to impairments of healthy organ formation. Dysmorphologies as part of the FASD can also manifest in this period (Nulman et al., 2018; Sulik et al., 1984). During the gastrulation (16 to 24 days after conception), essential processes of the embryogenesis like the development of cells, the neural tube as well as medial and lateral growth take place. Toxic substances such as alcohol disrupt the formation of different cell types and processes of cell regeneration. In consequence, this leads to adverse effects in the human offspring (King et al., 2018; Nulman et al., 2018; Sulik et al., 1984). In the second and third trimester of pregnancy, foetal growth takes place. The consumption of alcohol during this period was found to be associated with intrauterine and somatic growth delays (Ernhart et al., 1985; Nulman et al., 2018).

Effects on the first two years of life concerned the development of FAS and FASD that is primarily associated with alcohol exposure in high amounts (Le

Daré et al., 2019; Nulman et al., 2018). The FASD involves clinical pictures that comprise key symptoms such as small body sizes, underweight, facial abnormalities, microcephalus and developmental disorders in infants (Nulman et al., 2018). Beside morphological effects, various functional effects of prenatal alcohol exposure on the neurological and cognitive development of infants like sensation-avoiding behaviour are reported (Halliday et al., 2017). Behavioural effects of prenatal alcohol exposure were presented concerning the stress perception and temperament of infants (Alvik et al., 2013; Haley et al., 2006; Schoeps et al., 2018). In the further course of development, temperamental abnormalities like frequent screaming, crying and sleep disorders can develop into externalizing behavioural abnormalities (Degnan et al., 2011; Schoeps et al., 2018).

Furthermore, results revealed evidence for epigenetic effects caused by prenatal alcohol exposure. Epigenetic effects comprise various changes in the gene activity of affected children (Nulman et al., 2018; Schmidt et al., 2012). For an overview of epigenetic mechanisms in the context of alcohol consumption, see Table 2, publication I (Appendix A).

In total, this literature review added an overview on effects of high amounts of alcohol consumption on early developmental stages of affected children that was previously missing in literature. It showed that pathological consequences like physical- neuropsychological- and behavioural abnormalities are already noticeable in the first two years of life and provides a basis for further investigations.

3.2 Topic 2: Effects of low to moderate alcohol and nicotine exposure

The second literature review concerns topic 2 and the research question II, on how low to moderate prenatal alcohol and nicotine exposure affects early child development during pregnancy and in the first two years of life (publication II).

3.2.1 Methods of topic 2

The literature search process was carried out systematically and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009). The collected literature on this topic was summarized in publication II (see appendix B). A systematic literature review is an independent scientific method that aims to identify and evaluate all relevant publications on a topic in order to derive conclusions for the examined research questions (Feak et al., 2009). It includes a critical and reproducible summary of the results of available literature, regarding current gaps and existing research needs on a particular topic or question. The methodical-formal approach reduces distortions and increases the reliability of the literature search and selection process (Linares-Espinós et al., 2018). The search procedure is mainly focused on electronic literature databases (e.g., PubMed or Web of Science), but also includes a manual search (screening of reference lists of relevant publications) and the preselection of literature that has not yet been published. This generates a comprehensive overview of existing literature. Inclusion and exclusion criteria are defined in advance and a protocol documents all information and steps of a systematic literature review in order to enable transparency of the selection criteria and reproducibility (Aromataris & Pearson, 2014).

In order to increase the objectivity of the literature selection process, the literature search procedure was conducted independently by two authors of the

publication II. Two other authors carried out the final full text assessment. Studies with different ratings were discussed between the authors and were incorporated once consensus had been reached. Important information of the included studies was extracted by one author and subsequently checked for accuracy and completeness by two additional authors. Possible disagreements that occurred during the data extraction were discussed and resolved between the authors. As a systematic approach predefines specific criteria in comparison to a narrative literature review, the risk of bias and the quality of included studies was checked, using the Newcastle-Ottawa Scale (Wells et al., 2017). This enabled the evaluation of three aspects: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. The detailed methodological approach, comprising search strategies, data identification -and extraction is described in publication II. Results are additionally described in section 3.2.2.

The systematic approach was applied in order to focus on a special research question comprising a confined scope and to provide the most valid evidence to guide clinical decision-making and inform policy development concerning the empirical research of topic 3. The systematic literature review serves as a base for specifying further research questions for topic 3 and further analyses with the BRISE-data.

3.2.2 Results of topic 2

The results of topic 2 give an overview on current literature addressing the effects of low to moderate level prenatal alcohol and nicotine exposure on early

child development and are presented in publication II. They comprise the fertilization, the embryogenesis, the foetal period and first two years of life.

Results on effects of low to moderate prenatal alcohol exposure reveal mainly negative developmental outcomes. These comprised alterations of early neurologic development, which may raise the risk of addiction and other developmental abnormalities for the foetus (Krishnamoorthy et al., 2010), smaller head circumferences and lower total grey matter volume (Donald et al., 2016) or lowered sensory regulatory responses (Williams Brown et al., 2010) and smaller body sizes as well as behavioural problems as compared to controls (Sundelin-Wahlsten et al., 2017). Furthermore, impairments in cognition and intellectuality (Donald et al., 2015) as well as behavioural problems in terms of anxiety and depression (O'Leary et al., 2010) were reported.

Yet, some studies found no effects (e.g., Bakhireva et al., 2018). on development or reported higher scores in developmental tests of affected children in comparison to controls (McCormack et al., 2017).

In comparison to research on effects of prenatal alcohol exposure, only a small amount of research focuses on nicotine effects. Research shows mainly negative effects of low to moderate amounts of prenatal nicotine exposure on early child development. This comprised adverse foetal kidney volumes which might predispose a child to the development of hypertension and kidney disease in later developmental stages (Taal et al., 2011) or increased levels of the inflammatory cytokines IL-8 (Chahal et al., 2017) which result in permanent changes in neonatal inflammation, and may consequently lead to respiratory disorders, like bronchitis or asthma (Chahal et al., 2017). Furthermore, Electroencephalography experiments indicated impairments in auditory sensory

gating. These impairments cause reduced auditory discrimination and learning, attention re-orienting and/or arousal during wakefulness as well as disrupted sleep behaviour (King et al., 2018). For example, affected children showed less orientation with a head-turn to a novel auditory stimulus during wakefulness in comparison to controls. Effects of second-hand smoke exposure during pregnancy were associated with lower neurodevelopment in affected children. They showed poorer fine-motor-skills, as for example hand and finger movements, and impaired communication skills in vocalizing, listening and understanding (Mohamed et al., 2018).

Overall, the second literature review provided an overview on effects of low to moderate amounts of alcohol and nicotine consumption on early developmental stages of affected children. It clarified that not only high- but also low to moderate amounts can affect early child development. Effects comprised decreased sensory sensibility, smaller body sizes, impairments in children's orienting, communication and motor skills and increased cognitive capacities. This work highlighted the need for further investigations with non-clinical populations in order to analyse consumption prevalence, reasons for consumption and resulting effects on early developmental stages.

A detailed description and an overview of results of effects of prenatal alcohol exposure on early child development are presented in the text and Table 1 of publication II and results of effects of prenatal nicotine exposure on early child development are presented in the text and Table 2 of publication II (Appendix B).

4 Empirical research

Based on gained knowledge about the current state of literature concerning alcohol and nicotine consumption during pregnancy, the empirical research comprises a comprehensive analysis of the BRISE-data addressing topic 3 and concerned research questions III, IV, and V.

4.1 Topic 3: Consumption prevalence and predictive factors

The main focus of the analyses is the detection of consumption prevalence of pregnant women in the BRISE-sample and factors that may predict the consumption.

4.1.1 Methods of topic 3

The specific methodology describing the study design, participants, inclusion and exclusion criteria, as well as all applied measures is described in publication III (Appendix C). The following section gives an overview on statistical methods, applied for the data analyses of the BRISE-sample concerning topic III.

Statistical analyses

Methods concerning statistical analysis that are used for publication III are described in this section.

Descriptive statistics of the cross-sectional analyses were calculated to analyse the prevalence of alcohol and nicotine consumption during pregnancy. The prevalence was calculated for the consumption of alcohol, nicotine or the combination of both substances. Furthermore, consumption prevalence was estimated for each substance separately accordingly to established subsamples: For (i) the consumption pre-confirmation of pregnancy, (ii) the

consumption post-confirmation of pregnancy and (iii) the consumption at any time point during pregnancy.

We further calculated descriptive statistics for migration backgrounds and all variables entering the subsequent statistical analyses as potential predictors for consumption.

Multivariable binary logistic regressions were conducted to determine predictive factors of alcohol and nicotine consumption during pregnancy for each substance separately. Alcohol or nicotine consumption were defined as dependent variables, whereas age (in years), education, pregnancy planning, social support, life burdens and an Islamic cultural background of women were included as independent variables. This statistical method was chosen as it accomplishes the requirements to approach the current research question. If associations between several independent and dependent variable are examined as part of a logistic regression analysis, this is referred to as a multivariate logistic regression. If the dependent variable is scaled binary, as in the current analyses, the multivariate binary logistic regression model is an appropriate approach (Dreo, 2015). The total sample size of N=260 of the original sample of 300 women was incorporated in the main analysis as these participants answered to consumption related questions during pregnancy. With regard to the detection of predictive factors, we compared the groups that consumed at any time point during pregnancy with the group that did not consume alcohol/nicotine. Thus, predictive factors for substance consumption were determined by comparing consumers with abstainers. Adjusted odd ratios are presented for each predictor as included in combination with the other predictors in the regression model. The respective reference categories for each predicting factor are established as followed: Age (highest age), education

("lower" education), pregnancy planning (pregnancy was "planned"), social support and burdens (highest sum scores), Islamic cultural background (no "Islamic cultural background"). The two regression models differed in their respective dependent variable. In one model the dependent variable was either alcohol consumption and no alcohol consumption during pregnancy. In the other model the dependent variable was either nicotine consumption and no nicotine consumption during pregnancy. In order to except multicollinearity as a precondition to calculate a logistic regression model, it was checked in advance that the factors which were included as independent variables in the model do not correlate too strongly with one another. A collinearity diagnosis was carried out subsequently. The tolerance value of >0.1 and the variance inflation factor of <10 pertained the appropriate range for each model. In addition, we controlled for possible confounder-, mediator- or moderator effects of birth order (1st child or not) and time point of the interviews (T0 or T0post, i.e., pre- or post-partum). The number of women regarding established subsamples that consumed both substances in combination as well as the subgroups for consumption pre- and post-confirmation of pregnancy were small. Consequently, we compared the group of women that consumed at any time point during pregnancy with abstainers for each substance respectively in the main analysis. Statistical analyses for publication III were performed using IBM SPSS Statistics Version 26 and R Version R 3.6.1. A reporting checklist according to the STROBE statement (Von Elm et al., 2008) was used and is presented in Publication III (Appendix C).

4.1.2 Results of topic 3

The results of topic 3 incorporate publication III and research questions III, IV, and V. They present data of the BRISE-sample refer to analyses on consumption prevalence of alcohol and nicotine during pregnancy and additional risk factors that may predict the consumption behaviour.

The participating women had a mean age of 31.1 years (SD: 5.8). The education level of 67.3 % of the women was classified as "lower" and that of the remaining 32.3 % as "higher" (see "Method"- and "Measure"-section of publication III), with a maximum of an upper secondary education. Of all women, 59.5 % indicated to have planned their pregnancies. On average, participants had a high social support (mean=58.7, SD: 12.7, range: 14-70) and a low extent of extra burdens during their pregnancy (mean=5.6, SD: 6.4, range: 0-33). In total, 53.5 % of the women either migrated or had at least one parent that had migrated to Germany. A migration background that included a country with a predominant Muslim culture was reported by 16.9 % of the sample.

Descriptive statistics on consumption prevalence revealed that 45 % of the participating women reported to have consumed either alcohol or nicotine during their pregnancy. Of those, 14.5 % stated to have consumed both substances in combination at some point during their pregnancy. Prevalence of alcohol consumption indicated that 35 % of the overall sample drank alcohol during the course of their pregnancy. Of these, 92.3 % quit drinking alcohol following confirmation of pregnancy (i.e., within the first trimester). Thus, the majority of women that consumed alcohol during pregnancy stopped consumption at some point during the first trimester. Only 7.7 % continued drinking alcohol post-confirmation of pregnancy. Prevalence of nicotine

consumption indicated that 16.5 % of the women smoked at some point of their pregnancy. Of those, 62.8 % stopped smoking after confirmation of the pregnancy, while 37.2 % continued smoking. In total, 25 % of the women stated to have never consumed alcohol or nicotine in their life. Of the 16,9 % of women that had an Islamic cultural background, 65.9 % stated that they never drank alcohol, 72.7 % that they never smoked cigarettes in their life and 56.8 % that they did neither. A number of 25 % of the women that did not consume alcohol during pregnancy and a number of 23.8 % of the women that did not consume nicotine during pregnancy stated to have stopped the consumption various months or years prior getting pregnant. An overview of consumption prevalence is presented in Table 1 of publication III and a more detailed description of consumption prevalence is provided in publication III in addition. The comparison of consumers with abstainers in multivariable binary logistic regressions indicated that some of the included independent variables may be seen as a predictor for the consumption during pregnancy.

Results for alcohol consumption as dependent variable revealed that a higher age (OR: 1.066 (95 % CI:1.005-1.132), p=.033)), an unplanned pregnancy (OR: .359 (95 % CI:.187-.691), p=.002)), an increased social support (OR: 1.037 (95 % CI: 1.008-1.068), p=.012)) and a non-Islamic cultural background (OR: .042 (95 % CI: .005-.321), p=.002)), seemed to predict the consumption of low to moderate amounts of alcohol of pregnant women. The other factors that were included in the model, like maternal education and burdens did not seem to be predictors for alcohol consumption.

For the consumption of low to moderate amounts of nicotine, results revealed that a lower level of education (OR: .154, (95 % CI: .050-.479), p=.001)) and an unplanned pregnancy (OR: .298 (95 % CI: .136-.654), p=.003)) might predict

the consumption of nicotine during pregnancy. Maternal age, an Islamic background, social support and burdens did not seem to predict the consumption of nicotine.

In summary, 45 % of the total sample consumed alcohol and/or nicotine during pregnancy. 92.3 % quit drinking and 62.8 % stopped smoking after confirmation of pregnancy. A better social support, a higher age, an unplanned pregnancy and not having an Islamic cultural background predicted the consumption of alcohol. Smoking was predicted by a lower level of education and an unplanned pregnancy. These analyses addressed current gaps in literature by adding investigations on prevalence data in pregnant women regarding all stages of a pregnancy and about factors influencing consumption behaviour. The sample included non-clinical women and families with special living circumstances that were hard to reach. Results on low to moderate consumption amounts provided data for the development of future research to generate consistent approaches and adequate prevention strategies.

Information on model likelihood ratios, R-squares and calculation that require a logistic regression are presented in the results-section of publication III. An overview of the results of the statistical analyses is presented in Table 3, publication III.

5   Discussion

The aim of this dissertation was to examine (i) the prevalence of alcohol and nicotine consumption during pregnancy, (ii) additional socioeconomic factors that may predict the consumption and (iii) effects of prenatal exposure on early child development. In total, this resulted in three related subject areas or components of the dissertation (see Figure 1): Topic 1 comprised an extensive literature review concerning effects of high consumption amounts of alcohol during pregnancy on early child development. Topic 2 included a systematic literature review on the effects of low to moderate amounts of alcohol and nicotine consumption during pregnancy on early child development. Topic 3 comprised an analysis of the BRISE-sample, concerning the prevalence of alcohol and nicotine consumption during pregnancy and additional risk factors that may predict the consumption during pregnancy.

Figure 1: Three aspects of the Dissertation
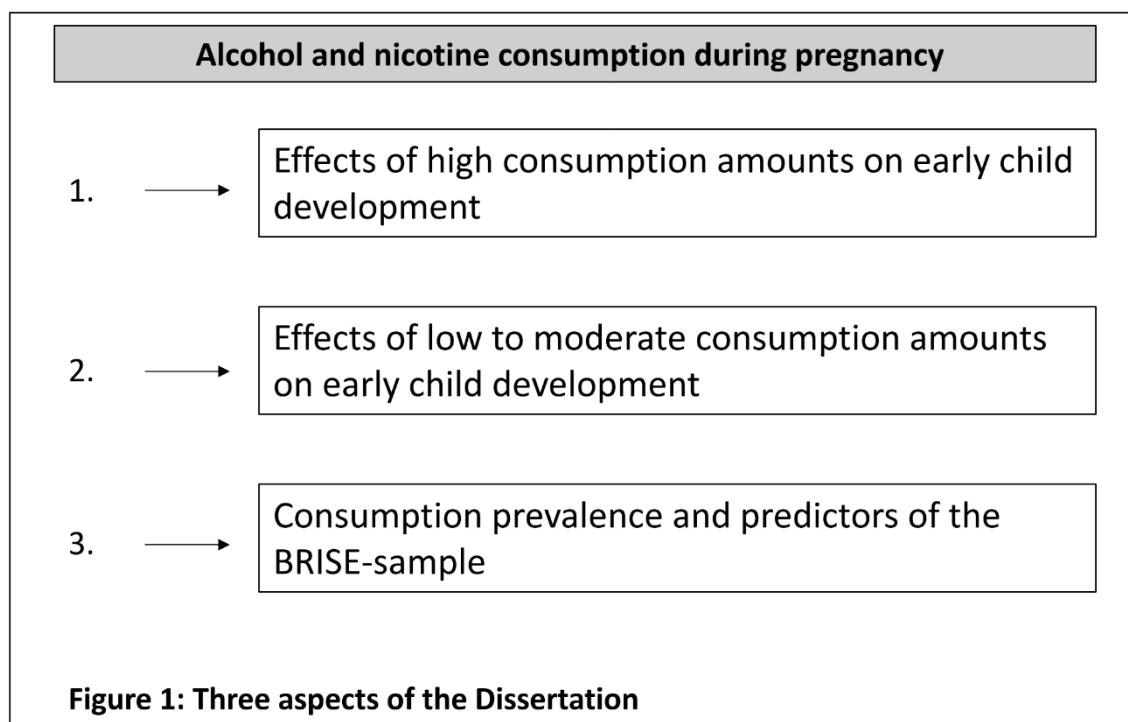
In the following sections, described subject areas are discussed. First, the results are individually discussed for each topic, followed by a section

highlighting the importance of an interplay of these three topics and related publications. Finally, the limitations of the current research and the presented analyses of the dissertation are discussed and possibly implications for further research and clinical practice are described.

5.1 Effects of prenatal alcohol and nicotine exposure

Research questions concerning effects of prenatal alcohol and nicotine exposure comprised topic 1 and topic 2. The research question about how high consumption amounts of alcohol during pregnancy affect early child development was concerned in topic 1 and publication I (*Research question I*). The research question about how low to moderate consumption amounts of alcohol and nicotine during pregnancy affect early child development was covered in topic 2 and publication II (*Research question II*).

5.1.1 Topic 1: Effects of high prenatal alcohol exposure

Effects caused by high consumption quantities during pregnancy seem to be extensively analysed and reported in current literature. Nevertheless, the exact pathology regarding early developmental outcomes in affected children remain unclear (Nulman et al., 2018). The majority of investigations concerned long-term effects of heavy prenatal alcohol exposure on the development of affected children, adolescents and adults that are detected at later developmental stages (Mattson et al., 2011). While effects on fertility, processes during sensible time windows of pregnancy and birth outcomes are established as well in research (Forray, 2016; Nulman et al., 2018; O'Leary et al., 2012), only a low number of studies focused on the timespan after birth, including the first two years of life. Effects through high consumption amounts that were detected in the first two years of life in affected children, comprise effects on behavioural,

neuropsychological and physical development. The low number of studies could be related to the fact that it is easier and more conclusive to determine deficits at later stages of development. These may be identified more clearly and measured more reliably (Subramoney et al., 2018). Based on information of the mother, it can only be determined to a limited extend whether a child was affected by heavy prenatal alcohol exposure. Consequently, it is difficult to detect whether consequential damage that becomes noticeable within the first two years of life can possibly be traced back to prenatal substance exposure. In some cases, the spectrum of behavioural deficits in a child is broad and there may be various risk factors. Thus, it can be difficult to identify retrospectively, whether the consumption of alcohol of the mother was a significant prenatal risk factor resulting in observed deficits. Current studies showed that the degree of deficits and negative developmental outcomes in children that were prenatally exposed to alcohol, deviates considerably (Nulman et al., 2018; Pop-Jordanova & Demerdzieva, 2022). Regarding the FAS phenotype, there are a range of known syndromes that partially overlap with the FAS symptoms. Concerning morphological symptoms known syndromes with similar physical outcomes like those in children with FAS are for example the Foetal Hydantoin syndrome or the Dubowitz syndrome (Leibson et al., 2014). In addition, morphological outcomes of FAS may appear as those at later developmental stages and differ across different ethnic groups. Known syndromes that cover cognitive and behavioural deficits overlapping with the FAS symptomatic are for example the Turner syndrome, or the ADHD (Pop-Jordanova & Demerdzieva, 2022). Additionally, it is described in literature that mental disorders may be genetically predisposed (O'Connell & Coombes, 2021). Thus, children of mothers with a high risk for developing mental health deficits, may show such deficits although

they were not prenatally exposed to alcohol. Consequently, it may be challenging to differentiate between genetic and environmental causes like alcohol exposure (Nulman et al., 2018). As FAS or even FASD often appear in form of the absence of morphological but the presence of cognitive and behavioural deficits, the diagnostic criteria may overlap with those for other mental health disorders (McLennan, 2015). Hence, the lack of evidence for early prenatal outcomes of children prenatally exposed to alcohol in current literature displays the difficulty to treat adequately. Recent research areas like epigenetics may help to understand how alcohol acts at molecular levels in detail. Initial research and related evidence of epigenetic mechanisms provide relevant contributions to a better understanding of the effects of prenatal alcohol exposure and consequences for affected children (Loke et al., 2018; Schmidt et al., 2012; Sharp et al., 2018). This contributes predictions regarding consequential damage that is already noticeable in the first two years of life. Nevertheless, it seems that the amount of research on effects that occur during the first two years of life has to increase in order to be able to complete current known outcomes of FAS and FASD.

5.1.2 Topic 2: Effects of low to moderate prenatal alcohol and nicotine exposure

Only few studies investigated effects of low to moderate amounts of prenatal alcohol and nicotine exposure on early child development. In comparison to effects based on high consumption amounts, reported evidence appeared to be controversial. A possible explanation of the small amount of research could be that previous research was primarily focused on effects of high-level consumption. Thus, it was focused to consolidate knowledge about obviously pathological outcomes. However, as the pathogenesis based on high-level

consumption has been extensively studied, current analyses have started to focus on effects of smaller consumption quantities. According to current statistics on prevalence, the consumption of low to moderate amounts during pregnancy have their realities across the world (Dukes et al., 2017; Muggli et al., 2016). This underlines the need of research in this field. Prevalence of the consumption of low to moderate amounts may again be related to current gaps of knowledge about risks and negative effects and the lack of adequate prevention strategies.

The controversial effects of prenatal alcohol and nicotine exposure on early child development may be due to methodological challenges for the assessment of outcomes based on lower doses. It is possible that the measures used to detect morphological or mental developmental deficits which are frequent in children that were prenatally exposed to high amounts of alcohol or nicotine or diagnosed with related disorders, are less useful to identify effects based on low to moderate consumption (Subramoney et al., 2018). Furthermore, consumption during pregnancy is often considered in isolation by research on early developmental processes. Further environmental and socioeconomic factors may (i) influence the consumption behaviour of the pregnant women, but also (ii) the development of affected children. Based on the small amount of research and controversial outcomes it can be assumed that there is no safe limit of alcohol or nicotine that can be consumed during pregnancy without risks for a healthy child development.

The comparison with effects of high-level consumption remains challenging as research for low to moderate amounts still remains rare, based on heterogeneous measures. Similar to those for high-level consumption, results for low to moderate consumption showed that deficits do not appear in one

specific domain but in different developmental areas (Römer et al., 2020). Deficits include lowered sensory regulatory responses (Bakhireva et al., 2018) or lower communication and fine motor skills (Mohamed et al., 2018). Thus, there is evidence that low and moderate consumption during pregnancy may also impair early child development in a complex way. Nevertheless, consumption of low to moderate amounts during pregnancy is more commonly practiced and socially accepted than the consumption of high amounts. This concerns different societies and regions across the world (Dukes et al., 2017; Muggli et al., 2016) and may be related to current gaps of knowledge of the society about the risks and negative effects of toxic substances on early child development, especially in low to moderate amounts (Popova et al., 2022).

5.2 Consumption prevalence and predictive factors

Research questions concerning consumption prevalence of alcohol and nicotine during pregnancy and additional socioeconomic factors that predict this consumption were addressed in topic 3. The research questions on consumption prevalence of alcohol and nicotine during pregnancy in the BRISE-sample (*Research question III*) and on the way, how this consumption prevalence is distributed concerning different subgroups (*Research question IV*), were studied for publication III. The research question on additional socioeconomic factors that may predict the consumption of alcohol and nicotine during pregnancy (*Research question V*) was also addressed in publication III.

5.2.1 Topic 3: Consumption prevalence

The BRISE-sample included women consuming both substances, alcohol as well as nicotine during pregnancy. We found that almost half of the entire sample (45 % of the women) consumed alcohol or nicotine during pregnancy.

Possible explanations may be that both substances are legal in Germany and the majority of regions across the world (Anderson et al., 2018). In general, the consumption of alcohol and nicotine is socially accepted, also by women planning to get pregnant or those who are already pregnant. The consumption of low to moderate amounts and its consequences on pregnancy and child development have not been adequately addressed in comparison to the effects of high consumption amounts (Römer et al., 2019). During the last decade, consumption prevalence of both substances decreased in Germany (Deutsche Hauptstelle für Suchtfragen e.V. (DHS), 2022). Nevertheless, current results are consistent with previous data reporting that alcohol and nicotine remain the most consumed substances by women in childbearing age and during pregnancy (Forray, 2016; Popova et al., 2017).

Concerning the BRISE-sample, 25 % of women stated to have never consumed alcohol or nicotine in their life. As both substances are legal in most parts of the world, these numbers are higher than expected. Possible explanations could be that 16.9 % of the sample that responded to consumption-related questions had an Islamic cultural background. Thus, they or their parents migrated to Germany from a country with >90 % of the population being Muslim. Of those women, 65.9 % stated that they never drank alcohol, 72.7 % that they never smoked cigarettes in their life and 56.8 % that they did neither. In the Islamic culture especially alcohol but also nicotine and other drugs are avoided (Bahar et al., 2005). This may be one possible explanation of the low prevalence of alcohol and nicotine consumption the BRISE-sample. Additional explanations could refer to personal decisions to avoid the consumption of alcohol and nicotine, the tendency to answer consumption related questions according to expected social

desirability or be health-related (Latkin et al., 2017; Skarbek-Kozietulska et al., 2012).

Concerning the avoidance of toxic substances prior to getting pregnant, 25 % of the women that did not consume alcohol during pregnancy and 23.8 % of the women that did not consume nicotine during pregnancy stated to have stopped consuming alcohol/nicotine various months or years prior getting pregnant. It is possible that these women were aware of the negative consequences resulting from prenatal alcohol or nicotine exposure. Further reasons could again be personal decision, the tendency to answer in a socially desirable way or aspects concerning mental or physiological health.

The prevalence of alcohol consumption during pregnancy was higher in this sample than the prevalence of nicotine consumption. However, 92.3 % of the women that consumed alcohol during pregnancy stated they consumed only during the timespan pre- and not post-confirmation of pregnancy. That means, they stopped drinking alcohol at some point during the first trimester. Only 7.7 % stated to have consumed post-confirmation of pregnancy. Thus, for the majority of the pregnant women it seems to be normal to consume pre-confirmation of pregnancy.

The number of women that stated to have consumed nicotine was smaller in comparison to the prevalence of alcohol consumption during pregnancy. Possible explanations may be that nicotine is not a substance that, like alcohol, is consumed at social gatherings, but rather in the form of subgroups. Furthermore, the serious effects caused through nicotine consumption are clearly marked and illustrated on cigarette packaging and other medial sources. This does not apply to alcohol. In contrast to the group that consumed alcohol, the women that consumed nicotine differed in their consumption patterns across

the pregnancy phases. In this group, 62.8 % of the women consumed nicotine prior to and 37.2 % after confirmation of pregnancy. This may be explained y the fact that consumption of even low amounts of nicotine leads to physical addiction (Henningfield & Zeller, 2009) and is, harder to quit despite knowing to be pregnant than the consumption of alcohol in consequence.

5.2.2 Topic 3: Predictive factors

Research that focused on alcohol consumption of low to moderate amounts during pregnancy found that women who consumed were older (≥ 25 years) and higher educated (high school degree or higher (Melchior et al., 2015)). However, these results could only partly be confirmed through analysis with the BRISE-sample as not a higher level of education but a higher age seemed to predict the consumption of alcohol. Furthermore, current literature indicated that the lack of support from the social environment of the mother or the experience of burdens like conflicts with the partner increase the consumption of alcohol during pregnancy (Powers et al., 2013; Skagerstróm et al., 2011). In contrast, analyses of the BRISE-data revealed evidence that greater support by the social environment increases the chance of consumption of low to moderate amounts of alcohol during pregnancy. Nevertheless, it appears remarkable that a supportive social environment increases alcohol consumption. A possible explanation could be that women living in a stable social environment are more in company with friends and family. Consequently, they may be more often involved in social events where alcohol consumption takes part. As an occasional consumption in low to moderate amounts is socially accepted, this could explain why a stable social environment promotes alcohol consumption during pregnancy. Current literature underlines this assumption, reporting that

one reason for alcohol consumption was stated by pregnant women to be the pressure of the social environment to participate at drinking events (Popova et al., 2022). Nevertheless, the results from the BRISE-sample may be difficult to compare to previous evidence as almost the entire group of alcohol consumers consisted of women who only consumed pre-confirmation of pregnancy. This phase of pregnancy is usually not considered in particular. Thus, it can be assumed that most women consumed alcohol during the early phase of their pregnancy only due to a lack of knowledge concerning negative consequences and the social acceptance of alcohol consumption. As these women do not consume alcohol as a strategy to cope with difficult life challenges, predictive factors should not have the same effects as in samples of high consumption amounts. A further predictor of alcohol consumption in low to moderate amounts seemed to be an unplanned pregnancy. This could be explained by the assumption that women who did not focused to get pregnant did not control their consumption behaviour. Thus, consumption should be avoided even if it could be possible to get pregnant due to a lack of contraception during sexual activities. The influence of the social environment on the consumption of alcohol is also indicated by women with an Islamic cultural background. Analyses of the BRISE-data revealed that an Islamic cultural background is a significant associating factor for not drinking alcohol during a pregnancy. In the Islam especially the consumption of alcohol but also nicotine and other drugs are generally avoided. This often leads to an avoidance of these drugs during pregnancy as well (Bahar et al., 2005).

Studies that focused on factors influencing the consumption of nicotine during pregnancy in low to moderate amounts showed that consuming women are more likely to have a lower age and a lower level of education (lower than high

school degree (El-Khoury et al., 2016; Melchior et al., 2015). The results of the BRISE-sample went again partly in line with previous findings. It was found that a lower level of education but not a lower age was associated with the consumption of low to moderate amounts of nicotine during pregnancy. For lower educated people immediate stress-reducing, mood-lifting and arousing effects of nicotine could be a stronger motivator for smoking than later occurring harmful effects on health and the risk to become physically addicted to nicotine (Cummings et al., 2004). A lower education is known to be one key variable of low socio-economic status and often co-varies with a higher risk of lower income, unemployment as well as social burdens and emotional stress affecting everyday life. Affected persons with fewer possibilities of coping with these challenges are more likely to use compensating strategies like smoking (Hauge et al., 2012). The finding that a lower education increased the likelihood of nicotine consumption during pregnancy may primarily be related to the pre-pregnancy living situation of the women that participated in the BRISE-study rather than specific burdens that could occur during pregnancy (Hauge et al., 2012; Powers et al., 2013). A correlation of lower education or lower socio-economic status with increased prevalence of nicotine consumption has been estimated not only for women during pregnancy, but for also for the general population (National Center for Chronic Disease Prevention and Health Promotion (US), 2014). Information about smoking-related health risks is represented on cigarette packages in Germany. Nevertheless, it is furthermore known that access to general health information is more difficult for people with lower education which additionally may explain the prevalence of smoking during pregnancy (Samkange-Zeeb et al., 2022). While previous finding that indicated associations between a lower social support or higher burdens and

the consumption of nicotine (El-Khoury et al., 2016; Hauge et al., 2012) could not be confirmed, an unplanned pregnancy seemed to be significantly associated with smoking during pregnancy. This could be referred to similar possible reasons as those for alcohol consumption like that women who did not planned a pregnancy did not control their consumption behaviour.

Additional analysis did not reveal evidence for mediating or moderating effects of predictive factors in the BRISE-sample. These aspects could be given further attention in the second data-wave of the BRISE-sample with larger sample size.

5.3 A multifactorial interplay of components to investigate prenatal alcohol and nicotine exposure

Research regarding the presented dissertation clarified that the analyses of prenatal substance exposure require a consideration of various interrelated aspects. Investigations on effects caused by prenatal alcohol and nicotine exposure need a detailed recording of consumption prevalence during pregnancy. This should comprise the entire pregnancy, including the time until confirmation of pregnancy. Further, it is essential that estimations of coherent data on prevalence are based on consistent definitions for consumption patterns like high, moderate and low. Another component that influences the consumption prevalence, as well as resulting effects on child development, are socioeconomic factors like age, education or social environments of consumers. All topics that are focused in this dissertation address alcohol and nicotine consumption during pregnancy and concerned specified relevant aspects. The combination of these aspects like the consumption prevalence, factors predicting the consumption as well as effects on early child development were covered within the three publications and the elaboration of the framework paper of this dissertation. An overview of the connection between the subject

areas of the dissertation is presented in Figure 2. The literature research on topics 1 and 2 generated the basis for further analysis of data concerning the BRISE-sample. In order to understand the effects of alcohol and nicotine consumption on early child development, current literature was examined. For this purpose, the effects of high-level exposure on the development of the first two years of life of affected children and the clinical diagnosable disorders were addressed in the context of publication I and the framework paper. To prepare the analyses of the non-clinical BRISE-sample, the effects of low to moderate amounts were subsequently addressed in publication II. Based on knowledge considering the results from current literature, the first data wave of the BRISE-sample was analysed. For an extensive and adequate research on alcohol and nicotine consumption during pregnancy and its effects, it seems to be crucial to include further mentioned aspects. Consequently, consumption prevalence and socioeconomic factors that might predict the consumption during pregnancy were determined for publication III. These aspects were included in investigations on consumption behaviour during pregnancy and resulting effects to focus this subject area in its entirety and to draw adequate conclusions. Through a continuous and coherent recording of prevalence of alcohol and nicotine consumption, the extent of the problem in multifaceted populations can be monitored. This would enable worldwide comparison and prevention in further steps. As it turned out to be essential to cover all stages of pregnancy, the analysis of the BRISE-data included the time-periods pre- and post-confirmation of pregnancy to represent consumption prevalence during the entire pregnancy. Socioeconomic factors that might predict the consumption of alcohol and nicotine during pregnancy were additionally included.

Consequently, information about circumstances like the level of education, the age, support from the social environment, burdens like problems with the partner or whether the pregnancy was planned or not, leading to consumption could be generated. Thus, it is possible to understand which factors may predict prenatal exposure to alcohol and nicotine, especially for low to moderate amounts. In addition, knowledge of these predictive factors and on consumption prevalence enables a conclusive interpretation of effects on early child development. Finally, there is an important interplay of these different aspects that are addressed by this dissertation through a logical composition of the three publications. All specified aspects are interrelated and should be considered to gain comprehensive results in investigations on the consumption of alcohol and nicotine during pregnancy.
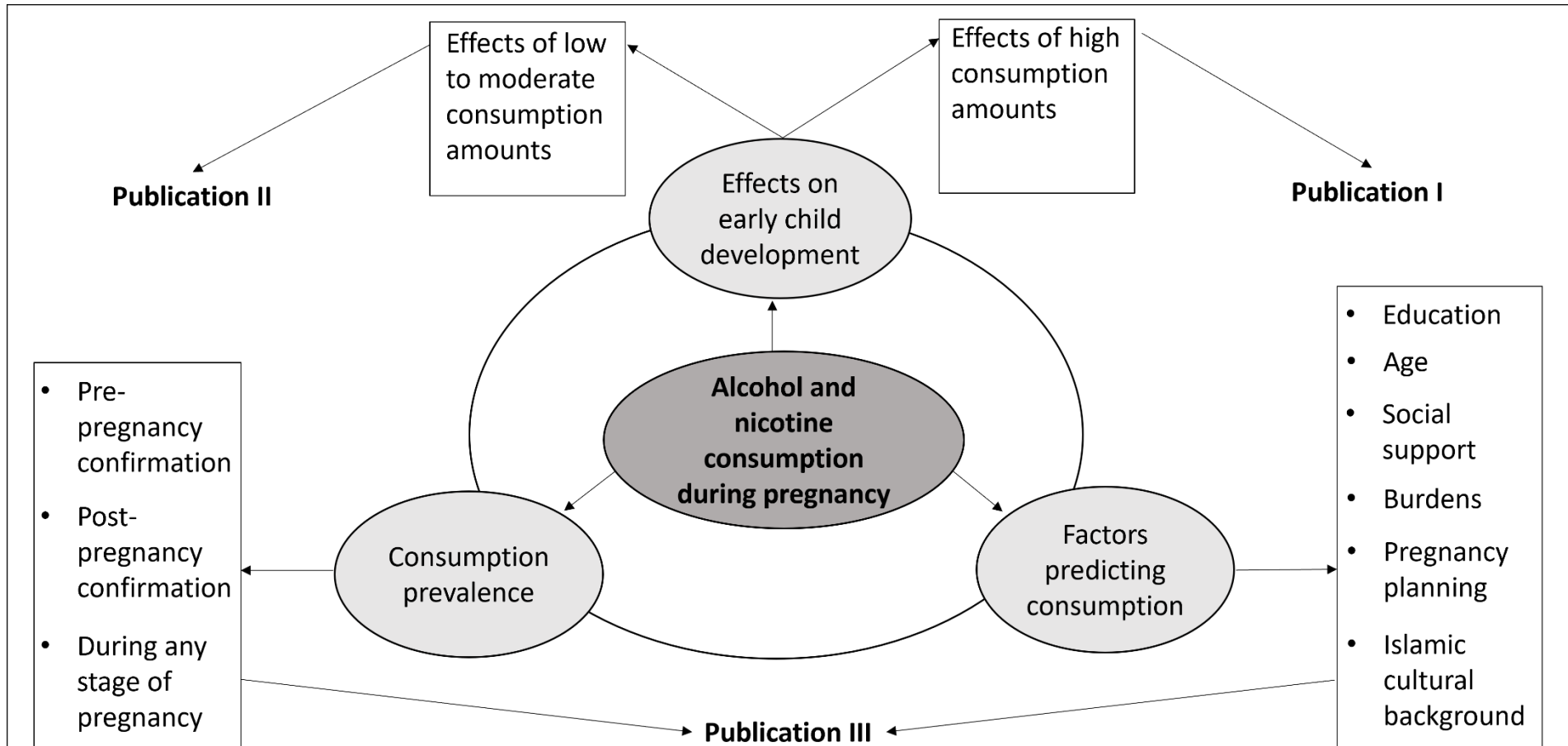
Figure 2: A multifactorial interplay of components to investigate prenatal alcohol and nicotine exposure

Outgoing from alcohol and nicotine consumption during pregnancy, arrays (⟶) indicate the affiliated components effects-, prevalence- and predictors of consumption that are connected with each other in investigations on prenatal substance exposure and that are specifically addressed in the three publications of the dissertation.

5.4   Limitations

The following sections discuss limitations of current research detected through the literature research for topic 1 and topic 2 and through the analyses with the BRISE-sample regarding topic 3.

5.4.1   Limitations of current research

Investigations on alcohol and nicotine consumption during pregnancy including consumption prevalence, factors that predict the consumption and resulting effects on early child development are currently addressed in literature. Nevertheless, there are some decisive limitations that complicate a generation of comprehensive and consistent results.

The specific mechanism of the effects of alcohol and nicotine on the course of pregnancy and the affected child is not precisely understood (Pop-Jordanova & Demerdzieva, 2022). Research with animal models can contribute to knowledge translation on human organisms. Nevertheless, a direct transfer of results is complicated. Both methods differ in aspects like the differences of species in placental transport, embryonic metabolism, and the species variability in bio-transformation processes. Furthermore, they differ in the ratio per kilogram of a teratogenic dose and in various physiological and pharmacological mechanisms contributing to blood concentrations of a dose exposed to. Studies in human organisms are challenging regarding ethical standards and pregnancy protective regulations that have to be considered. This may lead to more limited possibilities in study designs.

Several confounders like additional risk factors that influence the consumption behaviour during pregnancy but also the pre- and postnatal development of the child exacerbate exact conclusions. Additional risk factors could be factors addressed in analysis with the BRISE-sample like the social surroundings,

burdens, biological age, education or whether a pregnancy was planned or not. Further factors may be poly-drug use, parental genetics or comorbidities (Nulman et al., 2018; Tran et al., 2023). Thus, it is challenging to diagnose a FAS or FTS specifically and to differentiate it from other clinical pictures. Various clinical syndromes and associated symptoms overlap with those resulting from prenatal alcohol or nicotine exposure (see also section 5.1.1.).

Furthermore, current studies analysed primarily effects that become noticeable in later developmental stages. Results of alcohol and nicotine exposure regarding effects on early child development concerning the first two years of life remain sparse. This impedes adequate and timely treatment options for affected patients (Nulman et al., 2018).

While the majority of research primarily focused on the effects of high amounts of prenatal substance use, the influence of low and moderate levels of alcohol and nicotine is still poorly understood (Halliday et al., 2017; Todorow et al., 2010). The number of studies on effects and further aspects like consumption prevalence or additional risk factors that correlate especially with consumption of low to moderate amounts is insufficient. There is evidence that these components differ, depending on the amount of consumed substances. Low to moderate alcohol and nicotine consumption may correlate with other risk factors and consumption prevalence resulting in different child outcomes as those in clinical samples. Although the consumption of low to moderate amounts during pregnancy seems to influence the course of a pregnancy and developmental processes of affected children (Römer et al., 2020), current research lacks coherent consents.

A decisive effect that complicates suitable comparisons is the methodical heterogeneity applied across studies. Data on consumption prevalence are

currently based on incoherent defined consumption patterns (see section 1.1.1.). Further, the minority of research included the first weeks of pregnancy, thus, the timespan between conception and the confirmation of pregnancy. As such, important phases with decisive developmental processes like cell division and organic development are not included, although they are highly relevant for resulting child outcomes (King et al., 2018; Nulman et al., 2018). This results in underestimations of current prevalence data, particularly for low and moderate consumption amounts. Likewise, as the definitions of different consumption levels, data on prevalence are presented more often and more precisely described for alcohol consumption in comparison to nicotine consumption. Adequate global comparisons are consequently impossible. Additional risk factors that influence the consumption behaviour of pregnant woman and the postnatal development of affected children are frequently not involved. Especially not in studies on low to moderate consumption amounts. Furthermore, factors like maternal education or poly drug use are obviously considered to be influential (Baron et al., 2013; Melchior et al., 2015; Murphy et al., 2013). This exacerbates a comprehensive assessment of consumption behaviour and conclusive links to effects on early child development.

Literature search, identification and summarization concerning topic 1 and 2, was realized through two different methodological approaches (see sections 3.1.1. and 3.2.1). The literature review that was applied to generate results for topic 1 was carried out extensively but non-systematically. This allowed to generate a broad data spectrum and detailed revisions and selections of detected studies. Thus, a high risk of bias could be avoided and a high quality of included studies could be realized. It was suitable to approach topic 1 as the detection of data concerning the first two years of children were included in

literature on consumption of high amounts of alcohol and nicotine that is already frequently addressed in literature. The systematic approach that was chosen to analyse topic 2 predefines specific criteria in comparison to a narrative literature review. Consequently, it was indispensable to check the risk of bias and the quality of included studies in a separate step. Nevertheless, the systematic approach turned out to be the most appropriate approach, especially to address topic 2 as it was focussed on a special research question that is rarely addressed in literature. The detailed and structured literature search -and selection process enabled to provide valid data that represent relevant findings as a base for further research, the development of adequate preventions and the empirical research of topic three,

5.4.2 Limitations of the analyses of the BRISE-sample

The analyses of the BRISE-sample include important components, such as consumption prevalence at different stages of pregnancy, as well as additional risk factors. However, these data should be interpreted with caution, as they are based on information provided by the pregnant woman. The evaluation of data assessed through interviews is generally debatable, as answers may correspond to patterns in the sense of social desirability (Latkin et al., 2017). Analyses of aspects that are partly based on retrospectively collected data seem critical in addition. Drinking and smoking patterns at the time of pregnancy may be wrongly recalled in reminiscence (Subramoney et al., 2018). By means of these measures, the assessment of prevalence of prenatal alcohol or nicotine exposure as well as on further risk factors is rather constricted. Nevertheless, this data represents a general consent of what may be seen to be unproblematically with regard to alcohol and nicotine consumption. For

example, most women seem to believe that the consumption of alcohol until confirmation of pregnancy does not pose a risk for a healthy child development. This aspect provides important information for developing preventive measures. An additional limitation is the small sample size. If the sample size is too small, possible existing significant differences between the groups that consumed alcohol or nicotine during pregnancy or abstained may not be recognized as they would with a larger sample. As a result, at least no valid statements on existing subgroups that consumed pre- or post-confirmation of pregnancy could be made. The investigation of mediator and moderator effects is also more difficult due to the increasingly complex model through interaction effects and the associated loss of degrees of freedom.

5.5 Implications

The following sections discusses implications for further research, further possibly analyses with the longitudinal data of the BRISE-project and for clinical practice.

5.5.1 Implications for further research

To generate a complex understanding regarding the effects of prenatal alcohol and nicotine exposure, more research on effects on early developmental stages comprising the first two years of life is required. Deficits that would currently be recognized at later stages, could be discovered from early on and be treated accordingly.

In addition to the focus on high consumption levels, more research on low and moderate consumption levels is essential. This would enable clarifications on effects and resulting establishments of general consents regarding possible negative effects based on the consumption of low to moderate amounts.

In order to ensure better comparability across studies, it is important to include various aspects such as consumption prevalence concerning different stages of pregnancy and additional risk factors. This requires uniform definitions of the individual consumption quantities like low moderate and high. Further research projects could for example use the following consensus of previous studies that was also used for the analyses of the BRISE-data: Low to moderate consumption of alcohol could be defined as less than four to six alcoholic drinks per occasion, less than seven drinks per week and no binge drinking on more than one occasion during their pregnancy (Flak et al., 2014; Popova et al., 2017; Römer et al., 2020). Low to moderate consumption of nicotine could be defined as less than 20 cigarettes a day (Clifford et al., 2012; Römer et al., 2020). Some studies reported results that correspond for example more the high-level consumption amounts. However, due to variations in definitions, they were classified as moderate consumption amounts. These controversies would be eliminated with coherent definitions of consumption amounts. A precise differentiation between low and moderate consumption amounts would be decisive to generate comparable data on consumption prevalence, associated factors and resulting effects on affected children.

Further aspects that could improve the collection of representative data on consumption prevalence is the use of biomarkers for alcohol (Eichler et al., 2016; Jaffee, 2018; Thon et al., 2013) and nicotine (Burstyn et al., 2009; Fischer et al., 2017; Ng et al., 2018; Taghavi et al., 2018). For analyses, direct metabolic products of the toxic substances were used (Jaffee, 2018; Taghavi et al., 2018). Ethanol metabolites such as ethylglucuronide, ethylsulfate or phosphatidylethanol served as classic biomarkers for alcohol (Jaffee, 2018; Thon et al., 2013). Cotinine is known as a nicotine derivate and is a classical

biomarker for nicotine (Ng et al., 2018; Taghavi et al., 2018). This method of analysing amounts of alcohol and nicotine metabolites is considered a reasonable alternative to assess coherent prevalence (Chiandetti et al., 2017). A big advantage is the possibility of an early detection of morphological, cognitive, behavioural and mental disorders that may be missed if diagnostic measures are focused on outcomes that appear later in development. Furthermore, adequate counteractions and prevention strategies could be applied already in the first years of life. Like that, at-risk-children may be identified prior they exhibit a pathological symptomatology (Jaffee, 2018). Consequently, interdisciplinary research and thus, the connections between different research areas would be helpful to provide a broader methodological spectrum.

In addition, further research has to consider that the consumption of toxic substances should not be interpreted in isolation, but while regarding other environmental and genetic factors that influence the consumption behaviour during pregnancy and the developmental course of affected children during and after pregnancy.

5.5.2 Implications for further research with the BRISE-sample

The underlying analyses in the context of publication III and the dissertation provides an appropriate basis for further research with the BRISE-data. After the sample has been examined with regard to the consumption prevalence during pregnancy and additional predictive factors, further data waves can be analysed subsequently. First, current analyses can be repeated with a larger sample size and be compared with the current ones. Secondly, parameters of the postnatal phase can also be examined using data sets from further

measurement timepoints. The consumption prevalence after pregnancy, as well as other factors such as burdens or support from the social environment and possibly other relevant factors could be checked in connection with each other. In coherence with this, the course of early child developmental outcomes could be analysed using various methods. For this purpose, information from parents regarding different developmental aspects of the children as well as results from development tests collected by the research team of the BRISE project could be examined. Furthermore, the effects of prenatal alcohol or nicotine exposure on neurocognitive markers could be checked using EEG, Eye tracking and behavioural observations. The current analysis included different aspects like the consumption prevalence during different stages of the pregnancy as well as additional factors that seemed to predict the consumption behaviour. Consequently, this provides a comprehensive basis for further analysis on early child developmental outcomes.

5.5.3 Implications for the practical field

For adequate prevention, intervention and diagnostics, it would be helpful to transfer current research results to specialists from all relevant professional groups regarding clinical and social sectors. A general consensus that is represented towards the target and patient groups in the context of gynaecological preventive screenings or meetings with midwives could be developed. For example, it is known that quitting alcohol or nicotine consumption at any stage of pregnancy is associated with improved pregnancy outcomes, but there is evidence that quitting consumption in the first trimester provides the greatest benefits (The American College of Obstetricans and Gynecologists, 2020) However, it would be essential to prevent the

consumption of alcohol or nicotine during the first days and weeks of pregnancy, hence, during any stage of pregnancy. Consequently, early abortions and developmental impairment could be avoided (Diamanti et al., 2019; Pop-Jordanova & Demerdzieva, 2022). As such, quitting consumption when planning a pregnancy or when it could have come to a pregnancy through unprotected sexual activities, should be a clinical priority. In this context, it would be necessary to inform women in childbearing age and the society about current results presenting that consumption of alcohol or nicotine poses a high risk for early child development, even in low to moderate amounts. The continuous and consistent recording of prevalence as a basis for the prevention of consequential damage for child development through prenatal alcohol and nicotine exposure is still essential. Identifying additional perinatal risk factors as part of early detection screenings could be decisive and advisable. It is important to consider the causes of consumption behaviour prior, during and after pregnancy, in the planning of preventive measures. Therefore, it has to be considered that the consumption of toxic substances should not be interpreted in isolation, but rather in combination with environmental and genetic factors that influence the consumption behaviour during pregnancy and the developmental course of affected children prior, during and after pregnancy. Occupational groups of the social and health care system like gynaecologists, paediatricians, midwifes or clinical child psychologists could use this knowledge to identify at-risk families early on. For example, strategies might involve pregnancy screenings or paediatrician early detection or psychological care. Postnatal care and support by midwives and child- or family services as well as counselling of substance addictions could counteract some of the possible prenatal consumption effects adequately.

Knowledge about effects that can occur in form of negative or even pathological outcomes during the first two years of life and corresponding methods, may support paediatricians in screening affected children with regard to early symptoms linked to prenatal alcohol or nicotine exposure. Through to a close, cross-professional network, preventive and interventive offers and measures could be designed more efficiently. Thus, priorities referring to the expenditure of the health- and social system, could be adjusted (Popova et al., 2022).

6 Conclusions

In their combination, the results of the present dissertation contribute to the development of further investigations and prevention strategies concerning the consumption of alcohol and nicotine during pregnancy. Analysis of current literature revealed that the consumption of high but also of low to moderate amounts of alcohol and nicotine affect early child development, concerning the first two years of life. Developmental outcomes through high consumption amounts comprised negative effects on physical, neuropsychological and behavioural development. Results based on low to moderate amounts appeared to be more controversial, revealing higher scores in cognition tests, decreased sensory sensibility, smaller body sizes or impairments in children's orienting, communication and motor skills. Investigations with the BRISE-data gave evidence that nearly the half of the total sample consumed alcohol and/or nicotine during pregnancy, whereas 92.3 % quit drinking and 62.8 % stopped smoking following confirmation of pregnancy. Factors predicting the consumption of alcohol comprised a better social support, a higher age, an unplanned pregnancy and not having an Islamic cultural background. A lower level of education and an unplanned pregnancy predicted smoking.

Analysis showed that it is important to consider various components when addressing the subject area of prenatal alcohol and nicotine exposure.

A continuous assessment of consumption prevalence involving all stages of pregnancy and all consumption amounts like low moderate and high should be studied. This enables global comparisons in order to gain an overview of the extent of the problem. It seems to be essential to inform the society about potential harmful effects of the consumption of toxic substances in early stages of pregnancy regarding all amounts.

The inclusion of further socioeconomic factors should be considered to clarify which factors may predict the consumption during- and after pregnancy in order to reach at-risk-families and women adequately.

Interdisciplinary research providing consistent methods, in close cooperation with politics, administration and professionals of the social- and health sector can provide empirical evidence to improve preventive and interventive strategies.

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Appendix A: Publication I

Römer, P., Reinelt, T., Petermann, F., & Teickner, C. (2019). Alkoholkonsum während der Schwangerschaft: Welche Auswirkungen auf die frühkindliche Entwicklung sind bekannt? *Kindheit und Entwicklung*, *28* (1), 6-18.

Übersicht

Alkoholkonsum während der Schwangerschaft

Welche Auswirkungen auf die frühkindliche Entwicklung sind bekannt?

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Zusammenfassung. Kinder sind bereits im Mutterleib sensitiv für Umwelteinflüsse. Pränataler Alkoholkonsum zählt dabei zu den einflussreichsten Risikofaktoren für die frühkindliche Entwicklung. Das Ziel ist es, einen Überblick über die aktuelle Forschungslage zum Thema Alkoholkonsum während der Schwangerschaft zu geben. Darüber hinaus wird der Forschungsstand zu Belastungen und Folgeschäden für die frühkindliche Entwicklung durch pränatale Alkoholexposition, aber auch zu weiteren Risikofaktoren zusammengefasst. Es wird gezeigt, dass das Wissen um die Prävalenz für Alkoholkonsum während der Schwangerschaft sowohl für die Erforschung der Folgen als auch für das Umsetzen von präventiven Maßnahmen ausschlaggebend ist. Die Prävalenzen unterscheiden sich nicht nur regional, sondern können auch durch andere Faktoren beeinflusst werden. Es wird deutlich, dass der Risikofaktor Alkohol und dessen mögliche Auswirkungen auf die frühkindliche Entwicklung nicht isoliert, sondern in Abhängigkeit von weiteren genetischen und Umweltfaktoren betrachtet werden müssen. Denn auch Folgen von weiteren perinatalen Risikofaktoren machen sich in den ersten beiden Lebensjahren bemerkbar. Beispiele für Entwicklungsstörungen in dieser Entwicklungsspanne sind externalisierendes Verhalten und kognitive Beeinträchtigungen. Inwieweit sich perinatale Risikofaktoren jedoch auf Entwicklungsverläufe von Kindern, die durch pränatalen Alkoholkonsum belastet sind, auswirken, erfasst eine umfassende Diskussion. Diese Lücke gilt es zu schließen um das Zusammenspiel perinataler Risiken genauer zu verstehen und adäquat entgegenwirken zu können.

Schlüsselwörter: Alkoholkonsum, Schwangerschaft, Risikofaktoren, frühkindliche Entwicklung, Prävention

Alcohol Consumption During Pregnancy: What Effects on Early Child Development Are Known?

Abstract: Children are already sensitive to environmental influences in the womb. Prenatal alcohol consumption is one of the most influential risk factors in early child development. The aim of this paper is to give an overview of the current research on alcohol consumption during pregnancy. In addition, the state of research on the burden and consequential damage for infant development caused by prenatal alcohol exposure, but also on other known risk factors, is summarized. It is shown that knowledge about the prevalence of alcohol use during pregnancy is crucial for both research on consequences and the implementation of preventive measures. The prevalence differs not only regionally, but may also be influenced by other factors. The average prevalence of alcohol consumption in women during pregnancy is highest in Europe (25.2 %; 95 % CI = 21.6 – 29.6 %). A large number of pregnancies worldwide are alcohol-related, although alcohol is known to be a risk factor for stillbirths as well as for abortions and premature births and can lead to serious developmental problems for the child. Currently, there is no fixed limit on the amount of alcohol that can be consumed during pregnancy without any harm to the unborn child. Compared with minor consumption, so-called binge drinking is of particular importance. There is a linear relationship between pregnant women's alcohol consumption and the severity of developmental disorders in affected children. Serious consequences of prenatal alcohol exposure can manifest themselves in early childhood, in the form of physical, neuropsychological, and behavioral abnormalities. In addition to anatomical implications, functional effects such as cognitive and behavioral problems are already noticeable in children up to the first 2 years of life. However, the exact pathogenesis is still unclear despite a large number of animal and human analyses. It is apparent that the risk factor of alcohol consumption and its potential effects on early child development should not be considered in isolation, but depending on other genetic and environmental factors. Moreover, it is now known that the consequences of other perinatal risk factors, apart from prenatal alcohol consumption, can already emerge during the first 2 years of life too. At the behavioral level, secondary effects of the prenatal risk factor of alcohol consumption and other perinatal risk factors mostly manifest themselves in the form of externalizing behaviors and cognitive deficits. However, the extent to which perinatal risk factors affect the course of development of children who are affected by prenatal alcohol consumption remains an unanswered question. This gap should be closed in the literature in order to understand the interaction of perinatal risks more accurately and to be able to counteract these risks adequately. The current state of knowledge is intended to help health professionals to identify at-risk mothers and their children at an early moment in order to give newborns the best possible start in life.

Keywords: alcohol consumption, pregnancy, risk factors, early child development, prevention

Der Konsum von Alkohol entwickelte sich in verschiedensten ethischen Gruppen und Kulturen, sodass Alkohol zur legal konsumierbaren Substanz wurde (Nulman, Shulman & Liu, 2018). Alkohol kann sich jedoch nicht nur auf den Konsumenten selbst schädlich auswirken, sondern auch auf Personen, die mit diesem in Verbindung stehen. Ein klassisches Beispiel hierfür ist die schädigende Wirkung des Alkoholkonsums von schwangeren Frauen auf deren im Mutterleib heranwachsende Nachkommen (Popova, Lange, Probst, Gmel & Rehm, 2017). Hierzu wurde aktuell bestätigt, dass Alkohol die am meisten konsumierte Substanz von Frauen im gebärfähigen Alter ist und dass, trotz des Wissens um die schädigende Wirkungsweise, weltweit Frauen während der Schwangerschaft alkoholische Getränke zu sich nehmen (Nulman et al., 2018).

Eine Vielzahl von Schwangerschaften weltweit ist alkoholbelastet (Popova, Lange, Probst, Gmel & Rehm, 2018), obwohl bekannt ist, dass Alkohol sowohl als Risikofaktor für Totgeburten (Kesmodel, Wisborg, Olsen, Henriksen & Secher, 2002), als auch für Schwangerschaftsabbrüche (Henriksen et al., 2004) und Frühgeburten (Albertsen, Andersen, Olsen & Grønbaek, 2004; Kesmodel, Secher & Olsen, 2000; Patra et al., 2011) gilt, und zu schwerwiegenden Entwicklungsstörungen des Kindes führen kann (del Campo & Jones, 2017; Lange, Rovet, Rehm & Popova, 2017).

Im Folgenden wird ein Überblick zu den Prävalenzen von Alkoholkonsum während der Schwangerschaft und den Auswirkungen pränataler Alkoholexposition auf die frühkindliche Entwicklung gegeben. Des Weiteren erfolgt eine Übersicht zu den mit Alkoholkonsum während der Schwangerschaft assoziierten Faktoren und den Einfluss perinataler Risikofaktoren im Hinblick auf Entwicklungsstörungen, die durch pränatale Risikofaktoren entstanden sind.

Es erfolgte eine umfangreiche Literaturrecherche unter Verwendung der Datenbanken PubMed und Science Direct. Folgende Begriffe wurden für die Literatursuche verwendet:

- Pregnancy: [„pregnant", „prenatal"];
- Alcohol consumption: [„alcohol", „high level alcohol exposure", „binge drinking", „FAS", „FASD"];
- Prevalence of drinking during Pregnancy: [„prevalence", „alcohol", „Germany"]
- Prenatal risk factors: [„predictors", „factors associated with prenatal alcohol drinking", „biological risk factors", „environmental factors", „socio-demographic factors", „use of measures"];
- Child development: [„early child development", „infant development", „epigenetic", „first two years of life", „first year of life"].

Zudem wurden die Bibliografien der genutzten Artikel nach weiterer, thematisch passender Literatur durchsucht.

Prävalenzen von Alkoholkonsum während der Schwangerschaft

Unter Einbezug von Berichten der Weltgesundheitsorganisation (WHO, 2013) wird angenommen, dass weltweit ca. 10 % der Frauen Alkohol während der Schwangerschaft konsumieren. Die fünf Länder mit der höchsten Prävalenz hinsichtlich des Alkoholkonsums während der Schwangerschaft (alle bis zu 60.4 %, 95 CI, 42.8–76.8), sind Irland, Weißrussland, Dänemark, das Vereinigte Königreich und Russland. Zu den Ländern mit der geringsten Prävalenz (d. h. = 0 %) gehören der Oman, die Vereinigten Arabischen Emirate, Saudi Arabien, Katar und Kuwait (Popova et al., 2017). Aktuellen Publikationen zufolge (Lange, Probst et al., 2017; Popova et al., 2017; Popova, Lange, Probst, Gmel & Rehm, 2018) ist die durchschnittliche Prävalenz des Alkoholkonsums bei Frauen während der Schwangerschaft im weltweiten Vergleich in Europa am höchsten (25.2 %, [95 % CI: 21.6 %-29.6 %]; Popova et al., 2017). Regionen, die die geringste Anzahl an Frauen, die während der Schwangerschaft Alkohol trinken vorweisen (östliche Mittelmeerregion und südostasiatische Region), sind allerdings auch bekannt als Regionen, in denen generell die Mehrzahl der Einwohner alkoholabstinent lebt. In Europa hingegen sind auch die Prävalenzen für Alkoholkonsum in der nichtschwangeren Bevölkerung am höchsten (Lange, Rehm & Popova, 2018).

Prävalenzen von Alkoholkonsum während der Schwangerschaft in Deutschland

Informationen zu Prävalenzen von Alkoholkonsum während der Schwangerschaft in der deutschen Bevölkerung liefern u. a. Daten des Kinder- und Jugendgesundheitssurveys [KiGGS]. Im Rahmen dieser Erhebungen wurden in den Jahren 2003 bis 2006 Daten von 17.641 Kindern und Jugendlichen in 167 für die Bundesrepublik repräsentativen Städten und Gemeinden erfasst. Zu vorgeburtlichen Einflussfaktoren auf die spätere Gesundheit wurden schriftliche Angaben der Eltern dieser Kinder (meist Angaben der Mütter) ausgewertet (Bergmann, Bergmann, Ellert & Dudenhausen, 2007; Hölling et al., 2012). Für den Alkoholkonsum ergab sich hieraus, dass ca. 1 % der befragten Frauen während der Schwangerschaft regelmäßig Alkohol konsumiert und ca. 14 % der Frauen gelegentlich Alkohol zu sich genommen hatten. Genaue Definitionen dazu, was „regelmä-

Tabelle 1. Angaben zu Prävalenzen von Alkoholkonsum während der Schwangerschaft auf weltweiter, europäischer und deutscher Ebene

Autoren	Anzahl der Schwangeren Alkoholkonsumentinnen in % (Gesamtanzahl = 100 %)		
	Global	Europa	Deutschland
Popova et al. (2017, 2018)	9.8 %	25.2 %	/
Bergmann et al. (2006)	/	/	58 % (≤ einmal pro Monat)
Bergmann et al. (2007)	/	/	1 % (regelmäßig) 14 % (gelegentlich)
Robert Koch-Institut (2014) und Landgraf et al. (2017)	/	/	20 % (moderate Menge) 8 % (riskante Menge) 12 % (Rauschtrinken, ≤ einmal pro Monat)

ßiger" und „gelegentlicher" Konsum bedeutet, werden nicht gegeben. Es traten außerdem Unterschiede in Bezug auf den Migrationshintergrund auf. So zeigte sich, dass 5 % der Frauen mit und 15 % ohne Migrationshintergrund während der Schwangerschaft alkoholische Getränke konsumierten. Ähnliche Zahlen weisen auch kleinere, regionale Stichproben auf, die jedoch je nach Stichprobe variieren: Im Zuge einer Umfrage mit 344 schwangeren Frauen aus 48 Berliner gynäkologischen Praxen ergab sich, dass 58 % der Schwangeren angaben, Alkohol während der Schwangerschaft getrunken zu haben, wobei sich dies bei der Mehrheit der Frauen auf weniger als einmal pro Monat beschränkte (Bergmann, 2006).

Daten aus 2012 liefert die Studie zur Gesundheit in Deutschland Aktuell [GEDA]. Im Rahmen dieser Studie wurden knapp 26.000 Personen, ab einem Alter von 18 Jahren, telefonisch interviewt. Es zeigte sich, dass rund 20 % der befragten schwangeren Frauen ein moderates und 8 % ein riskantes Alkoholkonsumverhalten aufweisen. Zur Erfassung des Alkoholkonsums wurde der *Alcohol Use Disorder Identification Test-Consumption (AUDIT-C)* eingesetzt (Bradley, Badrinath, Bush, Boyd-Wickizer & Anawalt, 1998). Ein moderates Trinkverhalten wurde mit einem bis drei Punkten definiert und ein riskantes mit vier Punkten. Ein Rauschtrinken (hier: ≥ sechs Getränke pro Gelegenheit, aber vgl. Nulman et al., 2018: ≥ drei Getränke pro Gelegenheit) trat bei 12 % der schwangeren Frauen seltener als einmal pro Monat auf. Bei ca. 4 % der Frauen kam dies einmal pro Monat vor und 0,1 % der Schwangeren gab an, dass dies mindestens einmal pro Woche zutraf (Landgraf, Giese, Heinen & Pingel, 2017; Robert Koch-Institut, 2014). Betrachtet man die Ergebnisse zu den Prävalenzen von Alkoholkonsum während der Schwangerschaft in Deutschland, wird deutlich, dass (a) die Zahlen diesbezüglich in den letzten zehn Jahren nicht gesunken sind, (b) je nach Studie stark variieren (s. Tab. 1), und (c) pränataler Alkoholkonsum weiterhin als ernst zu nehmendes Problem zu existieren scheint.

Laut des Bundesinstitutes für Risikobewertung (Wunsch, 2011) sind die Zahlen bezüglich der Prävalenzen von Alko-

holkonsum während der Schwangerschaft jedoch nicht verlässlich, da eine Vielzahl der Einschätzungen auf Interviewdaten basieren oder retrospektiv erhoben wurden.

Auswirkungen von Alkoholkonsum während der Schwangerschaft auf die frühkindliche Entwicklung

Die teratogenen Effekte von starkem und chronischem Alkoholkonsum während der Schwangerschaft auf das ungeborene Kind sind seit einigen Jahrzehnten bekannt (z. B. Lemoine, 1968; Spohr, 2005). Den schädigenden Wirkungsweisen pränataler Alkoholexposition im Hinblick auf die frühkindliche Entwicklung wurde vorerst jedoch wenig Aufmerksamkeit geschenkt (Nulman et al., 2018). Im Jahre 1968 wurden die Auswirkungen von Alkoholkonsum schwangerer Mütter auf deren Nachkommen erstmalig beschrieben (Lemoine et al., 1968). Erst Jahre später kam es zur Beschreibung eines dysmorphen Syndroms, woraufhin der Begriff „Fetales Alkohol Syndrom (FAS)" eingeführt wurde (Jones, Ulleland & Smith, 1973). Weltweit sind dabei ungefähr 15 von 10.000 Lebendgeburten jährlich von FAS betroffen. Das bedeutet, dass weltweit, pro Jahr etwa 119.000 Kinder mit FAS belastet sind (Popova et al., 2017, 2018). Für Europa werden die Prävalenzen von FAS am höchsten eingeschätzt. Der europäische Durchschnittswert ist dabei zwei bis sechs Mal so hoch wie der weltweite, der aktuell auf 14.6 pro 10.000 Lebendgeburten (95 % CI, 9.4–23.3) geschätzt wird (Popova et al., 2017). Dies deckt sich mit den erhöhten Prävalenzen für Alkoholkonsum während der Schwangerschaft in Europa im weltweiten Vergleich.

Fest steht, dass es sich bei einer Alkoholschädigung nicht um eine chromosomale Störung, sondern um eine teratogene Beeinflussung durch Ethanol und dessen Metaboliten handelt. Es besteht starke Evidenz, dass die

pränatale Ethanolexposition sowohl embryo- als auch fetotoxisch wirkt und ein breites Spektrum an Entwicklungsstörungen in verschiedenen Bereichen hervorruft (Barr et al., 2006; del Campo & Jones, 2017; May et al., 2013; Strandberg-Larsen et al., 2008). Aufgrund der noch unausgeprägten Bluthirnschranke des ungeborenen Kindes geht Alkohol über die Plazenta direkt in den fetalen Blutkreislauf über. Durch den biochemisch noch unreifen Organismus können Entgiftungsprozesse so nur verzögert stattfinden (Spohr, 2005). Die Art und der Schweregrad der Folgeschäden durch pränatale Ethanolexposition richten sich hierbei stark nach dem Muster des Trinkverhaltens der Schwangeren, also der Menge und der Häufigkeit an konsumiertem Alkohol. Zudem ist auch der Zeitpunkt des Konsums hinsichtlich der Auswirkungen auf die Entwicklung betroffener Kinder als ein relevanter Faktor zu berücksichtigen (Nulman et al., 2018).

Alkoholkonsum zu sensiblen Zeitfenster während der Schwangerschaft

Für die gesamte Teratologie sind verschiedene sensible Zeitfenster bekannt, die mit bestimmten Auswirkungen verbunden sind (s. Abb. 1). Während der *Präimplantationszeit* (acht bis 14 Tage nach der Konzeption) kann das *Alles-oder-Nichts-Prinzip* greifen. Hierbei kommt es durch Alkoholkonsum entweder zu einem embryonalen Tod oder zu einer gesund verlaufenden Schwangerschaft (Adam, 2012). Als die zentralste Periode gilt die Phase der *Gastrulation* (16 bis 24 Tage nach der Konzeption). Während dieses Zeitraums finden essentielle Prozesse in Bezug auf die Embryogenese statt. Zusammen mit medialem und lateralem Wachstum entwickelt sich das Neuralrohr des heranwachsenden Embryos. Es kommt zu einer schnellen Zellproliferation – die sich durch Zellteilung und Zellwachstum äußert und eine wichtige Rolle für die Entwicklung des embryonalen Organismus spielt – und zur Zellmigration (d. h. zu einer aktiven Ortsveränderung der Zellen). Wird die Zellproliferation durch toxische Substanzen, wie Alkohol, unterbrochen, kann dies nachstehend zu negativen Auswirkungen hinsichtlich der Entwicklung führen, indem die Bildung bestimmter Zelltypen und Prozesse der Zellerneuerung gestört werden (Nulman et al., 2018; Sulik, Lauder & Dehart, 1984).

Die Phase der *Organogenese* findet während der ersten 12 Schwangerschaftswochen statt. Kommt es in dieser Zeit zum Konsum alkoholischer Getränke, kann die Ausbildung der Organe des Embryos beeinträchtigt werden. In dieser Zeit können dadurch auch faziale Dysmorphologien, die im Rahmen eines FAS auftreten, entstehen (Nulman et al., 2018; Sulik, 1981). Während des zweiten und dritten Trimesters der Schwangerschaft findet das *fetale Wachstum* statt. Alkoholkonsum während dieser Phase korreliert mit einer intrauterinen und somatischen Wachstumsverzögerungen (Ernhart et al., 1985; Nulman et al., 2018). Diese sind keine vorrübergehenden Effekte, sondern äußern sich bei den betroffenen Neugeborenen in Form von geringem Geburtsgewicht und geringer Körpergröße, was nur in seltenen Fällen im Verlauf der Entwicklung ausgeglichen werden kann (Nulman et al., 2018). Die Entwicklung des zentralen Nervensystems, die Bildung von Synapsen und die Myelinisierung sind fortlaufende Prozesse, die sich durch die *gesamte Fetalperiode*, die Kindheit und die Jugend ziehen. Diese können zu jedem Zeitpunkt der Schwangerschaft, während allen drei Trimestern negativ durch Alkoholexposition des Kindes im Mutterleib beeinflusst werden. Ein Beispiel hierfür ist die Mikrozephalie, eine Fehlbildung des Gehirns, die häufig in Verbindung mit kognitiven Einschränkungen auftritt (Fryer, McGee, Matt, Riley & Mattson, 2007; Smith, Foundas & Canale, 1986).

Es gibt aktuell keine festgelegte Grenze für die Menge an Alkohol, die während der Schwangerschaft ohne Folgeschäden für das ungeborene Kind, konsumiert werden kann (Nulman et al., 2018). Im Vergleich zu geringfügigem Konsum kommt dem sogenannten Rauschtrinken (Binge Drinking: Nulman et al., 2018) eine besondere Bedeutung zu. Hier besteht ein linearer Zusammenhang zwischen Alkoholkonsum der Schwangeren und dem Schweregrad der Entwicklungsstörungen betroffener Kinder. Gravierende Folgeschäden pränataler Alkoholexposition können sich schon in der frühen Kindheit, in Form von physischen, neuropsychologischen und Verhaltensauffälligkeiten äußern (McCormack et al., 2017). Die genaue Pathogenese ist trotz einer hohen Anzahl an tierexperimentellen und Humananalysen jedoch noch immer nicht exakt geklärt (Nulman et al., 2018). Dies spiegelt sich in dem breiten Spektrum der Folgeerscheinungen pränataler Alkoholexposition wider, die unter dem Begriff „Fetale Alkohol Spektrumstörung" (FASD – fetal alcohol spectrum disorder*)* zusammengefasst werden (Nulman et al., 2018; Popova et al., 2018).

Durch pränatalen Alkoholkonsum bedingte Spektrumstörungen

Nach ICD-10 schließt FASD mehrere intrauterine Schädigungen ein, die durch Alkoholkonsum während der Schwangerschaft bedingt sind: Das Fetale Alkoholsyndrom als Vollbild (FAS), das partielle fetale Alkoholsyndrom (pFAS), die alkoholbedingte entwicklungsneurologische Störung (ARND =alcohol related neurodevelopmental disorder) und die alkoholbedingte angeborene Malformation (ARBD = alcohol related birth defects).
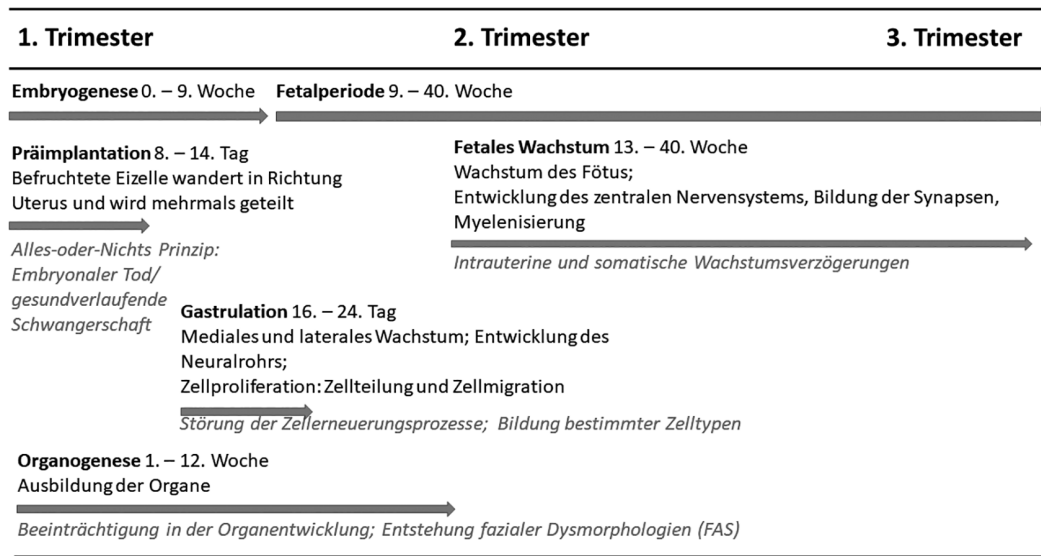
Abbildung 1. Auswirkungen des Alkoholkonsums zu sensiblen Zeitfenstern während der Schwangerschaft.

Dies stimmt mit der Definition des Diagnostischen und Statistischen Manuals Psychischer Störungen (DSM-5) überein, wobei hier der Terminus „Neurobehavioral Disorder associated with pranatal alcohol exposure (ND-PAE)" hinzukommt (American Psychiatric Association, 2013; Lange, Rovet et al., 2017).

Kasten 1. Übersicht über die Fetalen Alkohol Spektrumstörungen

FAS (Fetal Alcohol Syndrome)
Das fetale Alkoholsyndrom als Vollbild: Wachstumsstörungen, Fehlbildungen und Störungen des zentralen Nervensystems.

pFAS (Partial fetal alcohol syndrome)
Das partielle fetale Alkoholsyndrom: Nicht in allen Bereichen auftretende Merkmale des FAS. Hier treten zum Beispiel nur einige der fazialen Fehlbildungen zusammen mit Wachstumsstörungen und Störungen des zentralen Nervensystems auf.

ARND (Alcohol related neurodevelopmental disorder)
Alkoholbedingte entwicklungsneurologische Störung: Störungen des zentralen Nervensystems ohne körperliche Fehlbildungen, die sich z.B. in Verhaltens- und Lernschwierigkeiten äußern können.

ARBD (Alcohol related birth defects)
Alkoholbedinge angeborene Fehlbildungen: Anatomische Fehlbildungen der Organe, wie Herz, Nieren und/oder der Knochen. Auch Hören und Sehen können beeinträchtigt sein.

Allein durch die Definitionsbreite wird, wie Kasten 1 veranschaulicht, das weite Spektrum an möglichen defizitären Auswirkungen des pränatalen Alkoholkonsums auf die frühkindliche Entwicklung deutlich (Landgraf et al., 2017). Anatomische Auswirkungen äußern sich in einer breiten Facette von leichten morphologischen Anomalien bis hin zu schweren anatomischen Schädigungen, wie einer postnatalen Dystrophie, muskulärer Hypotonie, organischen Fehlbildungen und kraniofazialen Dysmorphien (Nulman et al., 2018).

Pränataler Alkoholkonsum und Auswirkungen auf neurokognitiver und Verhaltensebene in der frühen Kindheit

Neben anatomischen Auswirkungen lassen sind auch verschiedene funktionale Auswirkungen einer pränatalen Alkoholexposition auf die kognitive Entwicklung und Verhaltensentwicklung von Säuglingen und Kleinkindern nachweisen. So sind sowohl FASDs (Lange, Rovet et al., 2017) als auch eine moderate pränatale Alkoholexposition mit kognitiven Einschränkungen assoziiert (s. Huizink & Mulder, 2006 für einen Überblick). Dabei scheinen sich die Effekte insbesondere für 12 Monate alte, nicht aber jüngere Säuglinge zu zeigen (Testa, Quigley & Eiden, 2003). Auch im weiteren Entwicklungsverlauf sind FASDs mit Einschränkungen der kognitiven Fähigkeiten verbunden (Mattson, Crocker & Nguyen, 2011). Kognitive Beeinträchtigungen können sich dabei im Rahmen allgemeiner intellektueller Leistungsfähigkeit, Exekutivfunktionen, Selbstregulationsprozessen, Gedächtnisleistungen oder dem Spracherwerb zeigen (Mattson et al., 2011). FAS

gilt dabei schon seit vielen Jahren als eine der zentralen Ursachen für eine kognitive Beeinträchtigung (Abel & Sokol, 1987; Dörrie, Föcker, Freunscht & Hebebrand, 2014). Der durchschnittliche Intelligenzquotient bei Kindern mit einer FAS-Diagnose liegen zumeist im unteren Grenzbereich (nach ICD-10 = < 70), wobei das Spektrum kognitiver Einschränkungen von leichten Lernbeinträchtigungen bis hin zu starken geistigen Behinderungen reichen kann (Dörrie et al., 2014).

Neben diesen kognitiven Einschränkungen zeigen sich auch auf einer Verhaltensebene Auswirkungen von pränatalem mütterlichem Alkoholkonsum auf das Stressempfinden und das Temperament von Säuglingen (Alvik, Torgersen, Aalen & Lindemann, 2011; Haley, Handmaker & Lowe, 2006; Schoeps et al., 2018). Bei sechs Monate alten Säuglingen wurde ein auffälliges Temperament in Form von häufigem und heftigen Weinen, Unruhe, Reizbarkeit, Verärgerung und der Suche nach Aufmerksamkeit mit pränatalem Alkoholkonsum in Zusammenhang gebracht. Insbesondere wöchentliches Binge-Drinking geht mit einem häufigen Schreien sechs Monate alter Säuglinge einher. Mehrfaches wöchentliches Binge-Drinking konnte darüber hinaus als prädiktiv für Schlafstörungen nachgewiesen werden (Alvik et al., 2011). Ein schwierigeres frühkindliches Temperament (häufiges Schreien, Weinen, Schlafstörungen) im ersten Lebensjahr zeigt sich abgeschwächt allerdings auch für Säuglinge, deren Mütter nach Bekanntwerden der Schwangerschaft aufgehört haben zu trinken (Haley et al., 2006; Schoeps et al., 2018), sodass bereits die Embryogenese als kritische Phase für Alkoholkonsum während der Schwangerschaft zur Entwicklung von Temperamentsauffälligkeiten angesehen werden muss.

Diese Temperamentsauffälligkeiten können sich im weiteren kindlichen Entwicklungsverlauf zu externalisierenden Verhaltensauffälligkeiten ausweiten (vgl. Abulizi, Pryor, Michel, Melchior & Van Der Waerden, 2017; Degnan et al., 2011; Kiel, Bruckdorfer, Petermann & Reinelt, 2018; Schoeps et al., 2018). Dazu gehören z. B. die Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) und oppositionelles Trotzverhalten (vgl. Beauchaine & McNulty, 2013). Defizite in diesen Bereichen wurden bereits mit starkem pränatalen Alkoholkonsum in Verbindung gebracht (Mattson et al., 2011). So ergibt sich für Kinder, die pränatalem Alkoholkonsum ausgesetzt waren, im Verlauf der frühkindlichen Entwicklung eine signifikant (bis zu 15 Mal, vgl. Pineda et al., 2007) höhere Wahrscheinlichkeit für das Auftreten von ADHS im Vergleich zu Kindern ohne pränatale Alkoholexposition (Fryer et al., 2007). Bei der Durchführung neuropsychologischer Aufgabenstellungen treten bei betroffenen Kindern u. a. Auffälligkeiten in Form von verminderter Vigilanz, verlangsamter Reaktionszeit und Informationsverarbeitung auf (Burden, Jacobson & Jacobson, 2005; Mattson et al., 2011). Obwohl die Prävalenzen für die Entwicklung einer ADHS bei FAS-Kindern im Vergleich zu Kindern ohne FAS erhöht sind, wird angenommen, dass beide Störungsbilder separaten verhaltensneurologischen Profilen unterliegen (Mattson et al., 2011). Dies zeigt sich darin, dass beide Störungsbilder z. B. mit Einschränkungen der Aufmerksamkeit assoziiert sind, sich diese Einschränkungen jedoch auf unterschiedliche Art und Weise bemerkbar machen. Kinder mit ADHS zeigen beispielsweise eher Schwierigkeiten beim Fokussieren und Aufrechterhalten der Aufmerksamkeit, während Kinder, die von FAS betroffen sind, primär Probleme haben, die Aufmerksamkeit zu verschieben, Informationen zu kodieren oder Flexibilität bei Problemlösungen zu zeigen (Mattson et al., 2011).

Auch postnatal kann Alkoholkonsum der Mutter negativen Einfluss auf die Entwicklung des Kindes haben, wenn es gestillt wird und Alkohol dadurch über die Muttermilch auf den Organismus des Säuglings übertragen wird (Brown, Dakkak & Seabrook, 2018). Ethanol, als Hauptbestandteil von alkoholischen Getränken, geht aufgrund seiner molekularen Eigenschaften in fast gleichbleibender Konzentration vom Blut in die Muttermilch über. Die Auswirkungen von Alkoholkonsum der Mutter während der Stillperiode können sich u. a. in Form von Schlafstörungen oder Beeinträchtigungen der Immunfunktionen des Neugeborenen und verminderter Milchproduktion der Mutter äußern (Brown et al., 2018).

Epigenetische Prozesse

Ein weiterer, durch Alkoholkonsum bedingter Prozess, der erst in jüngster Zeit Aufmerksamkeit gefunden hat, umfasst epigenetische Prozesse. Durch chemische Substanzen und somit auch durch den Alkoholkonsum der Schwangeren kann es zu Veränderungen der Genaktivität des heranwachsenden Kindes kommen (Nulman, Shulman & Liu, 2018; Schmidt, Petermann & Schipper, 2012). Tabelle 2 gibt einen Überblick zu epigenetischen Prozessen im Kontext des mütterlichen Alkoholkonsums.

Inwiefern sich die Auswirkungen von Alkohol auf den ungeborenen Organismus äußern, geht bekanntlich damit einher, in welchem Maße während der Schwangerschaft Alkohol konsumiert wird. Dies kann dabei stark von weiteren Gegebenheiten wie Umwelt- und soziodemographischen Faktoren abhängen, die sich entsprechend auf die Schwangeren selbst oder deren Umfeld beziehen (Halliday et al., 2017; Nulman et al., 2018; Ulrich & Petermann, 2016).

Tabelle 2. Epigenetische Prozesse im Kontext des Alkoholkonsums von Schwangeren

Grundlegende Mechanismen	Alkoholkonsum von Schwangeren
Epigenetische Mechanismen Die Genaktivität wird durch Umwelteinflüsse über endokrine, immuno-logische und molekulare Prozesse verändert. Dabei geht es um eine Veränderung der Funktion des Genoms und nicht des Genoms selbst. Das bedeutet, die DNA-Sequenz bleibt unverändert (Schmidt et al., 2012). **Alkohol und epigenetische Prozesse** Auch chemische Substanzen, wie Alkohol, können als Einflussfaktoren hinsichtlich der Gen-Umwelt-Interaktion, die epigenetischen Verände-rungen unterliegt, gelten und damit einhergehende Folgen verursachen. Zu den bekanntesten epigenetischen Mechanismen gehört die DNA-Methylierung (Schmidt et al., 2012). **DNA-Methylierung** Hierbei handelt es sich um eine genetische Modifikation, bei der die Übertragung von Methylgruppen auf Nukleobasen an einer bestimmten Stelle der DNA dazu führt, dass darauffolgende und eigentlich zuvor bestandene genetische Informationen nicht mehr abgelesen werden können (Schmidt et al., 2012).	Studien beschäftigen sich mit der Analyse des Zusammenhangs prä-nataler Alkoholexposition und dadurch ausgelöste epigenetische Pro-zesse. So zeigten Loke, Muggli, Nguyen, Ryan und Saffery (2018) anhand einer Stichprobe von 187 schwangeren Frauen, dass pränatale Alkoho-lexposition plazentare, epigenetische Veränderungen der Nachkommen bewirkt. Es zeigte sich außerdem, dass die männlichen Nachkommen eine höhere Rate an plazentarer DNA-Methylierung aufwiesen. Dies entspricht früheren Ergebnissen aus Studien, die epigenetische Me-chanismen in Verbindung mit pränatalem Nikotinkonsum untersucht haben. Im Rahmen der Forschungsarbeiten von Sharp und Kollegen (2018) wurden anhand von Untersuchungen des Blutes der Nabelschnur von Neugeborenen, die in der pränatalen Phase dem Alkoholkonsum durch die Mutter ausgesetzt waren, kein Zusammenhang zwischen DNA- Me-thylierungsprozessen und pränataler Alkoholexposition gefunden. Diese Ergebnisse stehen sowohl in Kontrast zu den Ergebnissen von Loke und Kollegen (2018). Die Gründe für die widersprüchlichen Ergeb-nisse werden in den unterschiedlichen Analyseverfahren, aufgrund der kleineren Stichprobe und der unterschiedlichen Menge an konsumier-tem Alkohol vermutet (Sharp et al., 2018).

Mit Alkoholkonsum während der Schwangerschaft korrelierende Faktoren

Es existiert eine Vielzahl von Faktoren, die das Alkohol-konsumverhalten von schwangeren Frauen beeinflussen kann (z. B. Baio et al., 2010; Esper & Furtado, 2014; Kits-antas, Gaffney & Wu, 2015; Tran, Williams, Alati & Naj-man, 2015; Ulrich & Petermann, 2016; Washio, Mericle, Cassey, Daubert & Kirby, 2017). Zum einen bestehen Zu-sammenhänge zwischen Alkoholkonsum während der Schwangerschaft und soziodemographischen Faktoren, wie z. B. der Herkunft, dem Migrationsstatus und der Wohngegend (Melchior et al., 2015) oder dem Bildungs-stand und sozioökonomischen Status der schwangeren Frauen (Melchior et al., 2015; Murphy, Mullally, Cleary, Fahey & Barry, 2013; Pfinder, Feldmann & Liebig, 2013; Skagerström, Alehagen, Häggström-Nordin, Årestedt & Nilsen, 2013). Zum anderen bestehen auch Zusammen-hänge mit sozialen Faktoren, wie der Paarbeziehung (Po-wers, McDermott, Loxton & Chojenta, 2013), vor der Schwangerschaft erfahrenen Gewalteinflüssen (Skager-ström, Chang & Nilsen , 2011) oder sozialer Unterstüt-zung durch das Umfeld (Powers et al., 2013). Auch der Alkoholkonsum vor der Schwangerschaft oder der Kon-sum weiterer Substanzen, wie Nikotin, vor und während der Schwangerschaft scheint mit pränataler Alkoholexpo-sition in Zusammenhang zu stehen (Murphy et al., 2013; Nulman et al., 2018; Skagerström et al., 2013; Skager-ström et al., 2011).

Soziodemographische Faktoren

Beleuchtet man soziodemographische Faktoren, die mit Alkoholkonsum während der Schwangerschaft assoziiert sind, genauer, weisen bisherige Erkenntnisse daraufhin, dass Frauen mit Migrationshintergrund während der Schwangerschaft weniger Alkohol konsumieren als Frau-en ohne Migrationshintergrund. In der Studie von Mel-chior und Kollegen (2015) wurden die Daten anhand von Interviews mit in Frankreich lebenden Frauen gewonnen. Die Stichprobe bestand zum Großteil um Frauen aus Ländern, wie Nordafrika und Asien, in denen der Alko-holkonsum von Frauen laut WHO (2013) generell gering ist. Außerdem handelte es sich bei den Schwangeren mit Migrationshintergrund zumeist um Frauen mit geringe-rem sozioökonomischen Status. Die Tatsache, dass Schwangere mit Migrationshintergrund weniger Alkohol konsumieren als Schwangere ohne Migrationshinter-grund, wird auch durch Daten aus Deutschland gestützt, die im Rahmen der KiGGS-Studie erhoben wurden (Bergmann et al., 2007; Hölling et al., 2012; Lampert, Müters, Stolzenberg & Kroll, 2014). Die KiGGS-Studie umfasst Daten von 16.301 befragten Frauen aus Deutschland, die im Rahmen dieser Studie retrospektiv erhoben wurden. Hieraus ergab sich des Weiteren, dass sich der sozioökonomische Status, neben physischen Merkmalen wie dem Alter oder dem Körpergewicht der Schwangeren, als stärkster Prädiktor für Alkoholkonsum während der Schwangerschaft erwies. Die Prävalenzen bei Schwangeren mit einem hohen Bildungsabschluss la-gen im Vergleich zu denen bei Schwangeren mit einem

mittleren oder niedrigen Sozioökonomischen Status höher (Pfinder et al., 2013).

Ergebnisse einer Umfrage aus Schweden ergaben weitere mit Alkoholkonsum während der Schwangerschaft korrelierende Faktoren, wie das Leben in einer größeren Stadt (>200.000 Einwohner) und ein höheres Alter. Im Vergleich zu Schwangeren, die 24 Jahre oder jünger waren, ergab sich, dass Schwangere, die 40 Jahre oder älter waren, mit einer 11 Mal so hohen Wahrscheinlichkeit Alkohol zu sich nahmen. Die Wahrscheinlichkeit für Alkoholkonsum bei den 35- bis 39-jährigen Schwangeren lag noch achteinhalbmal höher. Ähnliche Prävalenzen ergaben Befragungsdaten von 368 schwangeren Frauen irischer Herkunft (Murphy et al., 2013). Außerdem gaben 84 % der insgesamt 1594 befragten schwangeren Schwedinnen an, in dem Jahr vor ihrer Schwangerschaft regelmäßig Alkohol konsumiert zu haben, und zwar bis zur medizinischen Feststellung der Schwangerschaft. Das bedeutet, dass Alkoholkonsum während früher Schwangerschaftsphasen stattfand (Skagerström et al., 2013). Um den Alkoholkonsum zu erfassen, wurde der *Alcohol Use Disorder Identification Test-Consumption (AUDIT-C)* eingesetzt (Bradley, McDonell et al., 1998).

Soziale Faktoren

Soziale Faktoren, die sich auf die Prävalenzen des Alkoholkonsums während der Schwangerschaft auswirken können, sind die Unterstützung des sozialen Umfeldes und die des Partners (Beijers et al., 2014; Powers et al., 2013; Skagerström et al., 2011). Fehlt es Frauen während der Schwangerschaft an sozialer Unterstützung durch deren Umfeld oder durch die Partnerschaft, steigen die Prävalenzen, Alkohol während der Schwangerschaft zu konsumieren (Powers et al., 2013). Die Erfahrung von Gewalt (in der Partnerschaft) gehört dabei zu den Prädiktoren für Alkoholkonsum vor und während der Schwangerschaft (Powers et al., 2013; Skagerström et al., 2011). Auch der fehlende Zugang zu unterstützenden Maßnahmen während der Schwangerschaft scheint die Prävalenz des Konsums zu erhöhen (Nulman et al., 2018). Ein weiterer Faktor, der häufig mit einem höheren Alkoholkonsum während der Schwangerschaft assoziiert ist, ist der Konsum von Nikotin (Murphy et al., 2013; O'Keeffe et al., 2015; Powers et al., 2013; Skagerström et al., 2013).

Schwangerschaftsspezifische Faktoren

Auch schwangerschaftsspezifische, medizinische Faktoren, wie z. B. Blutungen, Infektionen oder auch Diagnosen hinsichtlich Fehlbildungen des heranwachsenden Fetus, stehen in Zusammenhang mit pränataler Alkoholexposition. In einer niederländischen Kohortenstudie wurden Frauen in der Mitte ihrer Schwangerschaft zu verschiedenen Stresskategorien befragt. Neben Stressoren auf finanzieller oder familiärer Ebene wurden auch die schwangerschaftsspezifischen medizinischen Faktoren einbezogen. Es wurde dabei zwischen Frauen unterschieden, die zu dieser Zeit noch Alkohol tranken (n = 124) bzw. bereits aufgehört hatten (*n* = 1403). Die Ergebnisse zeigten, dass pränataler Alkoholkonsum mit schwangerschaftsspezifischen medizinischen Faktoren insofern einhergeht, dass Schwangere, die zur Befragungszeit noch Alkohol konsumierten, häufiger unter Faktoren wie vaginalen Blutungen oder Infektionen litten, als Frauen, die während der Schwangerschaft Alkoholabstinet lebten (Beijers et al., 2014). Zudem scheint bei nicht geplanten bzw. ungewollten Schwangerschaften ein erhöhtes Risiko für pränatalen Alkoholkonsum vorzuliegen (Beijers et al., 2014; Iversen et al., 2015).

Auswirkungen perinataler Risikofaktoren auf die frühkindliche Entwicklung

Neben pränatalem Alkoholkonsum existieren weitere Risikofaktoren, die die Wahrscheinlichkeit des Auftretens einer Verhaltensauffälligkeit oder Störung im Verlauf der frühkindlichen Entwicklung begünstigen. Zur Erfassung und Unterteilung perinataler Risikofaktoren und deren Auswirkungen existieren verschiedene Ansätze. Zunächst lassen sich Risikofaktoren definieren, die sich während und nach der Schwangerschaft auf die Frau selbst beziehen. Neben Substanzkonsum, wie Alkohol oder Nikotin, sind z. B. ein geringes Bildungsniveau (Demirci & Kartal, 2018), aber auch eine mangelhafte Ernährung oder psychische Belastung der Schwangeren auffällig (Ulrich & Petermann, 2016). Hiervon zu unterscheiden sind risikoassoziierte Faktoren, die sich auf die Umgebung und das Umfeld der (werdenden) Mutter und des Kindes beziehen. Diese sind unter anderem fehlende soziale Kontakte, Partnerschaftskonflikte oder mangelhafte Wohnsituationen (Esser & Schmidt, 2017; Powers et al., 2013). Dass einige dieser perinatalen Risikofaktoren bereits Auswirkungen auf die Embryogenese und Fetalperiode, die Phase während und unmittelbar nach der Geburt und die ersten beiden Lebensjahre eines Kindes haben, wird durch Ergebnisse mehrerer Studien bestätigt (s. Tab. 3).

Neben pränatalem Alkoholkonsum gilt Nikotinkonsum während der Schwangerschaft als einer der häufigsten Risikofaktoren für die frühkindliche Entwick-

Tabelle 3. Beispiele von Auswirkungen perinataler Risikofaktoren auf verschiedenen Zeitpunkte der frühkindlichen Entwicklung

Phase der Auswirkungen auf die kindliche Entwicklung	Autoren	Zugrunde liegende Risikofaktoren	Art der Auswirkungen
Schwangerschaft			
Gesamte Embryogenese und Fetalperiode	Godleski et al. (2016) und Tiesler et al. (2014)	Nikotinkonsum während der Schwangerschaft	Beeinträchtigung der Entwicklung von Organen, und der Bildung des ZNS
Geburtsphase			
Während / unmittelbar nach der Geburt	Tiesler et al. (2014)	Nikotinkonsum während der Schwangerschaft	Erhöhtes Risiko für Tod- und Frühgeburten; niedriges Geburtsgewicht
Erstes Lebensjahr			
6 Monate (bis 30 Monate)	Kumar et al. (2013)	Höheres Alter der Schwangeren, Verwandtenehe, genetische Vorbelastung	Neurologische Entwicklungsstörungen (sensorisch und motorisch)
3 Monate (bis 5 Jahre)	Demirci und Kartal (2018)	Kaiserschnitt, Alter (≥ 35 Jahre), niedriger Schulabschluss und geringer sozioökonomischer Status der Mutter	Störungen der sozialen und kognitiven Entwicklung
9 Monate	Shisler et al. (2016)	Nikotinkonsum während der Schwangerschaft	Störungen in fokussierter Aufmerksamkeit
Zweites Lebensjahr			
17 Monate	Galéra et al. (2011)	Nikotinkonsum während der Schwangerschaft	Leichte Aufmerksamkeitsdefizite
24 Monate	McDonald et al. (2016)	Psychische Probleme der Mutter	Hyperaktivität, Aggression, negative Emotionalität, Verzögerung der sozial-emotionalen Entwicklung

lung (Ulrich & Petermann, 2016). Pränataler Nikotinkonsum wirkt sich, ähnlich wie pränataler Alkoholkonsum, bereits während der Embryogenese und der gesamten Fetalperiode störend auf die Entwicklung der Organe und des ZNS des heranwachsenden Kindes im Mutterleib aus (Godleski, Eiden, Schuetze, Colder & Huestis, 2016; Tiesler & Heinrich, 2014). Des Weiteren können Auswirkungen des Nikotins mit einem erhöhten Risiko für Tod- und Frühgeburten und einem geringen Geburtsgewicht einhergehen (Tiesler & Heinrich, 2014). Bei neun Monate alten Kindern wurden bereits Defizite in fokussierter Aufmerksamkeit bemerkt (Shisler et al., 2016), die neben anderen Auffälligkeiten wie einem schwierigen Temperament auch als Vorläufer externalisierender Verhaltensauffälligkeiten gelten (Kiel et al., 2018).

Einen weiteren Risikofaktor stellen psychische Probleme auf Seiten der Mütter dar. Diesem Risikofaktor wurden bei 16 % der Zweijährigen auch Verzögerungen der sozial-emotionalen Entwicklung zugeschrieben (McDonald, Kehler & Tough, 2016). Entwicklungsauffälligkeiten und -störungen in Form von externalisierenden Verhaltensweisen wie oppositionellem Trotzverhalten, Wutanfällen, Hyperaktivität und Impulsivität zeigen sich bereits in der frühen Kindheit (Fisch et al., 2016; Kiel et al., 2018). Eine Studie von McDonald und Kollegen zeigte, dass 24 % der Kinder von insgesamt 1146 teilnehmenden Müttern

Verhaltensproblematiken wie Überaktivität, Aggression oder negative Emotionalität, schon im Alter von zwei Jahren, zeigten.

Weitere perinatale Risikofaktoren für die frühkindliche Entwicklung sind ein erhöhtes Alter, ein niedriger Schulabschluss bzw. geringer sozioökonomischer Status der Mutter, Verwandtenehen, bereits vorhandene neurologische Erkrankungen in der Familie, eine Geburt per Kaiserschnitt bzw. ein geringes Geburtsgewicht des Neugeborenen. In Untersuchungen mit Kindern im Alter von drei Monaten bis fünf Jahren (Demirci & Kartal, 2018) zeigten sich diese Risikofaktoren als Grund für Störungen der sozialen und kognitiven Entwicklung. Außerdem wurden diese Faktoren auch mit neurologischen Störungen, die neben motorischen und sensorischen Entwicklungsstörungen zumeist auch mit externalisierendem Verhalten zusammenhängen, in Verbindung gebracht. Die neurologisch bedingten Auffälligkeiten zeichneten sich bei einer Stichprobe von Kindern im Alter zwischen sechs bis 30 Monaten ab (Kumar, Bhave, Bhargava & Agarwal, 2013).

Einige der Risikofaktoren, die bereits pränatal das Alkoholkonsumverhalten der Schwangeren beeinflussen, bleiben auch in der postnatalen Phase bestehen. Hierzu zählen z. B. psychische Belastungen (McDonald et al., 2016; Ulrich & Petermann, 2016), ein höheres Alter (Demirci & Kartal, 2018) oder fehlende soziale Unterstützung

der Mutter (Powers et al., 2013). Es bleibt weiterhin ungeklärt, inwiefern genau perinatale Risikofaktoren die Entwicklung der durch pränatalen Alkoholkonsum belasteten Kinder zusätzlich beeinflussen. Die genaue Wechselwirkung perinataler Risikofaktoren und deren Effekte im Hinblick auf Folgeschäden, die durch pränatalen Alkoholkonsum entstanden sind, muss für die frühe Kindheit noch genauer analysiert werden. Daraus resultiert die Frage, wie Risikofamilien bestmöglich und früh identifiziert werden können und den perinatalen Risiken individuell wirksam vorgebeugt werden kann.

Schlussfolgerungen für die klinische Praxis

Zur Einschätzung, ob eine eindeutige Diagnose im Rahmen der FASD getätigt werden kann, bedarf es zunächst einer detaillierten diagnostischen Vorgehensweise. Die deutschen S3-Leitlinien zur Diagnostik des FAS (Landgraf, Nothacker & Heinen, 2013) dienen dabei als wichtige Orientierung (Landgraf et al., 2017). Hierzu wurden vier diagnostische Kriterien bestimmt, die in die Beurteilung einfließen: Mindestens eine *Wachstumsauffälligkeit*, drei definierte *faziale Auffälligkeiten*, funktionelle oder strukturelle *Auffälligkeiten des zentralen Nervensystems* (ZNS) und die Bestätigung des Alkoholkonsums der Mutter während der Schwangerschaft, wobei letztere nicht notwendigerweise vorliegen muss. Unter Berücksichtigung der genannten Kriterien ist zu beachten, dass es, wenn das zu untersuchende Kind sowohl Wachstumsauffälligkeiten, als auch faziale Auffälligkeiten und Auffälligkeiten des ZNS zeigt, einer FAS-Diagnose bedarf – auch wenn eine pränatale Alkoholexposition nicht mehr sicher zu stellen ist (Landgraf et al., 2017).

Ob ein Kind von pränataler Alkoholexposition betroffen war und Folgeschäden, die sich im Rahmen von Entwicklungsstörungen bemerkbar machen, womöglich darauf zurückzuführen sind, lässt sich über Angaben der Mutter nur bedingt feststellen. Ist die Facette an Verhaltensauffälligkeiten eines Kindes breit und liegen möglicherweise einer Vielzahl von Risikofaktoren vor, kann es rückwirkend schwer sein, zu identifizieren, ob Alkoholkonsum der Mutter als pränataler Risikofaktor bedeutsam war. Aktuelle Forschungsarbeiten beziehen deshalb sogenannte Biomarker für Alkohol mit ein (Eichler et al., 2016; Jaffee, 2018; Thon, Weinmann, Yegles, Preuss & Wurst, 2013). Dabei werden direkte Stoffwechselprodukte von Alkohol, die als Ethanolmetabolite in Erscheinung treten, zur Analyse genutzt. Ethanolmetabolite, wie Ethylglukuronid, Ethylsulfat oder Phosphatidylethanol, dienen da-

bei als klassische Biomarker für Alkohol (Jaffee, 2018; Thon et al., 2013). Derzeit findet die Nutzung von Biomarkern Anwendung in Bereichen der Notfallmedizin, bei Lebertransplantationen, bei der Bestimmung von Abstinenzlern im Rahmen von Alkoholbehandlungsprogrammen, bei Fahreignungstests und betrieblicher Gesundheitsprävention (Thon et al., 2013). Das Einsetzen von Biomarkern im Rahmen der FASD-Diagnostik wird kritisch betrachtet, findet jedoch seit einigen Jahren auch Anwendung, um frühzeitig auf pränatale Alkoholexposition rückschließen zu können (Fríguls et al., 2010; Thon et al., 2013; Zelner, Hutson, Kapur, Feig & Koren, 2012). Argumentiert wird u. a. mit der Möglichkeit, Verhaltensauffälligkeiten und psychischen Störungen, die zwar schon in der frühen Kindheit auftreten, in vielen Fällen jedoch erst zu späteren Zeitpunkten als solche diagnostiziert werden, bereits während den ersten Lebensjahren entgegenzuwirken bzw. vorzubeugen. Risikokinder könnten so identifiziert werden, bevor diese eine starke pathologische Symptomatik zeigen (Jaffee, 2018).

Hinweise zur Entwicklung und Wirkungsweise präventiver Vorgehensweise. Während eine Vielzahl von Frauen darauf bedacht ist, den Alkoholkonsum während der Schwangerschaft einzuschränken (Crozier et al., 2009), sind die aktuellen Schätzungen zu Prävalenzen von Alkoholkonsum während der Schwangerschaft und die damit einhergehende Anzahl an mit FASD geborenen Kindern weiterhin ein weltweites Problem (Popova, Lange, Probst, Gmel & Rehm, 2017; Popova et al., 2018). Es scheint jedoch kritisch zu sein, die tatsächliche Anzahl an schwangeren Alkoholkonsumentinnen vollständig feststellen zu können. Ebenfalls problematisch scheint die Erfassung der Häufigkeit und der genauen Menge des Konsums, sowie die Auswertung basierend auf retrospektiv erhobenen Angaben von Frauen. Womöglich entsprechen die Antworten Mustern im Sinne der sozialen Erwünschtheit oder Trinkmuster zur Zeiten der Schwangerschaft werden nur noch ansatzweise vorhanden erinnert.

Die kontinuierliche Erfassung von Prävalenzen als Grundlage zur Vorbeugung von Folgeschäden für die Entwicklung durch pränatale Alkoholexposition ist nach wie vor essentiell. Weitere perinatale Risikofaktoren im Rahmen von Früherkennungsuntersuchungen mit zu erheben, könnte ausschlaggebend und ratsam sein. Dabei ist es wichtig, die Ursachen des Konsumverhaltens während und nach der Schwangerschaft in die Planung präventiver Maßnahmen miteinzubeziehen. Durch ein enges, berufsgruppenübergreifendes Netzwerk ließen sich somit präventive Angebote und Maßnahmen effizienter gestalten und die Prioritäten hinsichtlich der Ausgaben des Gesundheitssystems, gerade für die am stärksten gefährdeten Risikogruppen, ließen sich anpassen (Popova et al., 2018).

Das Wissen über Faktoren, die mit pränataler Alkoholexposition korrelieren, ebenso wie weiterer Faktoren, die sich postnatal auf betroffene Kinder und deren Entwicklung auswirken können, soll es Kinderärzt_innen und Klinischen Kinderpsycholog_innen vereinfachen, z. B. im Rahmen der kinderärztlichen Früherkennung oder einer psychologischen Betreuung von Risikofamilien, diese früh zu identifizieren.

Im Zusammenhang mit gleichbleibenden Prävalenzen für Konsum während der Schwangerschaft zeigen diese Ergebnisse, dass allein die Aufklärung zu einem Zeitpunkt (z. B. zu Beginn der Schwangerschaft) durch eine Berufsgruppe (z. B. durch Gynäkologen) nicht genügt. Eine Begleitung durch verschiedene Berufsgruppen innerhalb des Sozial- und Gesundheitswesens, die idealerweise Hand in Hand arbeiten müssen, scheint nicht nur wünschenswert, sondern auch notwendig, um risikobelastete Familien zu identifizieren, zu begleiten und zu unterstützen.

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Appendix B: Publication II

Römer, P., Mathes, B., Reinelt, T., Stoyanova, P., Petermann, F., & Zierul, C. (2020). Systematic review showed that low and moderate prenatal alcohol and nicotine exposure affected early child development. *Acta Paediatrica*, *109* (12), 2491-2501.

REVIEW ARTICLE

ACTA PÆDIATRICA
NURTURING THE CHILD

WILEY

Systematic review showed that low and moderate prenatal alcohol and nicotine exposure affected early child development

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Abstract

Aim: We systematically reviewed the literature on the influence of low and moderate amounts of prenatal alcohol and nicotine exposure on early child development. This paper also suggests possible directions for future research in order to tackle the controversial findings identified.

Methods: The PubMed and Web of Science electronic databases were searched together with the reference lists of the selected papers. Empirical studies were included if they focused on the effects of low or moderate exposure, reported outcomes on child development within the first 2 years of life and were published in English between January 2009 and December 2019. The eligibility of the included studies was based on three authors reading the full text.

Results: The final sample comprised 17 papers. Of these, 13 focused on the effects of prenatal alcohol exposure and they reported decreased sensory sensibility, smaller body sizes and increased cognitive capacities. The other four looked at prenatal nicotine exposure, and they primarily found impairments in children's orienting, communication and motor skills.

Conclusion: Any amount of prenatal alcohol and nicotine exposure appeared to risk healthy child development. There were many reasons for consumption and numerous effects on the child, but representative data from interdisciplinary research were missing.

KEYWORDS

alcohol exposure, early child development, nicotine exposure, pregnancy, prenatal

1 | INTRODUCTION

From the time of fertilisation, human offspring are sensitive to environmental factors.[1,2] Toxic substances are the most influential factors for the development of the unborn child,[3] and alcohol and nicotine are increasingly being consumed during pregnancy.[3,4] Both substances pass directly through the placenta into the foetal blood circulation, causing toxic effects, for example on cell development.[4] In addition, the biochemically immature organism delays detoxification processes.[5] Hence, prenatal exposure to alcohol and nicotine is one of the highest risks for the course of a healthy pregnancy. Different consumption patterns, like high, moderate and low amounts of substances, may have distinct influences on early child development.[4] This review focused on the effects of low and moderate amounts of prenatal alcohol and nicotine exposure. The current literature lacks coherent definitions of

different consumption patterns, particularly for low and moderate consumption. High amounts are mostly defined as four to six alcoholic drinks per occasion [6,7] and between 10 and more than 20 cigarettes per day.[8] We referred to low and moderate consumption patterns in the same way that they were reported by the authors of each study, including their classification of low or moderate. Consequently, low and moderate amounts had to be clearly delinated by the authors from high amounts. Previous studies on prenatal alcohol and nicotine consumption tended to investigate mothers that consumed high amounts or that suffered from clinically relevant substance abuse. These studies demonstrated that alcohol and nicotine may have affected the unborn child during all stages of pregnancy, from fertilisation to embryogenesis and the foetal period.[4,9,10] Postnatal developmental deficits appeared in the form of a broad spectrum of negative, or even pathological, outcomes,[1] concerning behavioural, cognitive and morphological development.[3,11,12] Atypical development that is often assessed in the later stages of childhood may already be observable prenatally and in the first years of life.[5,9,10] Early detection, adequate prevention and interventions for affected children, and those who are at risk, might change the course of an otherwise atypical development. Studies on prevalence have indicated that low, moderate and high amounts of alcohol and nicotine are consumed by women throughout pregnancy across the world.[3,6] However, data are only available for certain countries, so far. In addition, data collection has been very heterogeneous, which complicates global comparisons. For example, the majority of studies have reported data on prevalence, without including the period between conception and the confirmation of pregnancy.[13] Consequently, prevalence may be underestimated, particularly for low and moderate consumption. In order to reduce the existing risk of biases, alternative methods, like the implementation of biomarkers of alcohol and nicotine, have been established.[14,15] Thus, the validity of data on prevalence, as well as the conclusions on the effects on early child development, should be improved. In comparison with the negative effects based on high amounts of consumption, the influence of low and moderate amounts of alcohol and nicotine exposure is scarcely understood.[16,17] The number of studies remains small, with inconsistent results. Previous review papers reported results that focussed on different developmental outcomes. An association between low amounts of nicotine exposure and reduced foetal size and growth has been found in the second trimester.[18] Further evidence for growth deficits has been associated with exposure to low amounts of alcohol.[19] Negative effects on behaviour, like social engagement, have found based on exposure to moderate amounts of alcohol.[7] However, some reviews did not find evidence for effects based on low or moderate amounts.[19,20] Nevertheless, the majority of the literature reviews[7,18-22] have indicated that there is neither a safe period, nor a safe amount, that can be consumed without risking negative effects among offspring. As previous research has lacked coherent results, it is crucial to describe and summarise the current findings of empirical research consistently. This review provides a comprehensive picture of the current knowledge on the effects

Key notes

- This review was carried out to clarify whether low and moderate prenatal alcohol and nicotine exposure represented a risk for healthy child development.
- The reviewed studies suggested that there was no safe limit of alcohol and nicotine that could be consumed during pregnancy without potentially harming the offspring.
- There were many reasons for consumption and numerous effects on the child, but representative data from interdisciplinary research are missing.

of low and moderate prenatal alcohol and nicotine exposure on early child development. In addition, we have used the findings of physiological measures and questionnaires to discuss which kind of studies may reveal consistent results. Our review also debated whether the use of consistent parameters, like the amounts of consumption and further risk factors, increased the comparability of results across studies. Finally, we focused on what parameters had been overlooked, but might provide further valuable insights, such as studies in non-Western countries.

2 | METHODS

2.1 | Search strategy

The PubMed and Web of Science electronic databases and the reference lists of the papers we identified were searched to identify relevant studies on the effects of low and moderate prenatal alcohol and nicotine exposure on early child development. These two databases were selected because their extensive collection of literature on natural science would maximise the number of potentially relevant studies identified. The search procedure, presented in Figure 1 and Table S1, was carried out in April 2019 and updated in December 2019. It followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[23] In order to detect relevant papers, appropriate keywords and comprehensive combinations of these keywords were used as search terms. This was done in order to generate an adequate amount of papers, avoiding preselection. To detect studies on the effects of low and moderate amounts of prenatal alcohol exposure, the following combinations of keywords were used: pregnancy OR prenatal AND low level alcohol exposure OR moderate level alcohol exposure OR alcohol exposure AND early child development. To detect relevant papers on the effects of low and moderate amounts of prenatal nicotine exposure, the following combinations of keywords were used: pregnancy OR prenatal AND low level nicotine exposure OR moderate level nicotine exposure OR nicotine exposure AND early child development. The reference lists of the relevant literature were screened for additional records.
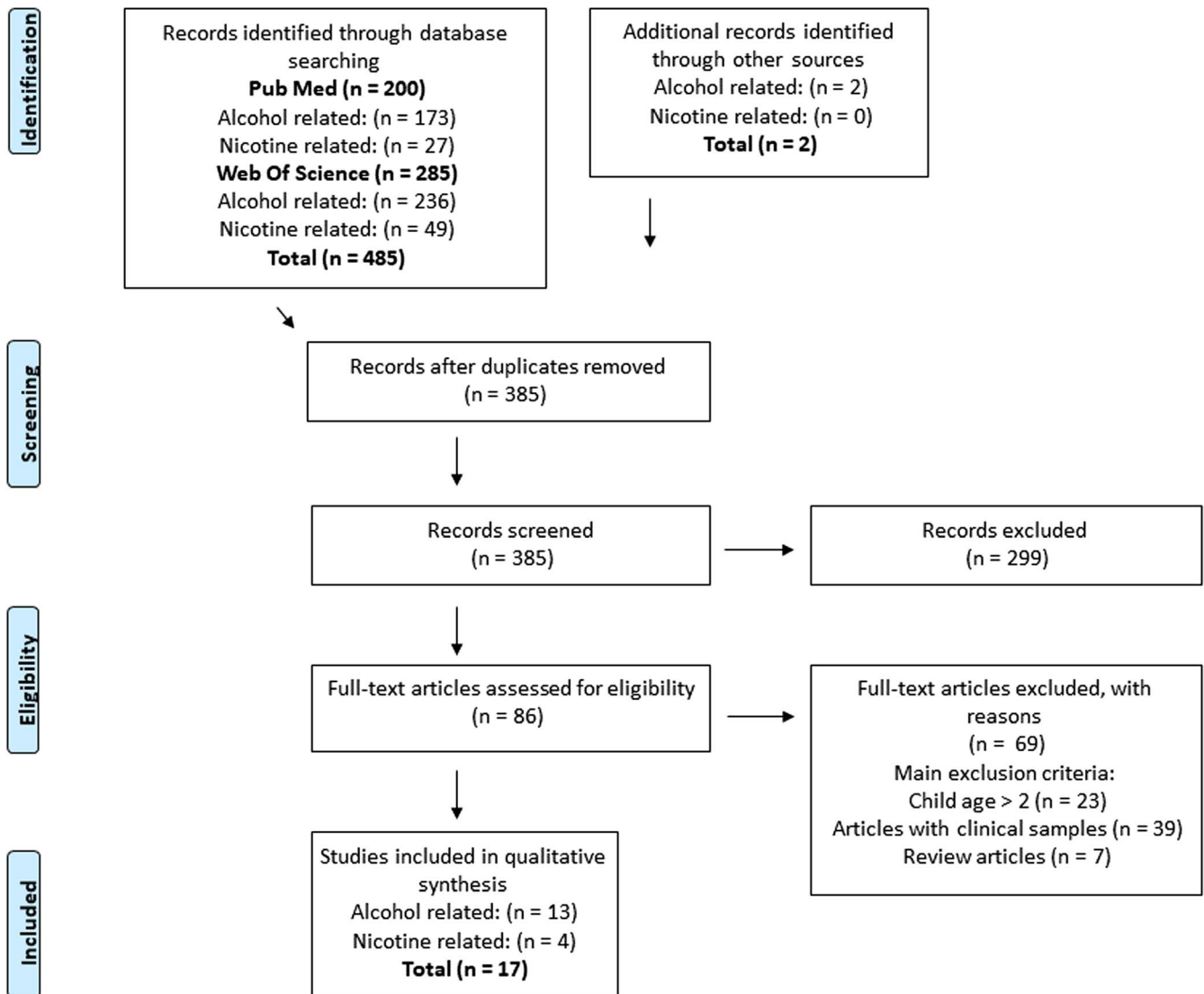
FIGURE 1 Flow chart of literature search procedure

2.2 | Selection criteria

The inclusion criteria were empirical research papers published between January 2009 and December 2019. This time span was chosen to present a state-of-the-art overview on the effects of low and moderate amounts of alcohol and nicotine consumption. The selection of the eligible studies followed a three-step procedure. First, duplicates and papers not published in peer-reviewed English-language journals were eliminated. Secondly, titles and abstracts were checked to exclude all papers that were obviously irrelevant to the aims of the current study. Finally, the remaining 86 studies assessed for eligibility were thoroughly read to ensure that they met all inclusion criteria.

To focus on early child development, only papers that addressed the effects on children up to, and including, 24 months of age were included. In addition, only studies with non-clinical samples and pregnant women who did not abuse substances were included. Thus, we only considered results of low to moderate levels of prenatal alcohol and nicotine exposures. The degree of exposure needed to be described

as low or moderate or clearly delineated from heavy, high and binge exposure. Following detailed screening, 69 papers were excluded. The main exclusion criteria were studies that investigated clinical samples, children older than 24 months and review papers. The entire literature search procedure was conducted independently by two authors (PR, CZ). Two other authors (BM, TR) additionally carried out the final full text assessment. Studies that were rated differently were discussed and included once consensus had been reached.

2.3 | Data extraction

The final sample comprised 17 papers, with 13 papers that focused on prenatal alcohol exposure and four papers on prenatal nicotine exposure. Information from the included papers was extracted by one author (PR) and subsequently checked for accuracy and completeness by two additional authors (PS, CZ). The data extraction was based on adequate methods according to the guidance for

TABLE 1 Effects of low to moderate levels of prenatal alcohol exposure on early child development

Authors/Year	Age of affected children	N	Defined consumption pattern of pregnant women	Measures	Main outcomes of affected children	Region/Country
Krishnamoorthy et al, 2010[25]	During early embryogenesis (as a model of early human development)	Sample of embryonic stem cells	Low-level ethanol exposure (equivalent to moderate level alcohol consumption)	Genome expression analysis	Altered mRNA levels for nicotinic acetylcholine receptor alpha5 subunits.	USA
Comasco et al, 2012[26]	Newborns	2264	Moderate level exposures (Score 4-7 in the AUDIT- Test)	Serum- and blood sample analysis	Higher birthweight for female offspring	Sweden
Bakhireva et al, 2018[27]	6 mo	93	Low to moderate level alcohol exposure	Bayley III Scales of Infant and Toddler Development	No neurobehavioural deficits. Higher scores in the parenting stress index	New Mexico
Williams-Brown et al, 2010[28]	9 mo	1070	1-3 drinks per week	Bayley II Scales of Infant and Toddler development	Lowered sensory regulatory responses in comparison with controls	USA
McCormack et al, 2018[29]	12 mo	1331	Low (≤7 drinks per week up to 2 drinks per occasion) to Moderate (≤7 drinks per week up to >2-≤4 drinks per occasion) level alcohol exposure	Bayley III Scales of Infant and Toddler development	Higher scores on cognition in children of mothers that consumed low levels of alcohol in comparison with controls; evidently affected through sociodemographic factors. No association with moderate amounts	Australia
Hutchison et al, 2019[30]	12 mo	1324	Low-level alcohol exposure	Bayley III Scales of Infant and Toddler Development	No association between low-level prenatal alcohol exposure and gross motor development	Australia
Muggli et al, 2017[31]	12 mo	415	Low-level alcohol exposure	Analysis of 3-dimensional craniofacial images. Performed with objective, holistic craniofacial Phenotyping using dense surface models of the face and head	Differences in the forehead between groups with low exposure vs. no exposure in the first trimester	Australia
Sundlein et al, 2017[32]	18 mo	291	Low to moderate level alcohol exposure	CBDQ	Smaller Body sizes; Negative influences on infant's behaviour and development	Sweden
Oullet et al, 2011[33]	19 mo	130	Low-level alcohol exposure	Saliva sample analysis	Disrupted pattern of cortisol activity in males	Canada
Halliday et al, 2017[16]	24 mo	60	Low-level alcohol exposure in tm 1; low/moderate alcohol exposure in tm 2 and/or 3	Bayley III Scales of Infant and Toddler development	No associations between low and moderate-level prenatal alcohol exposure and cognition and language scales	Australia

(Continues)

| | Age of affected children | N | Defined consumption pattern of pregnant women | Measures | Main outcomes of affected children | Region/Country |
Authors/Year						
Robinson et al, 2010[34]	24 mo	1952	Low to moderate level alcohol exposure	CBCL	No effects between low to moderate levels of prenatal alcohol exposure and behaviour problems	Australia
O'Leary et al, 2010[35]	24 mo	1890	Low-level alcohol exposure Moderate level alcohol exposure	CBCL	No association with infant behaviour problems; Anxiety and depression problems	Australia
O'Leary et al, 2009[36]	24 mo	1739	Low-level alcohol exposure	CBCL	No association with infant language delay	Australia

Abbreviations: ASQ-3: Ages and Stages Questionnaire; AUDIT Test: Alcohol Use Disorders Identification Test; CBCL: Child Behavior Checklist; CBDQ: Child behavior and development questionnaire; PAE: Prenatal alcohol exposure; TM: Trimester; WHO: World Health Organization.

TABLE 1 (Continued)

undertaking healthcare reviews from the Centre for Reviews and Dissemination, University of York, UK.[24] Minimal disagreements that occurred during the data extraction were discussed and resolved between the authors. Tables 1 and 2 summarise the consensus of the relevant information regarding alcohol and nicotine exposure, respectively. Both tables code the following aspects for each study: the authors and the year of publication, the age of the affected children, the total number of affected children and the defined consumption pattern of pregnant women. Furthermore, the coded tables applied measures to assess early child development and the main outcomes on the affected children. When possible, the data were differentiated according to the prenatal consumption pattern of pregnant women. Lastly, the sample's country of origin was listed.

2.4 | Quality and risk of bias assessment

The quality and risk of bias assessment for all 17 eligible studies according to the Newcastle-Ottawa Scale[40] is summarised in Tables S2 and S3. The Newcastle-Ottawa Scale was used to evaluate three aspects: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. These three aspects comprise different items. For each quality item, stars are given. The number of stars serves as a quality assessment. A maximum of nine stars were awarded for each study in total, and a higher score represented higher quality. The rating was conducted by one author (PR) and subsequently checked for accuracy and completeness by two additional authors (PS, CZ).

3 | RESULTS

The final sample of 17 studies comprised 11 cohort studies and six case-control and cross-sectional studies. The total number of studies in the final sample remained small, especially those for nicotine, which comprised only four studies. Research on both substances contained analyses on outcomes at different developmental stages. These stages included gestation, the newborn infant phase, 3-12 months after birth and the second year of life. An overview is presented in Tables 1 and 2.

3.1 | Quality and risk of bias

The included studies scored between six and nine stars on the Newcastle-Ottawa Scale. As a study can be awarded a maximum of nine stars, all the included studies presented adequate quality and a low risk of bias.

All of the six case-control and cross-sectional studies that were included presented adequate case definitions, consecutively representative series of cases and community controls. They reported no history of impairment at the end point of the analysis and were controlled for

TABLE 2 Effects of low to moderate levels of prenatal nicotine exposure on early child development

Authors/Year	Age of affected children	N	Defined consumption pattern of pregnant women	Measures	Main outcomes of affected children	Region/Country
Taal et al, 2011[37]	30 wk gestation	1031	<5 cigarettes per day >10 cigarettes per day	Ultrasound	Larger foetal kidney volume. Smaller foetal kidney volume	Netherlands
Chahal, et al, 2017[10]	Newborns (2-3 d)	3459	<20 cigarettes per day Second-hand smoke exposure	Blood sample analysis	Increased levels of the inflammatory biomarker IL-8 cytokines No increased levels of Il-8	New York
King et al, 2018[38]	3-5 mo	48	≤20 cigarettes per day	EEG; auditory paired-click paradigm	Smaller amplitude of the N550 component and reduced delta-band power within elicited K-complexes; Less orientation with a head turn to a novel auditory stimulus, in comparison with controls	USA
Mohamed et al, 2018[39]	24 mo	107	Second-hand smoke	ASQ-3	Lower neurodevelopment especially for communication and fine motor skills	Malaysia

Abbreviations: ASQ-3, Ages and Stages Questionnaire; EEG, Electroencephalography.

at least one other factor. In addition, they used adequate ascertainment of exposure and the same methods to analyse cases and controls.

All of the 11 cohort studies that were included presented cohorts that were representative of the community they studied. The selection of the non-exposed cohort was drawn from the same community as the exposed cohort. They reported outcomes of interest that were not present at the start of study and controlled for at least one other factor.

Ratings of certain items by the Newcastle-Ottawa Scale presented evidence for reductions in quality and a higher risk of bias for all 17 individual studies. For example, all the studies were controlled for one other factor, like maternal age, but only 15 studies controlled for any further factors, such as maternal socio-economic status. In addition, six studies lacked any follow-up analysis with regard to child outcomes, and in four studies, the outcomes were not based on blinded assessment. The assessment of alcohol or nicotine exposure was not obtained through biomarkers but based on questionnaires in 11 studies.

When the data quality and the risk of bias was considered across studies, disparities were possible because of the differences in the way the studies were designed or conducted. Furthermore, the studies presented methodological heterogeneity to assess prenatal alcohol and nicotine exposure, as well as the outcomes of the affected children. The exclusion of non-English papers may also have led to excluding critical studies. Yet, there is little evidence that the exclusion of non-English-language papers leads to a high risk of bias in systematic reviews.[41] Publication bias may exist, as results with positive developmental outcomes or no association between prenatal substance exposure and development may not be submitted or published.

3.2 | Effects of low and moderate alcohol exposure on early child development

Results on the effects of low to moderate prenatal alcohol exposure revealed different developmental outcomes in the children who were affected. Of the 17 included studies, six reported negative effects, five reported no effects and two found positive outcomes like higher scores in developmental tests in comparison with controls. The effects on gestation, for example on fertilisation, embryogenesis and the foetal period, were reported with a sample of embryonic stem cells as a model of early human development.[25] The low-level ethanol exposed group was reported to be equivalent to moderate level alcohol consumption. For this group, altered levels of messenger ribonucleic acid were found in nicotinic acetylcholine receptor alpha5 subunits during embryogenesis. This may lead to an alteration of gamma-aminobutyric acids and *N*-Methyl-D-aspartate receptor expression and, consequently, to abnormal development of the frontal cortex. These outcomes suggest that low to moderate alcohol exposure can alter early neurological development. This may raise the risk of addiction and other developmental abnormalities for the foetus and its further development.[25] One study related to the effects of moderate prenatal alcohol exposure higher birthweights for female offspring. However, the authors reported that the validity of results was limited by the low response rates.[26] The effects on infants aged 3-12 months revealed different results. No association between low prenatal alcohol exposure and neurobehavioural deficits was found in a study of 6-month-old infants.[27] Lowered sensory regulatory responses were found in 9-month-old infants in comparison with non-exposed controls.[28] Infants aged 12 months, whose

mothers consumed low amounts of alcohol during the second trimester, scored higher on cognition scales than controls. However, the authors pointed out that child cognitive development was evidently affected through sociodemographic factors like the social environment or socio-economic status of their mothers.[29] In addition, there was evidence for anatomical differences in the forehead between groups with low exposure versus no exposure during the first trimester.[31] Despite this, gross motor development 12 months after birth did not appear to be affected by prenatal low-level alcohol exposure.[30] One study looked at the effects on toddlers aged 13-24 months and showed that 18-month-old toddlers who were exposed to low and moderate amounts were less cautious when approaching strangers. In addition, they had smaller body sizes than the controls.[32] Another study showed disrupted patterns of cortisol activity in 19-month-old boys that were exposed to low amounts of alcohol during pregnancy.[33] The same study found different patterns for 24-month-old toddlers. Moderate alcohol exposure was associated with higher scores on anxiety and depression scales in one study.[35] Furthermore, an initial analysis of another study suggested a positive association between cognitive development and low-level alcohol consumption. However, the evidence was reduced by the influence of many other covariates, like maternal age or education. Hence, no associations between low-level prenatal alcohol exposure and cognition and language scales could be concluded.[16] No association with low-level prenatal alcohol exposure in 24-month-old toddlers was found for either language delays[36] or behavioural problems.[34,35]

3.3 | Effects of low and moderate nicotine exposure on early child development

In comparison with research on the effects of prenatal alcohol exposure, only four studies focused on nicotine effects. However, the research shows mainly negative effects of low to moderate amounts of prenatal nicotine exposure on early child development.

Findings for effects on gestation in 30 weeks old foetuses revealed a dose-dependent modification of the foetal kidney volume. A larger foetal kidney volume was found based on less than five cigarettes per day. A smaller kidney volume was found based on a consumption pattern of more than 10 cigarettes per day.[37] In addition to the liver, the kidneys are among the detoxifying organs of the human body. It remains unclear whether these differences in foetal kidney volume have postnatal consequences. For kidney function and blood pressure, it is known that smaller kidney volumes result in fewer nephrons. Nephrons are basic units of the kidney, which might predispose a child to the development of hypertension and kidney disease in later developmental stages.[37]

Concerning effects on newborn infants, increased levels of the inflammatory cytokines interleukin-8 were found based on a consumption pattern of less than 20 cigarettes per day. No increased levels of interleukin-8 were found in newborns infants whose mothers were exposed to second-hand smoke during pregnancy.

Interleukin-8 is an inflammatory mediator. Increased levels result in permanent changes in neonatal inflammation. This may lead to respiratory disorders, like bronchitis or asthma.[10]

Electroencephalography experiments indicated impairments in auditory sensory gating on infants aged 3-12 months. The results were based on consumption of up to 20 cigarettes per day. These impairments caused reduced auditory discrimination, learning, attention, re-orienting and arousal during wakefulness in infants aged 35 months. In addition, it led to disrupted sleep behaviour.[38] Affected infants showed less orientation with a head turn to a novel auditory stimulus during wakefulness, in comparison with controls. In addition, they showed a smaller amplitude of the N550 component and reduced delta-band power within elicited K-complexes during sleep. In typical development, the averaged so-called K-complex wave form shows a large amplitude and a late negative deflection, peaking between 500 and 650 ms. Hence, this peak is often labelled as N550 and appears during stage two of sleep maintaining into slow wave sleep. Smaller amplitudes of the N550 component could provide evidence for impaired sleep behaviour. Nevertheless, the study did not control for any confounders like maternal social surroundings and any support that may have had an impact on the neurodevelopment of children.[38]

The effects on 24-month-old toddlers revealed that second-hand smoke exposure during pregnancy was associated with lower neurodevelopment.[39] Affected children showed poorer fine motor skills, for example hand and finger movements, and impaired communication skills in vocalising, listening and understanding. However, the authors stated that the participants only lived within a small geographical area that was not representative of the whole country. In addition, the extent of second-hand smoke exposure was obtained from nicotine levels in the hair of pregnant women living in smoker households. Here, it was not considered that children of non-smoker households representing the control group could be exposed to second-hand smoke through other sources as well. For example, in other households or in restaurants, this may distort the results. Furthermore, neurodevelopment was only assessed by using a questionnaire that may lack adequate psychometric properties. This may have reduced the evidence of the presented results.[39]

4 | DISCUSSION

There were only 17 studies that investigated the effects of low to moderate amounts of prenatal alcohol and nicotine exposure during pregnancy. The results on the consequences for those children that were affected appear to be controversial. While six studies reported detrimental effects of alcohol exposure on early child development, five studies found no effect, and two studies even found positive effects. The four studies on prenatal nicotine exposure revealed negative effects, but further research to confirm these outcomes is vital. The small amount of research could be explained by previous research being primarily focused on the effects of high-level consumption. This may have been in order

to consolidate knowledge about pathological outcomes. As the pathogenesis based on high-level consumption has been extensively researched, current analyses have started to focus on the effects of consuming smaller quantities. Another effect of the small number of studies may be the focus on early child development. If the focus was extended to children who were older than 24 months of age, there would certainly be more literature. However, the amount of research that has analysed the effects of low to moderate consumption amounts remains small compared to the literature that focused on the effects of high amounts. Hence, the lack of representative research on this important public health topic is notable.

4.1 | Developmental consequences

The consequences for early child development resulting from prenatal exposure to low and moderate amounts of alcohol and nicotine remain controversial. Although the quality and risk of bias assessment yielded adequate results for all the included studies, some aspects make it difficult to draw reliable conclusions. For example, determining the exposure to alcohol and nicotine and developmental outcomes differed across studies. In addition, further factors, like maternal age or education that may have influenced the reported outcomes, were not assessed in all studies. The majority of the studies also lacked follow-up analyses. Considering the contradictory results, no amount of nicotine or alcohol can be considered without risks for healthy child development. Comparisons with the effects of high-level consumption remain challenging, as research for low to moderate amounts is rare. Effects based on high-level consumption appear in the form of a broad spectrum of disorders, which are clinically defined as foetal alcohol spectrum disorders for alcohol and foetal tobacco syndrome for nicotine. These include neurocognitive and motor deficits or morphological changes.[3,4,11] Results for low to moderate exposure to alcohol or nicotine during pregnancy also elicit a variety of developmental deficits. Deficits include lowered sensory regulatory responses[27] or lower communication and fine motor skills.[39] Thus, there is evidence that low and moderate consumption during pregnancy may also impair early child development in a complex way. Consumption of low to moderate amounts during pregnancy is more commonly practiced and more accepted than high-level intake in different societies and regions across the world.[13,42] In addition, it may be related to current gaps of knowledge about the risks and negative effects of toxic substances on early child development. Specific outcomes and further child development also depend on other moderating factors. Risk factors that affect the prenatal and postnatal health of the mother and child have been extensively discussed. These risk factors include mental health problems,[43] a higher age and low socio-economic status of the mother, Caesarean birth and low birthweight of the child.[44] Such moderating factors have to be considered by investigating further child development.

4.2 | Methodological challenges and relevant confounders

The current literature lacks a coherent definition of different consumption patterns. Definitions vary in amounts and frequencies of consumption like per week or per occasion. They vary in time frames of consumption, like within 1 hour or 1 day and in indications for one drink or one cigarette. Hence, there are variations concerning the exact content of alcohol or nicotine.[8,45]

In addition to definitions, the validity of the means of data collection has to be considered. Evaluation based on retrospectively collected data or data based on interviews seems critical. Answers may conform to social desirability. Drinking and smoking patterns during pregnancy may be inaccurately recalled.[9]

The controversial effects of prenatal alcohol and nicotine exposure may be explained by methodological challenges in assessing outcomes based on lower doses. It is possible that the measures that are usually used to detect deficits based on high amounts are less useful when it comes to low and moderate amounts. Measures for detecting deficits based on high exposure are more focused on global developmental deficits. These are frequent in children exposed to high amounts or diagnosed with related disorders. Instruments to measure developmental outcomes should be designed in such a way that small abnormalities and precursors of deficits can be captured.[9] Although most studies control for additional factors, consumption during pregnancy has been considered in isolation in some research. Further confounding environmental and social risk factors may influence the consumption behaviour of pregnant women and consequently the outcomes of affected children.[8,46] Correlations are documented for alcohol and nicotine consumption and sociodemographic factors, for example origin or migration status.[47] Previous findings indicate that women living in Europe, with a cultural background like North Africa, consume less than women without such a background. In regions like North Africa, only low amounts or no alcohol or nicotine are consumed. Consequently, infants born to women with such migration backgrounds are less at risk for atypical perinatal development.[47] In addition, socio-economic status appears to correlate with the drinking and smoking patterns of pregnant women.[47-49] Prenatal alcohol consumption, particularly low to moderate amounts, appears to be associated with higher socio-economic status.[47,49] In contrast, nicotine consumption seems to correlate with lower socio-economic status.[47,50] Furthermore, social environments have been associated with prenatal alcohol and nicotine consumption.[8,46,50] Studies on both substances show that if pregnant women lack social support from their environment, the probability of drinking and smoking and damaging affected infants' development increases.[47] Experiencing violence, for example in a partnership, or critical life events, such as deaths, are also among the predictors of alcohol and nicotine consumption.[46,51,52] Lack of access to supportive measures, like sessions with midwives or antenatal classes, also increase the likelihood of prenatal substance use.[4] In addition, polydrug use and pre-pregnancy substance

consumption have been associated with alcohol and nicotine consumption during pregnancy.[4,50,53] These factors are relevant confounders for analysing the effects of alcohol or nicotine exposure on early child development. The consumption of substances during pregnancy does not constitute the only risk factor for healthy child development.

4.3 | Implications for further research and clinical practice

Current estimates of the prevalence of alcohol and nicotine use during pregnancy demonstrate a global problem.[42,54] Society lacks awareness towards the harmful effects of different kinds of consumption patterns on early child development. In order to identify women at risk, and to facilitate preventive measures, knowledge about the effects of different consumption amounts is needed. Consequently, it is crucial to collect prevalence data with respect to coherent definitions of low, moderate and high consumption levels.[45] To overcome the methodological challenges discussed in this paper, research needs to be interdisciplinary and incorporate disciplines and research areas like psychology, biology, pharmacology or epigenetics. Current research on the detection of consumption behaviour has used biomarkers for alcohol[14,15] and nicotine.[54,55] For analyses, direct metabolic products of the substances have been used.[15,54] These methods for analysing the amounts of metabolites are considered reasonable alternatives, or additional methods, for assessing the coherent prevalence of consumption and the consequent child outcomes.[56] A considerable advantage is the possible early detection of developmental impairments. This may be missing if diagnostic measures are focused on outcomes that appear later in development. Furthermore, adequate prevention strategies could be applied as early as the first years of life. In this way, at-risk children may be identified before they exhibit atypical development.[15] Other research fields like epigenetics are currently being established in order to detect the influence of substances on gene activity. This activity is altered by environmental conditions and influences endocrine, immunological and molecular processes. When women are exposed chemical substances during pregnancy, this can cause epigenetic effects in the offspring, starting in the womb.[55,57,58] It is useful to include analyses on epigenetic effects in further research, as they provide results on the effects in the earliest developmental stages. In addition, they inform about whether epigenetic processes influence the pathogenesis of psychological disorders, as well as whether these processes are bound to certain developmental stages.[57] Furthermore, future research should interpret the consumption of toxic substances in combination with other environmental factors that influence consumption behaviours and the developmental courses of affected children. Social and healthcare experts, like gynaecologists, paediatricians, midwives or clinical child psychologists, could use this knowledge to identify at-risk families early on. For example, strategies might involve pregnancy screening, early detection by paediatricians or psychological care. Postnatal care and support by midwives and child-family services, as well as counselling for substance addiction, could adequately counteract some of the prenatal consumption effects.

5 | CONCLUSION

This review showed that the number of studies on the effects of low to moderate prenatal alcohol and nicotine exposure on early child development was small. The results on perinatal outcomes appear to be controversial and complex. Our findings illustrate the need to clarify current controversies and elucidate the apparent global problem of low and moderate levels of alcohol and nicotine consumption during pregnancy. The results were heterogeneous. Consequently, guidelines should clearly state that there is no safe period and no safe amount of alcohol and nicotine that can be consumed during pregnancy without any harm to the unborn child. First, a continuous assessment of the prevalence of high, low and moderate levels of consumption during pregnancy is essential. This could prevent the consequential damage to affected children. Secondly, social and environmental factors that influence consumption and child development should be included in further analyses. Finally, interdisciplinary research is essential to be able to benefit from the methodical possibilities of certain research areas to establish consistent methods and reduce existing biases.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5,6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4,5,6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6,7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6,7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8, 9, Supplementary Tables 2 and 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8, 9, Supplementary Tables 2 and 3
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8,9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6,7,8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,10, Supplementary Table 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10,11,12,13, 14,Tables 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, Supplementary Table 2 and 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14,15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14,15,16,17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17,18,19
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

The Newcastle-Ottawa Scale (NOS) for assessing the quality of studies included into present systematic review

The NOS was used in order to evaluate quality and risk of bias of all included studies and was downloaded from the following website:

http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Studies that met at least five NOS criteria were considered as studies with high quality.

1. **Newcastle-Ottawa Quality Assessment Scale: Case Control/Cross- Sectional Studies**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?

    a) yes, with independent validation *

    b) yes, eg record linkage or based on self reports

    c) no description

2) Representativeness of the cases

    a) consecutive or obviously representative series of cases *

    b) potential for selection biases or not stated

3) Selection of Controls

    a) community controls *

    b) hospital controls

    c) no description

4) Definition of Controls

    a) no history of disease (endpoint) *

    b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

    a) study controls for at least one other factor *

    b) study controls for any additional factor (e.g. maternal age, maternal social environment or

socioeconomic status) *

Exposure

1) Ascertainment of exposure

    a) secure record (e.g. surgical records or biomarkers) *

    b) structured interview where blind to case/control status *

    c) interview not blinded to case/control status

    d) written self report or medical record only

    e) no description

2) Same method of ascertainment for cases and controls

    a) yes *

    b) no

3) Non-Response rate

    a) same rate for both groups *

    b) non respondents described

    c) rate different and no designation

The detailed assessment procedure of every included article

Table S 2: The detailed assessment procedure of case-control/ cross-sectional studies included into present systematic review

	Selection				Comparability	Exposure			Total Score
	1	2	3	4	1	1	2	3	
King et al., 2017	a)	a)	a)	a)	a)	a)	a)	a)	8
Chahal et al., 2016	a)	a)	a)	a)	a), b)	a)	a)	a)	9
Sundelin et al., 2016	a)	a)	a)	a)	a), b)	b)	a)	b)	8
Comasco et al., 2012	a)	a)	a)	a)	a), b)	a)	a)	b)	8
Krishnamoorthy et al., 2010	a)	a)	a)	a)	a)	a)	a)	a)	8
Oullet-Morin et al., 2010	a)	a)	a)	a)	a), b)	b)	a)	a)	9

2. **Newcastle-Ottawa Quality Assessment Scale: Cohort Studies**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

    a) truly representative of the average consumption behaviour in the community *

    b) somewhat representative of the average consumption behaviour in the community *

    c) selected group of users e.g. nurses, volunteers

    d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

    a) drawn from the same community as the exposed cohort *

    b) drawn from a different source

    c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

    a) secure record (e.g. surgical records or biomarkers) *

    b) structured interview

    c) written self report

    d) no description

4) Demonstration that outcome of interest was not present at start of study

    a) yes *

    b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

    a) study controls for at least one other factor *

    b) study controls for any additional factor (e.g. maternal age, maternal social environment or socioeconomic status) *

Outcome

1) Assessment of outcome

    a) independent blind assessment *

    b) record linkage

c) self report

d) no description

2) <u>Was follow-up long enough for outcomes to occur</u>

a) yes *

b) no

3) <u>Adequacy of follow up of cohorts</u>

a) complete follow up - all subjects accounted for *

b) subjects lost to follow up unlikely to introduce bias ≥70% follow up or description provided of those lost *

c) follow up rate < 70 % and no description of those lost

d) no statement

The detailed assessment procedure of every included article

Table S 3: The detailed assessment procedure of cohort studies included into present systematic review

	Selection				Comparability	Outcome			Total Score
	1	2	3	4	1	1	2	3	
Hutchison et al., 2019	a)	a)	c)	a)	a), b)	a)	b)	d)	6
Mohammed et al., 2018	b)	a)	a)	a)	a), b)	d)	b)	d)	6
Halliday et al., 2017	a)	a)	b)	a)	a), b)	a)	b)	d)	6
Muggli et al., 2014	a)	a)	b)	a)	a), b)	a)	b)	d)	6
Taal et al., 2011	a)	a)	b)	a)	a), b)	a)	a)	b)	8
O´Leary et al., 2010	a)	a)	b)	a)	a), b)	c)	a)	b)	7
Robinson et al., 2010	a)	a)	b)	a)	a), b)	c)	a)	b)	7
Bakhireva et al., 2018	a)	a)	a)	a)	a), b)	a)	a)	b)	9
McCormack et al., 2018	b)	a)	b)	a)	a), b)	a)	b)	d)	6
Williamsbrown et al, 2010	b)	a)	b)	a)	a), b)	a)	b)	d)	6
O´Leary et al., 2009	a)	a)	b)	a)	a), b)	c)	a)	b)	7

Appendix C: Publication III

Römer P, Kemmerich R, Petermann F, Mathes B, Zierul C. Alcohol and nicotine consumption during pregnancy: Prevalence and Prdictors among Women in Bremen, Germany. *Sucht*, *69* (3), 99-111.

Alcohol and Nicotine Consumption during Pregnancy

Prevalence and Predictors among Women in Bremen, Germany

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[a] The authors share the senior authorship.

Abstract: *Aims:* The consumption of alcohol and nicotine during pregnancy relate to a multitude of personal and socioeconomic factors. Since even the consumption in non-clinical populations pose a health risk to children, epidemiologic data related to factors potentially contributing to an increase in consumption during pregnancy were investigated. *Methodology:* Cross-sectional analyses were based on interview data from 260 pregnant women taking part in a longitudinal intervention project (Bremer Initiative to Foster Early Child Development). Women had a below-average family income, a migration background, or faced other social and cultural challenges. Descriptive statistics were calculated to determine consumption prevalence. Logistic regression models were conducted to estimate associations of alcohol or nicotine consumption with personal and socioeconomic factors. *Results:* Of the total sample (mean age: 31.1 years), 45 % consumed alcohol and/or nicotine during pregnancy. 92.3 % quit drinking and 62.8 % stopped smoking following confirmation of pregnancy. Better social support and higher age increased the likelihood of alcohol consumption, while this was decreased by an Islamic cultural background. Smoking was predicted by a lower level of education. Unplanned pregnancies predicted the consumption of both, alcohol and nicotine. *Conclusions:* A multitude of factors influence alcohol and nicotine consumption in non-clinical populations. Preventive strategies should include pre-pregnancy stages and health information needs to mirror factors contributing to consumption.

Keywords: alcohol exposure, nicotine exposure, prevalence, predictors, pregnancy

Alkohol- und Nikotinkonsum während der Schwangerschaft: Prävalenzen und Prädiktoren von Frauen aus Bremen, Deutschland

Zusammenfassung: *Zielsetzung:* Alkohol -und Nikotinkonsum bei Schwangeren hängt mit vielfältigen persönlichen und sozioökonomischen Faktoren zusammen. Da auch der gesellschaftlich akzeptierte Konsum in der nichtklinischen Bevölkerung ein Gesundheitsrisiko für das ungeborene Kind darstellen kann, wurden epidemiologische Daten und verschiedene Faktoren untersucht, die die Wahrscheinlichkeit eines Konsums während einer Schwangerschaft erhöhen könnten. *Methodik:* Es wurden Querschnittsanalysen basierend auf Interviewdaten von 260 schwangeren Frauen, die an einem längsschnittlichen Interventionsprojekt (Bremer Initiative to Foster Early Child Development, BRISE) teilnahmen, durchgeführt. Die Frauen hatten ein unterdurchschnittliches Familieneinkommen, einen Migrationshintergrund oder standen vor anderen sozialen und kulturellen Herausforderungen. Zur Bestimmung der Konsumprävalenz wurden deskriptive Statistiken berechnet und zur Ermittlung von Assoziationen zwischen Alkohol- oder Nikotinkonsum und persönlichen und sozioökonomischen Faktoren wurden logistische Regressionen durchgeführt. *Ergebnisse:* Von der Gesamtstichprobe (Durchschnittsalter 31.1 Jahre), konsumierten 45 % Alkohol und/oder Nikotin während der Schwangerschaft. Bessere soziale Unterstützung und ein höheres Alter erhöhten die Wahrscheinlichkeit des Alkoholkonsums, während ein islamischer Kulturhintergrund diese verringerte. Das Rauchen wurde durch ein niedrigeres Bildungsniveau vorhergesagt. Ungeplante Schwangerschaften prognostizierten sowohl Alkohol- als auch Nikotinkonsum. 92.3 % haben das Trinken und 62.8 % das Rauchen nach Schwangerschaftsbestätigung eingestellt. *Schlussfolgerungen:* Vielfältige Faktoren beeinflussen den Alkohol- und Nikotinkonsum in nichtklinischen Populationen. Präventionsstrategien sollten Phasen vor der Schwangerschaft einbeziehen und zusätzlich zu Gesundheitsinformationen soziale Faktoren, die den Konsum begünstigen, berücksichtigen.

Schlüsselwörter: Alkoholexposition, Nikotinexposition, Prävalenzen, Prädiktoren, Schwangerschaft

Introduction

The consumption of alcohol and nicotine during pregnancy poses one of the highest health risks for the unborn child. Risks for the developing organism may arise at every stage of the pregnancy, including fertilization, embryogenesis and the fetal period (Chahal et al., 2017; Nulman et al., 2018; Subramoney et al., 2018; Ulrich & Petermann,

2016). Yet, both substances are among those toxic substances most frequently consumed by women of childbearing age across the world (Forray, 2016). The consumption has not only negative effects for the children who are affected, but also for the consumer. According to the World Health Organization, alcohol and nicotine consumption is a causal factor in a multitude of diseases and injuries, and results in approximately 75 000 deaths in Germany each year (Deutsche Hauptstelle für Suchtfragen, 2022). Any dose of alcohol or nicotine consumption confers a health risk (Le Daré et al., 2019).

While the focus of previous research was primarily on the consumption of large quantities of alcohol and nicotine (Popova et al., 2017), the evidence relating to effects caused by low or moderate amounts remains rare. Studies demonstrating substance-induced physical, neuropsychological, and behavioural abnormalities in children have raised awareness for the dangers of legal drug use during pregnancies. Since consumption among non-clinical groups of pregnant women has not been studied to a similar extent, and harmful effects to the child's health and cognitive abilities are less well researched for lower doses, a certain degree of consumption may be common and even socially accepted. For example, the German Health Update Study from 2012 indicated that from a non-clinical population almost a third (103 of 374 pregnant women) stated to have drunk alcohol during their pregnancy. Usually, the consumption does not start during pregnany but can be ascribed to general consumption prevalence of society and thus, of women in their fertile age (Lange et al., 2015).

Despite different findings, systematic reviews cannot rule out negative effects of low-to-moderate prenatal alcohol or nicotine consumption on child development (Henderson et al., 2007). A more recent meta-analysis and systematic review related low-to-moderate consumption of alcohol during pregnancies to preterm births, reduced birth size for gestational age and decreased sensory sensibility (Mamluk et al., 2017; Römer et al., 2020). Low-to-moderate nicotine consumption was found to lead to impairments in orienting-, communication- and motor skills (Römer et al., 2020).

Thus, it remains important to reach (pregnant) women with different demographics and inform them about possible negative consequences of legal drug use for their unborn child and about potential support to change consumption behaviour. To improve strategies targeting women prone to consumption of legal drugs during their pregnancies, more information about the prevalence of consumption in different social groups and about social factors related to legal drug use during pregnancies is needed (Römer et al., 2020). We have recently stressed that knowledge about influential factors leading to abstinence or con-

tinuation of drinking and smoking during a pregnancy may relate to a combination of reasons. The lack of social support during pregnancy seems to increase the probability of alcohol and nicotine consumption (Powers et al., 2013). Furthermore, experiences of violence and other burdens may affect consumption behaviours prior and during pregnancy (Hauge et al., 2012; Powers et al., 2013; Skagerström et al., 2011). A higher educational level (> high school degree), increased age (≥ 25 years) and an unplanned pregnancy are associated with prenatal alcohol consumption (Melchior et al., 2015; Murphy et al., 2013), while a lower educational level, lower maternal age as well as an unplanned pregnancy are associated with low to moderate nicotine consumption (Baron et al., 2013; El-Khoury et al., 2016; Melchior et al., 2015). Data from a 12 federate states of Germany indicated that 33.7 % of all pregnancies were unplanned (Helfferich et al., 2016). Furthermore, women's cultural background can play a role, which may be related to the extent to which the consumption of alcohol and nicotine is the social norm (Melchior et al., 2015).

The number of studies investigating low-to-moderate use of legal drugs in non-clinical populations is low (Römer et al., 2020). Comprehensive data on consumption prevalence of women in their fertile age seems also lacking, although this knowledge may be important for understanding and preventing consumption during pregnancies (Forray, 2016). This problem is increased, since different social groups are often not equally well represented in survey data. For instance, it is known that people with a lower level of education, a lower income, a higher number of social challenges and a migration background are less likely to take part in scientific research (Zeisler et al., 2019). Research has also shown that these women have often a greater need for and, at the same time, are more difficult to reach with information and support regarding their health and psychological well-being (Samkange-Zeeb et al., 2022; Zeisler et al., 2019).

Further, the majority of current data on prevalence in non-clinical groups does not include the time period between conception and confirmation of pregnancy (Muggli et al., 2017). However, a large part refers to the first trimester, during which life-defining developmental steps in cells and essential organs, like the heart and the brain, are taking place (Nulman et al., 2018).

The current study provided data on how socioeconomic factors relate to alcohol and nicotine consumption during pregnancy in a non-clinical population living in an urban area of Germany. Included districts are characterized by a below average family income and a high percentage of families with a migration background. More specifically, we sought to examine to what extent age, education level, pregnancy planning, social support, burdens and cultural background predicted alcohol- or nicotine consumption.

According to previous research, we hypothesized that women who smoke cigarettes are often younger and less educated, while women who drink alcohol are often older and better educated (El-Khoury et al., 2016; Melchior et al., 2015). In countries with a predominant Muslim culture, the consumption of alcohol and nicotine is socially less accepted. Hence, having a cultural background related to these countries may be an important factor that prevents from the consumption during pregnancy. We further hypothesized that alcohol and nicotine consumption is generally increased when women face an unplanned pregnancy (Baron et al., 2013; Muggli et al., 2016), lack of social support or considerable burdens (Hauge et al., 2012; Powers et al., 2013; Skagerstróm et al., 2011). To address current gaps in the literature we aimed to investigate prevalence data in pregnant women for pre- and post-pregnancy confirmation (i.e., before and after women learned about their pregnancy). Knowledge about consumption prevalence during all stages of a pregnancy and about factors influencing consumption behaviour, especially in low-to-moderate amounts, may guide future research to develop adequate prevention strategies. Those should be adaptable, sensitive and inclusive with regard to the specific pregnancy state and living circumstances of pregnant women in order to ensure prevention benefits for women from hard-to-reach populations.

Methodology

Study Design

The current study is part of the Bremer Initiative to Foster Early Child Development (BRISE, German: Bremer Initiative zur Stärkung frühkindlicher Entwicklung [Schütte et al., 2020]). BRISE is a longitudinal intervention project investigating early development of children growing up in families with social and cultural challenges. The project has started in 2017 and is currently funded until 2025. Families remain part of the initiative between pregnancy and the children's first year of primary school. During this time, several measurement time points are being scheduled depending on the child's age. BRISE aims to identify strategies supporting healthy pregnancies and educational equality.

Recruitment Process and Data Collection

Women or families living in pre-selected urban areas of Bremen, Germany were recruited by scientific staff of the University of Bremen as well as by gatekeepers in the so-

cial and health care system. Recruiting strategies included advertising the program across the whole city. This comprised the distribution of flyers and posters in the targeted living areas, direct contact with potential participants, the representation of the project at family-focused events and cooperation with professional gate-keepers, who are working with pregnant women and young families, e.g., women's healthcare workers and family-related institutions. Furthermore, new parents in the participating areas received a letter that introduced BRISE. All participants gave their written consent in advance of their participation in BRISE. Data for this study was collected via home-based interviews by researchers holding a Master's degree in Psychology or a related discipline at minimum. The researchers also underwent specific trainings in research methods, design and ethics, as well as in safety education (i.e., regarding emergency response and estimating children's best interest). The interviews included questions referring to the consumption behaviour of alcohol and nicotine during pregnancy, age, education, whether the pregnancy was planned, social environment, life burdens and migration background.

Participants

A detailed description of sample characteristics is presented in Table 1 (see results). The current data set is based on the first measurement point of the longitudinal study, which was conducted during the third trimester of pregnancy (T0) or, if that was not possible, within the first 18 weeks postpartum (T0 post). Thus, each woman provided one dataset.

Participating women are part of the first and second wave of BRISE, incorporating mothers of 300 children. The first two BRISE waves included 150 children each. Allocation to a wave followed the date of the 1st participation in an interview. This normally coincided with measurement point T0 and T0post, but for 32 women was a later measurement time point scheduled within the first months after childbirth. All T0 and T0post data included in the first two BRISE waves was gathered before the 1st lockdown following the outbreak of the COVID19 pandemic.

Seven mothers gave birth to twins, providing one dataset, and one mother participated with siblings. For consistency, only data of the first pregnancy was included in the current analysis. Considering that 32 women did not take part in either T0 or T0post, a sample of n=260 women answered the questions relevant for their alcohol and nicotine consumption behaviour during pregnancy and were included in the data analyses. All women were, with regard to alcohol and/or nicotine usage during their pregnancy, categorized as either "consumers" or "no consumers".

In our sample women consumed at maximum one to 15 cigarettes per day and one to seven drinks per week. According to definitions of consumption patterns across current studies (described below), consumption behaviours could be described as low-to-moderate (Missing information for n=1).

Inclusion and Exclusion Criteria

Women or families joined the study between the third trimester of pregnancy and the 18th week postpartum. A screening interview insured that the registration address of the sampled families belonged to pre-determined liv-

Table 1. Sample characteristics

Characteristic	Sample of n=260 women (answered on consumption related questions)	Sample of n=91 women (alcohol consumers during pregnancy)	Sample of n=43 women (nicotine consumers during pregnancy)
Maternal Age			
< 25	17.3 % (n=45)	12.1 % (n=11)	25.6 % (n=11)
25–29	21.9 % (n=57)	18.7 % (n=17)	16.3 % (n=7)
30–34	33.9 % (n=88)	33 % (n=30)	30.2 % (n=13)
≥ 35	26.9 % (n=70)	36.2 % (n=33)	27.9 % (n=12)
Educational level (ISCED11)			
Lower	67.7 % (n=176)	55.0 % (n=50)	88.5 % (n=38)
Higher	32.3 % (n=84)	45.0 % (n=41)	11.5 % (n=5)
Pregnancy planning			
Pregnancy was planned	59.5 % (n=155)	50.5 % (n=46)	37.2 % (n=16)
Pregnancy was not planned	40.5 % (n=105)	49.5 % (n=45)	62.8 % (n=27)
Social support			
Low	7.9 % (n=20)	3.4 % (n=3)	9.5 % (n=4)
Moderate	12.5 % (n=33)	11.2 % (n=10)	21.4 % (n=9)
High	79.6 % (n=207)	85.4 % (n=78)	69.0 % (n=30)
Burdens			
Low	80.1 % (n=208)	74.7 % (n=68)	70.7 % (n=30)
Moderate	16.3 % (n=43)	22.0 % (n=20)	22.0 % (n=9)
High	3.6 % (n=9)	3.3 % (n=3)	7.3 % (n=3)
Migration background			
General migration background	53.5 % (n=139)	37.4 % (n=34)	44.2 % (n=19)
Islamic cultural background	16.9 % (n=44)	1.1 % (n=1)	9.3 % (n=4)
Measurement time point			
T0 (during the third trimester)	44.6 % (n=116)	48.4 % (n=44)	53.5 % (n=23)
T0 post (postpartum)	55.4 % (n=144)	51.6 % (n=47)	46.5 % (n=20)
Partnership			
Yes	90.2 % (n=230)	90.1 % (n=82)	75.6 % (n=31)
No	9.8 % (n=25)	9.9 % (n=9)	24.4 % (n=10)

Notes. ISCED11 = International Standard Classification of Education. Results for social support and burdens are presented in sum-scores. Social support: A sum-score from 14 to 32 is classified as a low social support, a sum-score from 33 to 51 is classified as a moderate social support and a sum-score from 52 to 70 is classified as a high social support. Burdens: A sum-score from zero to ten is classified as low burdens, a sum-score from 11 to 21 is classified as moderate burdens and a sum-score from 22 to 33 is classified as high burdens.

ing quarters of Bremen, Germany. Pre-determination of living quarters was implemented prior to the start of the study in order to achieve comparability of the average socio-economic background in the neighbourhood of participating families and to ensure access to cooperating family support programmes. Upbringing of the women's infants had to further meet at least one criterion of pre-determined social challenges, e.g., family migration background and/or parental low income (Schütte et al., 2020). Families with insufficient German or English language skills to answer the questionnaires and those who did not meet the inclusion criteria were excluded from the study. Families who had to be excluded were referred to other programmes and networks that were also able to offer adequate support.

Measures

Participants in the third trimester of their pregnancy or in their early postpartum period were questioned on various topics. For the current study, the answers that were subsequently used for analysis were in response to questions on alcohol and nicotine consumption patterns, age, education, pregnancy planning, social environment, life burdens and cultural background. The consumption of alcohol and nicotine was determined as follows: First, we asked participants if they have ever consumed alcohol or nicotine in their life. If the answer was "yes", we then asked if they had consumed alcohol or nicotine during their pregnancy. The questionnaire further indicated if they had stopped consumption while being pregnant, providing information whether they had stopped once they had confirmation of pregnancy or months or even years prior to getting pregnant. Women who continued drinking after confirmation of pregnancy were asked about their consumption behaviour to determine whether they did consume more than four to six alcoholic drinks per occasion, more than seven drinks per week or binged alcohol on more than one occasion during their pregnancy. According to the literature, discontinuing drinking after confirmation of the pregnancy or drinking below the aforementioned frequencies and amounts, was regarded as low-to-moderate drinking (Flak et al., 2014; Popova et al., 2017; Römer et al., 2020). We also determined the amount of nicotine consumption. According to previous research, here less than 20 cigarettes a day indicated low-to-moderate consumption behaviour (Clifford et al. 2012; Römer et al., 2020). The definitions for low-to-moderate consumption during pregnancy were established to separate these consumption amounts from those of high amounts and thus, to detect possible predictive factors for a non-clinical sample and often socially accepted consumption be-

haviours. Current literature still lacks consistent definitions of consumption behaviours (Römer et al., 2020); while they are not specifically related to consumption during pregnancy, they refer more often to the consumption in the general population.

For more information on integrated variables, like response categories and methodological preparation see electronic supplementary material (ESM) 1.

Statistical Analyses

In this cross-sectional analysis we first calculated descriptive statistics to analyze the prevalence of pregnant women's alcohol and nicotine consumption. We estimated the prevalence for alcohol, nicotine or the combined use of both substances pre- and post-pregnancy confirmation. Descriptive statistics concerning migration background and all variables that were entered into the subsequent statistical analyses are described below.

Second, we conducted a multivariable binary logistic regression to determine predicting factors of alcohol as well as nicotine consumption during pregnancy separately for each substance. We included alcohol or nicotine consumption as dependent variables. The independent variables that could function as predictors were age (in years), education, pregnancy planning, social support, life burdens challenges and an Islamic cultural background.

Adjusted Odds ratios are presented for each predictor as included in combination with the other predictors in the regression model. The respective reference categories for each predicting factor are established as followed: Age (highest age), education ("lower" education), pregnancy planning (pregnancy was "planned"), social support and burdens (highest sum scores), Islamic cultural background (no "Islamic cultural background"). The two regression models differed in their respective dependent variable. In one model the dependent variable was either alcohol consumption and no alcohol consumption during pregnancy. In the other model the dependent variable was either nicotine consumption and no nicotine consumption during pregnancy. The absence of multicollinearity of included independent variables was checked and confirmed in advance and a collinearity diagnosis was carried out subsequently. The tolerance value of >0.1 and the variance inflation factor of <10 pertained the appropriate range for each model. In addition, we controlled for possible confounder-, mediator- or moderator effects of birth order (1st child or not) and time point of the interviews (T0 or T0post, i.e. pre- or post-partum). Due to power estimations and regarded small sample sizes of sub-samples that consumed pre -or post-pregnancy confirmation, changing consumption behaviour following

confirmation of pregnancy, could not be considered for the logistic regressions. Statistical analyses were performed using IBM SPSS Statistics Version 26 and R Version 3.6.1. A reporting checklist, according to the STROBE statement is presented in attached reporting statement (von Elm et al., 2008).

Results

Prevalence of Alcohol and Nicotine Consumption during Pregnancy

Consumption prevalence for both substances is presented in Table 2. Of the entire sample, 25% stated to have never consumed alcohol or nicotine in their life, whereas 25% stopped consuming alcohol and 23.8% nicotine months or years before their pregnancy.

Furthermore, 45% of the participating women reported to have consumed either alcohol or nicotine during their pregnancy. Of those, 14.5% stated to have consumed both substances at some point during their pregnancy. To be more precise, the prevalence of alcohol consumption indicated that 35% of the overall sample drank alcohol at some point during their pregnancy. Of these, 92.3% quit drinking alcohol following pregnancy confirmation (i.e., within the first trimester). The prevalence of nicotine consumption indicated that during the course of their pregnancy, 16.5% of the women smoked. Of these women, 62.8% stopped smoking after confirmation of the pregnancy, while 37.2% continued smoking.

16.9% of the participating women had an Islamic cultural background and of those 65.9% stated that they never drank alcohol, 72.7% that they never smoked cigarettes in their life and 56.8% that they did neither. Thus, they comprise 38.5% of the women who stated that they never consumed alcohol or nicotine in their life.

Descriptive Statistics of Included Predictor-Variables

The mean age of the participating women was 31.1 years (Standard Deviation: 5.8). With a maximum of an upper secondary education, the education level of 67.3% of the women was classified as "lower" and that of the remaining 32.3% as "higher". In total, 59.5% of the participants indicated their pregnancies as planned. Women had on average a high level of social support (Mean=58.7, Standard Deviation: 12.7, Range: 14–70) and 90.2% stated to live in a partnership. The extent of extra burdens challenges during their pregnancy was low (Mean=5.6, Standard Deviation: 6.4, Range: 0–33). Of all woman, 53.5% either migrated or had at least one parent that had migrated to Germany. For 16.9% of the sample the migration background included a predominantly Muslim country.

Predictors Alcohol and Nicotine Consumption

The statistical analysis regarding predicting factors of alcohol and nicotine consumption is summarized in Table 3.

Predictors Alcohol Consumption

The dependent variable differentiated the group of women who consumed or abstained from alcohol during their pregnancy. The overall model likelihood ratio was significant (χ^2=51.1, p=.000) with R-squares of .195 (Cox and Snell) and .266 (Nagelkerke).

The analysis revealed that a higher age (OR: 1.066 (95% CI:1.005–1.132), p=.033), an unplanned pregnancy (OR: .359 [95% CI:.187-.691], p=.002), an increased social support (OR: 1.037 [95% CI: 1.008–1.068], p=.012) and a non-Islamic cultural background (OR: .042 [95% CI: .005-.321], p=.002), were associated with the consumption of low-to-moderate amounts of alcohol of pregnant women.

Table 2. Prevalence of alcohol and nicotine consumption during pregnancy

	Alcohol consumption	Nicotine consumption
Proportion of those who stopped consuming before pregnancy	25% (n=65 of 260)	23.8% (n=62 of 260)
Proportion of those who consumed at some point during pregnancy	35% (n=91 of 260)	16.5% (n=43 of 260)
Proportion of those who quit following pregnancy confirmation.	32.3% (n=84 of 260)	10.3% (n=27 of 260)
Proportion of those who continued following pregnancy confirmation.	2.6% (n=7 of 260)	6.2% (n=16 of 260)
	Alcohol/Nicotine consumption	
Proportion of those who consumed alcohol or nicotine during pregnancy	45.0% (n=117 of 260)	
Proportion of those who consumed alcohol and nicotine during pregnancy	14.5% (n=17 of 260)	

Predictors of Nicotine Consumption

The overall model likelihood ratio was again significant (χ^2=32.0, p=.000) with R-squares of .128 (Cox and Snell) and .213 (Nagelkerke). A lower educational level (OR: .154, [95 % CI: .050-.479], p=.001) and an unplanned pregnancy (OR: .298 [95 % CI: .136-.654], p=.003) predicted the consumption of nicotine during pregnancy.

Discussion

This study aimed at gaining knowledge about the prevalence of alcohol and nicotine consumption in a hard-to-reach, non-clinical population of pregnant women, who are confronted with social and cultural challenges. We were interested in whether age, pregnancy planning, maternal education, cultural background, burdens or availability of social support were associated with women's consumption patterns during their pregnancy. This was analyzed by way of a regression analysis, where consumption was predicted by these different factors within a cross-sectional design.

Both substances are legal and socially accepted in Germany, where the study took place, mirroring the majority of regions across the world (Anderson et al., 2018). Acceptance of low-to-moderate consumption of alcohol and nicotine, which was characteristic for the current sample, often extends to women who want to get or are pregnant (Jensen et al., 1998). Research still lacks information on coherent results regarding effects that can be attributed to certain consumption quantities (Römer et al., 2019). Thus, it is officially recommended to avoid any consumption of alcohol and nicotine during pregnancy (Deutsche Gesellschaft für Ernährung, 2014; Guerby et al., 2020). Alternatives, such as electronic cigarettes, may also harm the unborn child (Römer et al., 2021). Since legal drug use seemingly affects nearly half of the participating women, it is important to gain a better understanding of factors that may increase or decrease the likelihood of legal drug consumption during pregnancy.

A quarter of the women in our sample (25 %) stated to have never consumed alcohol or nicotine in their life. One reason of this seemingly high proportion may reflect that this study included many families with a migration background, with 16.9 % of the participating women having a cultural background that shaped by the Islamic religion. Especially alcohol, but also nicotine and other drugs are generally forbidden in Islam, which leads to women avoiding these drugs during pregnancy as well (Bahar et al., 2005). Reasons for stating to have never used alcohol or nicotine or stopping at some point in their life included an interest in a healthy lifestyle. The orientation towards a healthy lifestyle may also be related to the high proportion of women (62.9 %) who planned their pregnancy. However, it cannot be ruled out that in some cases there might have been a tendency of participants to answer questions in line with expected socially desirable re-

Table 3. Predicting factors for low to moderate alcohol and nicotine consumption during pregnancy

Predicting factor	OR (95 % CI)	P value	Regression coefficient B
Alcohol			
Maternal Age	1.066 (1.005–1.132)	**.033***	.064
Educational level (ISCED)	1.655 (.876–3.125)	.120	.504
Pregnancy planning	.359 (.187–.691)	**.002***	-1.023
Social support	1.037 (1.008–1.068)	**.012***	.037
Burdens	1.020 (.971–1.072)	.434	.020
Islamic migration background	.042 (.005–.321)	**.002***	-3.177
Nicotine			
Maternal Age	1.030 (.965–1.009)	.375	.029
Educational level (ISCED)	.154 (.050-.479)	**.001***	-1.868
Pregnancy planning	.298 (.136–.654)	**.003***	-1.210
Social support	.996 (.966–1.026)	.786	-.004
Burdens	1.034 (.977–1.094)	.246	.003
Islamic migration background	.325 (.089–1.194)	.091	-1.123

Notes. *p<.05; ** p<.01; *** p<.001. OR = Odds Ratio; CI = Confidence Interval. Bold numbers indicate significant predictors for alcohol and nicotine consumption.

sponses (Latkin et al., 2017; Skarbek-Kozietulska et al., 2012).

Previous studies focusing on the consumption of low-to-moderate amounts of alcohol during pregnancies demonstrate that prevalence of alcohol consumption during pregnancies may be influenced by a multitude of personal, socio-economic and cultural aspects of a population. Our results are partly in line with these findings. The current data indicated that women with a higher age, better social support, an unplanned pregnancy and without an Islamic cultural background are more likely to drink low to moderate amounts of alcohol during their pregnancy. Importantly, expecting or knowing to be pregnant seemed to have a profound effect on the avoidance of alcohol. Not only planning, and therefore expecting or hoping to becoming pregnant, were associated with the avoidance of alcohol consumption, but almost the entire group, who did consume alcohol, stopped drinking following pregnancy confirmation. We assume that most women consumed alcohol during the early phase of their pregnancy due to a lack of awareness of their pregnancy and due to the general social acceptance of alcohol consumption in Germany. The finding, that women often stopped consuming alcohol following pregnancy confirmation may indicate that they did not consume alcohol as a strategy to cope with difficult life challenges that may co-occur with a pregnancy. It rather seems that knowledge of potential harmful consequences of alcohol consumption guided the women's behaviour following or even before confirmation of pregnancy in most instances (McCormack et al., 2017).

In comparison to previous studies, it seems odd that the existence of burdens had no effect, and a supportive social environment even increased alcohol consumption. These findings underline the importance of distinguishing between drinking in non-clinical populations and clinically relevant consumption patterns, where this is often the case (Gosdin et al., 2022). It also needs to be considered that the women, who were included in this study, all face certain challenges (see inclusion criteria), meaning a certain amount of burdens may be reflected uniformly across the entire group as a continuous variable in life. Additional challenges that were reported seemed low and may have not been as influential as in both, women with alcohol-dependencies or with mostly an above-average socio-economic status (Gorard & See, 2009). Since drinking seems unrelated to reported burdens, social support may consequently also not be needed to overcome drinking. It may rather reflect social integration and, thus, the participation in social events facilitating drinking. This may be particularly true for the first trimester, when the pregnancy is unknown or recommended not to be announced. The influence of social influences on drinking is also demonstrated by women with an Islamic cultural background: in concordance with religious expecta-

tions, it is a significant predictor for not drinking alcohol during a pregnancy in our statistical model. Thus, our results support the notion that drinking while being pregnant may be related to a multitude of factors comprising social status, social influences and life planning. More research about effects on the child of low-to-moderate alcohol consumption during the early phases of a pregnancy appears to be an important step in future research, since consumption during this phase seems most common.

Reasons for smoking during pregnancy are as well described as those for alcohol consumption, but not entirely similar. Our results are, again, partly in line with those from previous studies. Pregnancy planning generally increased the likelihood of non-smoking during pregnancy, which paralleled the findings for alcohol consumption. Our statistical model also indicated that a lower educational level predicts the consumption of nicotine during pregnancy. The relation between lower education or lower socio-economic status and increased likelihood of smoking, which has been established not only for pregnant women, but also for other populations too (National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health, 2014). It is known that access to health information is more difficult for people with lower education (Samkange-Zeeb et al., 2022). Cigarette packages in Germany, however, clearly and visibly inform about smoking-related health risks. It may be assumed that for lower educated people immediate stress-reducing, mood-lifting and arousing effects of nicotine may be a stronger motivator for smoking than later occurring harmful effects on general health and risking physical addiction to nicotine for abstinence (Cummings et al., 2004). This may be because lower education, as one key variable of low socio-economic status, often co-varies with a higher risk of lower income, unemployment as well as social burdens and emotional stress affecting everyday life, and fewer possibilities of coping with these challenges (Hauge et al., 2012). Thus, the finding that lower education increased the likelihood for smoking during a pregnancy may be related to the pre-pregnancy living situation of the women participating in this study rather than specific burdens occurring during the pregnancy (Hauge et al., 2012; Powers et al., 2013).

Fewer women (16.5%) stated to have consumed nicotine, but more than a third of these continued smoking after pregnancy confirmation. This may be because even low amounts of nicotine lead to physical addiction (Henningfield et al., 1997) and it is, therefore, harder to quit smoking than to stop drinking alcohol. In accordance, the proportion of women that stopped drinking after confirmation of the pregnancy was larger than the proportion of women who stopped smoking in the same time period. Future research regarding this finding is needed. Our study indicat-

ed that a combination of physical addiction, less access to health care information and a certain kind of living circumstances might cause women to continue smoking even after confirmation of pregnancy.

Despite interesting results, the study also faced certain limitations. The current analyses are limited due to data being based on interviews. If possible, interviews should be backed up by biological markers to reduce the effect of social desirability influencing responses (Chiandetti et al., 2017; Jaffee, 2018). Since hard-to-reach populations are often characterized by a lack of trust into medical research (Nicholson et al., 2015), they may rather oppose to biomarkers and future study designs need to address these concerns to gain more authentic prevalence data. Due to small sub-sample sizes regarding variables like an Islamic cultural background that entered the logistic regression model, calculations of current data should be repeated with representative sample sizes in order to reach a generalizable conclusion. Further, longitudinal studies are needed to better understand the influence of social and other factors on consumption behavior. Nevertheless, the current study enabled to evaluate the risk-assessment of women, regarding consumption of alcohol and nicotine during pregnancy. This relates primarily to the consumption before confirmation of pregnancy. It is essential to include this timespan when analyzing data on consumption prevalence. The early pregnancy is a sensible and fundamental timespan, that comprises complex developmental processes including fertilization, nidation, cell development, the formation of the first organ structures and cardiac activity (Nulman et al., 2018). Thus, not only the consumption of toxic substances after pregnancy confirmation but also and especially the early consumption until confirmation can result in harmful effects (McCormack et al., 2017; McCowan, 2009; Nulman et al., 2018; Sundermann et al., 2020). Regarding the estimation of consumption prevalence during early pregnancy, further analyses should also consider data of consumption prevalence of women in their fertile age to enable an adequate prevention.

Negative health outcomes caused by high level consumption amounts are already known (Nulman et al., 2018). Thus, consideration of low-to-moderate consumption would enable to gain a complex overview regarding health outcomes, prevalence and population-specific needs that facilitates the development of adequate preventive measures. To investigate consumption behaviours of women in childbearing age and during different stages of their pregnancy and resulting effects on their offspring, future research should include socioeconomic factors that are known to be associated with alcohol or nicotine consumption. It is, furthermore, important to include women with particular life-challenges like migration backgrounds or low income, since these populations are often underrepresent-

ed and their reasons for legal drug consumption might differ from populations with a higher socio-economic status.

The high percentage of women consuming legal drugs at the beginning of their pregnancy and especially the continuation of smoking after pregnancy confirmation poses possible health risks for unborn children in large proportions of non-clinical populations. This calls for more studies investigating these health risks to reduce current data controversies and establish better prevention strategies. Consistent representations of knowledge on effects of alcohol and nicotine consumption and its risks for the health of women and their children would be crucial.

Implications for the Practical Field

- Prevention strategies should reach women of all educational levels, and should precede as well as include the stage of confirmation of pregnancy.
- It seems important to inform adolescent women and their partners about the harming effects of legal drugs on an unborn child and potential difficulties to quit consumption.
- Prevention strategies should take housing situations that increase the motivation of drug taking seriously and, therefore, should not be restricted to health education, only. Support for women with difficulties to quit consumption is also needed.

Conclusions

Appropriate estimations of consumption prevalence regarding all stages of pregnancy and the inclusion of socioeconomic factors that are known to be associated with the consumption should be considered in future research. Not being aware of the pregnancy, while not planning to have a child, seemed to be important factors for both, drinking and smoking in non-clinical populations. Health education informing women about possible risks for an unborn child even for low-to-moderate and legal drug consumption should reach women in their adolescence, irrespective of pregnancy planning.

Electronic Supplementary Material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0939-5911/a000815
ESM 1. Measurements

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Electronic Supplementary Material 1: Measurements

Maternal Age

As a biological factor, we recorded the age by asking about the day, month and year of birth of the women.

Educational level

To assess the educational status of participants, we asked about the school educational level as well as further educational degrees or working certificates. We scored the answers according to the levels of the International Standard Classification of Education (ISCED 11;(Hetmeier, HW., Schmidt, A., Vogel, 2017)). Educational levels according to the ISCED11 are classified as follows: 0=Early childhood Education, 1= Primary education, 2=Lower secondary education, 3= Upper secondary education, 4= post-secondary non-tertiary education, 5= Short-cycle tertiary education, 6= Bachelor or equivalent, 7= Master or equivalent, 8= Doctoral or equivalent. Maternal education was split into the categories "lower" (including mothers with an upper secondary education degree or less, according to levels 0-3) and "higher" (including mothers with a post-secondary education degree and more, according to levels 4-8). In Germany, an upper secondary education according to the ISCED 11 involves a degree following 11 to 13 years of school education or basic vocational training. Post-secondary education or a degree that is based on it, may include non-university degrees of higher vocational education or university degrees (Bachelor, Master, Doctoral or equivalent), both requiring an upper secondary education degree before entering.

Pregnancy planning

Pregnancy planning was assessed by asking if the pregnancy was wanted. Response options were (i) Von mir gewollt, auch der Zeitpunkt war gewollt (pregnancy was wanted at this point in time,), (ii) Von mir grundsätzlich gewollt, aber eigentlich lieber später (pregnancy was basically wanted, but at a later point in time), (iii) Von mir nicht eindeutig gewollt, ich war zwiespältig (pregnancy was not explicitly wanted, I was ambivalent), (iiii) Von mir nicht gewollt (pregnancy was not wanted). Assessment of pregnancy planning included nominal-scaled qualities. Pregnancy-planning responses were, therefore, pooled into the categories "planned" (pregnancy was wanted at this point in time) and "not planned" (pregnancy was wanted at a later point in time, becoming pregnant was ambivalent or not wanted), before entering the regression model (Helfferich, Klindworth, Heine & Wlosnewski, 2016).

Social support

Circumstances related to the participants' social environment, the comfort and support by their social surrounding was assessed using the 14 item "Fragebogen zur Sozialen Unterstützung" (F-SozU "Social Support Questionnaire"(Fydrich, T., Sommer, G., Tydecks, S., & Brähler, 2009)). Questions comprised everyday-situations, e.g., if participants easily find someone that cares about the apartment when they are not available, or if they have a very trusted person that they can always count on. Response options were (i) Trifft überhaupt nicht zu (does not apply at all), (ii) Trifft eher nicht zu (rather not true), (iii) Teils, teils (partly), (iiii) Trifft eher zu (rather true) and (iiiii) Trifft genau zu (applies precisely). Results for social support are presented in sum-scores that can range from 14 to 70. Extend of social support is classified as follows: A sum-score from 14 to 32 is classified as a low social support, a sum-score from 33 to 51 is classified as a moderate social support and a sum-score from 52 to 70 is classified as a high social support (Fydrich, T., Sommer, G., Tydecks, S., & Brähler, 2009).

Burdens

We asked whether burdening events occurred during the pregnancy and how the women experienced them using the ten-item "Fragebogen zu Besonderen Belastungen ("Special Burdens questionnaire" (Thomson et al., 2014)). Examples are financial burdens, conflicts in partnership or conflicts with one´s own family. Response options were (i) Gar nicht belastend (not at all burdening), (ii) Etwas belastend (somewhat burdening), (iii) Überwiegend belastend (predominantly burdening), (iiii) Stark belastend (strongly burdening). Results for burdens are presented in sum-scores that can range from zero to 33. Extent of burdens are classified as follows: A sum-score from zero to ten is classified as low burdens, a sum-score from 11 to 21 is classified as moderate burdens and a sum-score from 22 to 33 is classified as high burdens (Thomson et al., 2014).

Islamic cultural background

If women or their parents migrated to Germany from a country with more than 90 % of the population belonging to the Islamic religion, they were rated as having a cultural background shaped by Islam, hence referred to as Islamic cultural background. This was done due to research showing that in countries with Islam being the predominant religion, alcohol consumption is less common in general and during pregnancy in particular (Bahar et al., 2005).

Literature

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Appendix D: Representation of personal contributions
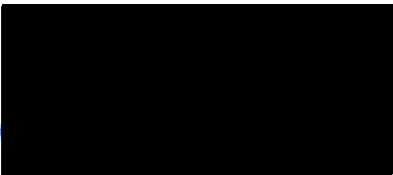
The present cumulative dissertation is based on three publications published in national and international journals with peer-review process. The publications were prepared by the doctoral candidate with the first authorship. The personal contribution of the doctoral candidate and author of this dissertation concerning the working steps of the publications used for this dissertation are presented in Table 2 in three gradations. The individual working steps are listed and the contribution of the doctoral candidate are represented through the graduation completely (taking over the entire work step), predominantly (taking over the majority of the work step) or equivalent (same sharing by the doctoral candidate and co-authors). Complete means that the working step was carried out alone, but an exchange with the co-authors whose suggestions have been incorporated.

Table 2: Presentation of the doctorands contribution to the publications incorporated in the present dissertation

Working step	Publication I	Publication II	Publication III
Theoretical Conception	predominantly	predominantly	predominantly
Literature search	completely	completely	completely
Study planning	predominantly	predominantly	predominantly
Data collection	predominantly	predominantly	predominantly
Data analyses	completely	completely	predominantly
Discussion and interpretation	completely	completely	completely
Manuscript preparation	predominantly	predominantly	predominantly
Revision	equivalent	equivalent	equivalent

Annotations: **Publication I**: Römer P, Reinelt T, Petermann F. Teickner C. Alcohol consumption during pregnancy-which effects on early child development are known? Alkoholkonsum während der Schwangerschaft-Welche Auswirkungen auf die frühkindliche Entwicklung sind bekannt? *Kindheit und Entwicklung*, 2019; 28 (1), 6–18; **Publication II**: Römer P, Mathes B, Reinelt T, Stoyanova P, Petermann F, Zierul C. Systematic review showed that low and moderate prenatal alcohol and nicotine exposure affected early child development. *Acta Paediatrica*, 2020, 109 (12), 2491-2501; **Publication III**: Römer P, Kemmerich R, Petermann F, Mathes B, Zierul C. Alcohol and nicotine consumption during pregnancy: Prevalence and Predictors amonng Womrn in Bremen, Germanny. *Sucht*, 2023; 69 (3), 99–111

The author of the present dissertation, Pia Römer M.Sc., and the co-authors, Prof. Dr. Birgit Mathes, Prof. Dr. Franz Petermann†, Dr. Claudia Zierul, Dr. Tilman Reinelt, Dr. Polina Stoyanova and Robin Kemmerich M.Sc., of the publications relevant to the dissertation, agree with their signature to the presentation of the doctorands contribution to the publications. In addition, the co-authors gave their consent to use the present publications for the doctoral procedure of Pia Römer M.Sc.

██████████	†
Place, date, signature (Prof. Dr. Birgit Mathes)	Place, date, signature (Prof. Dr. Franz Petermann†)
██████████	██████████
Place, date, signature (Dr. Claudia Zierul)	Place, date, signature (Dr. Tilman Reinelt)
██████████	██████████
Place, date, signature (Dr. Polina Stoyanova)	Place, date, signature (Robin Kemmerich M.Sc.)
██████████	
Place, date, signature (Pia Römer)	

Appendix E: Statutory declaration

I declare that I have prepared the present cumulative dissertation independently and without unauthorized help. No sources and tools other than those listed were used. The ideas adopted from other works were identified as such. I declare that I did not submit the present work either nationally or internationally to another committee as an examination performance.

Bremen, 15.06.2023

-█████████-------------------------------
(Pia Römer, M. Sc.)

Appendix F: Declaration of consent for the examination for plagiarism

I declare that I agree that the Dissertation can be examined with qualified software on allegations of plagiarism.

Bremen, 15.06.2023   --------------------------------
                                                        (Pia Römer, M. Sc.)