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Lifestyle-related risk factors during pregnancy: even low-to-moderate drinking during pregnancy increases the risk for adolescent behavioral problems

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ABSTRACT

Background: This study aimed to establish the associations between lifestyle-related risk factors during pregnancy with a special focus on low-to-moderate prenatal alcohol exposure (PAE) and behavioral problems in adolescents.

Methods: We used a sample of 6,149 German adolescents (11–17 years) from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). To investigate behavioral problems, the Strengths and Difficulties Questionnaire (SDQ) was applied.

Results: The prevalence of behavioral problems was: 17.0% hyperactivity, 12.0% conduct problems, 13.8% emotional symptoms, 22.2% peer relationship problems, and 11.9% total difficulties score. Simultaneously, 14.1% of the adolescents experienced low-to-moderate PAE. Adjusting for confounders, low-to-moderate PAE resulted in an increased risk of hyperactivity (Odds Ratio (OR) 1.39, Confidence Interval (CI) [1.15, 1.69]) and peer relationship problems (OR 1.20, CI [1.00, 1.44]). Similarly, smoking during pregnancy significantly increased the risk of hyperactivity and peer-relationship problems in adolescent offspring.

Conclusions: Low-to-moderate PAE is clearly linked to an increased risk of behavioral problems in adolescent offspring.

Abbreviations: ANOVA: One-way-analysis of variance; BMI: Body mass index; CAPI: Computer assisted personal interview; CI: Confidence interval; HPA: hypothalamic-pituitary-adrenal; KiGGS: German health interview and examination survey for children and adolescents; OR: odds ratio; PAE: Prenatal Alcohol Exposure; RKI: Robert Koch Institute; SDQ: Strengths and Difficulties Questionnaire; SES: Socioeconomic status; SPSS: Statistical package of social sciences

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Alcohol; adolescence; smoking; mental health; pregnancy

Background

Alcohol intake during pregnancy is a major lifestyle-related risk factor and causes irreversible alterations and abnormalities in human fetal brain development (Gautam, Nuñez, Narr, Kan, & Sowel, 2014; Guerri, Bazinet, & Riley, 2009; Jarmasz, Basalah, Chudley, & Del Bigio, 2017; Long, Little, Beaulieu, & Lebel, 2018; Ngai et al., 2015). Associations between alcohol intake during pregnancy and behavioral problems in infants, children and adults have been reported previously (Day, Helsel, Sonon, & Goldschmidt, 2013; Disney, Iacono, McGue, Tully, & Legrand, 2008; Pfänder, Liebig, & Feldmann, 2014; Sayal, Heron, Golding, & Emond, 2007; Sood et al., 2001). Larkby, Goldschmidt, Hanusa, and Day (2011) found an increased risk of conduct disorders in children and adolescents at an average exposure of one and more drinks per day (Larkby et al., 2011). Two smaller studies published in the 1990ies in a sample of 14-years-olds suggest that heavy drinking and binge drinking during pregnancy result in learning problems/memory deficits, antisocial behavior, attention deficits, and delinquent behavior (Larkby et al.,

2011; Olson et al., 1997). However, data on the effect of prenatal alcohol exposure (PAE) on the full range of behavioral problems – including hyperactivity, conduct problems, emotional symptoms, peer relationship problems, and the total difficulties score – in adolescents are not yet available. Thus, it is still unclear whether even low-to-moderate levels of PAE have an impact on different behavioral problems, such as hyperactivity, conduct problems, emotional symptoms, peer relationship problems, and total difficulties score. Therefore, investigating the effects of low-to-moderate PAE on behavioral problems in adolescents with a large population-based study will be the focal point of this research work.

Tobacco smoking during pregnancy is a further relevant lifestyle-related risk factor and often occurs in combination with smoking during pregnancy (Pfänder, Feldmann, & Liebig, 2013; Pfänder, Kunst, Feldmann, van Eijsden, & Vrijkotte, 2014). Numerous studies demonstrate that tobacco smoking during pregnancy is a risk factor for behavioral problems (for review see (DiFranza, Aligne, & Weitzman, 2004)). Accordingly, tobacco smoking during pregnancy is

hypothesized to be a relevant confounder in the chain between maternal alcohol intake during pregnancy and behavioral problems.

We hypothesize that lifestyle-related risk factors during pregnancy – specifically low-to-moderate levels of maternal alcohol intake during pregnancy – are associated to several dimensions of behavioral problems (hyperactivity, conduct problems, emotional symptoms, peer relationship problems, and the total difficulties score) in adolescents. We use a large, nationwide and representative German health survey while adjusting for a wide range of salient covariates. There is no other alcohol study known in the research on PAE and its association with behavioral problems in adolescents with such a large number of subjects (Larkby et al., 2011; Olson et al., 1997).

Methods

Kiggs-study

Data are drawn from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS-Study). This is the first representative survey in Germany on the health of children and adolescents between 0 and 17 years. The study was commissioned by the German Federal Ministry of Health and implemented by the Robert Koch Institute (RKI). Ethics approval was obtained from the ethics committee of the Charité Berlin and the Federal Office for the Protection of Data on February 20, 2003. Written informed consent according to the Helsinki Declaration was obtained from the participants and their parents or guardians before the subjects entered the study. More details on the design of the survey, the fieldwork and the process of recruitment are reported elsewhere (Kurth et al., 2008). Briefly, four study teams were following a random route plan through 167 sample points all around Germany with an oversampling of non-ethnic German children and children from Eastern Germany. The participants were enrolled in the time period between May 2003 and May 2006. The study consists of a core survey and five additional modules. Age-appropriate questionnaires for parents and also for adolescents from the age of 11 onwards were designed, covering topics such as general mental and somatic health, social environment, living conditions, sense of well-being, family structures, and socio-demographics. The children and adolescents took part in physical examinations and tests. Central laboratories carried out blood and urine samples and physicians administered a computer assisted personal interview.

Study sample

Of the total sample of 28,299 participants, including 1,512 undeliverable survey contacts, 17,641 children and adolescents in the age group between 0 and 17 years and their parents could be surveyed (Kurth et al., 2008).

Of the 17,641 participants, we excluded twin or multiple births, those younger than 11 years, subjects with PAE because of self-reported regular drinking, those without information on maternal alcohol intake or on the behavioral

outcomes, and those with information in the parent's questionnaire given by others than the biological parents, leaving a baseline sample of 6,156 adolescents and their parents.

Independent variable: alcohol consumption during pregnancy

Alcohol intake during pregnancy was measured retrospectively (average time since birth: 14.4 years) with the categories 'no/low-to-moderately/regularly' (Pfinder, Kunst, Feldmann, van Eijsden, & Vrijkotte, 2013). In our sample, the number of self-reported regular drinkers during pregnancy was too low for group comparisons. Thus, we excluded self-reported regular drinkers and classified the mothers into the groups of 'abstainers' and 'low-to-moderate drinkers' (Pfinder, Liebig, et al., 2014).

Dependent variables: Behavioral problems (hyperactivity, conduct problems, emotional symptoms, peer relationship problems, total difficulties score)

Behavioral problems were measured with the Strengths and Difficulties Questionnaire (SDQ). Briefly, the SDQ is a broadly used and validated 25-item screening questionnaire that is designed to be administered via self-reporting. The SDQ was designed to screen for behavioral problems in children and adolescents. The questionnaire shows satisfactory psychometric properties (Goodman, 2001). The SDQ is divided into five scales with five items each: hyperactivity, conduct problems, emotional symptoms, peer relationship problems, and pro-social behavior. Each item scores between 0 and 2 and, thus, each scale can reach scores between 0 and 10 with higher scores indicating higher levels of disorders. The scores of each item (excluding items from the pro-social behavior scale) are summed up to construct an overall measure of behavioral problems: the total difficulties score (max. 40).

Scores on and above the 90th percentile show high correlation with clinically significant problems; hence, this cutoff point is widely used to identify potential cases of mental health problems (Elgen et al., 2012; Goodman, 2001). In our sample, the cutoff-points for the 90th percentile and above were for each scale: hyperactivity ≥ 6 ; conduct problems ≥ 4 ; emotional symptoms ≥ 5 ; peer relationship problems ≥ 4 ; total difficulties score ≥ 16 .

Covariates

The KiGGS-Study included a wide range of variables that may confound or mediate the relationship between alcohol intake during pregnancy and behavioral problems in the youth offspring: gender, maternal age at birth, parity (0/ ≥ 1), age, gestational age at delivery (continuous), birth weight (continuous), exposure to smoke at home (daily/several times a week/once a week/seldom/never), smoking during pregnancy (no/yes, low-to-moderately/yes, regularly), victim of sexual harassment (no/yes, by youths/yes, by adults/no response), and SES (high/middle/low).

Tobacco smoking during pregnancy was self-reported. Women were asked on whether they were smoking during pregnancy. Possible answer categories were 'no', 'yes, low-to-

moderately' and 'yes, regularly' (Pfinder, Liebig, et al., 2014). In accordance with suggestions of previous studies, low-to-moderate tobacco smoking during pregnancy may apply to ≤ 9 cigarettes per day (Cnattingius & Haglund, 1997; Lindley, Becker, Gray, & Herman, 2000; Lindqvist & Marsál, 1999). Thus, the category on regular tobacco smoking during pregnancy may refer to >9 cigarettes per day.

Statistical analyses

Multivariate logistic regressions were applied to calculate the odds ratios (ORs) and the 95% confidence interval (CI) of behavioral problems for levels of alcohol intake during pregnancy (abstainers were considered the reference) with adjustment for potential confounders (gender, maternal age at birth, parity, age, gestational age at delivery, birth weight, exposure to smoke at home, smoking during pregnancy, victim of sexual harassment and SES).

The Statistical Package of Social Sciences (SPSS) version 19.0 was used for all statistical analyses.

Results

We aimed to investigate the association between low-to-moderate alcohol intake during pregnancy and behavioral problems in adolescents. The sample characteristics are shown in Table 1.

As shown in Table 2, after adjustment for confounders, PAE resulted in an increased risk for hyperactivity (OR 1.39, 95% CI [1.15, 1.69]), and peer relationship problems (OR 1.20, 95% CI [1.00, 1.44]). The risks of conduct problems

(OR 1.24, 95% CI [0.99, 1.56]), emotional symptoms (OR 1.16, 95% CI [0.93, 1.45]) and the total difficulties score (OR 1.25, 95% CI [0.99, 1.58]) were increased, but not statistically significant.

The adjusted model showed that smoking during pregnancy significantly increases the risks of hyperactivity and peer relationship problems in adolescents. Even low-to-moderate fetal smoke exposure resulted in significantly increased risks of peer relationship problems (see additional file A1 for detailed results).

Discussion

Even after adjustment for confounders, we found an increased risk for a number of behavioral problems with even low-to-moderate alcohol exposure during pregnancy, as measured by the SDQ. Tobacco smoking during pregnancy was having an indirect effect in the chain between PAE and hyperactivity and peer relationship problems in adolescents. We will discuss these two findings in turn.

This study links even low-to-moderate PAE to behavioral problems in adolescents. In all subcategories of the SDQ, we found the risk of behavioral problems to be increased in the adolescent offspring of low-to-moderate drinkers. Statistical significant differences between the adolescent offspring of low-to-moderate drinkers and abstainers emerged for hyperactivity, conduct problems, peer relationship problems, and the total difficulties score. The risk of emotional symptoms did have the expected direction, however, was not statistically significant. Our findings for the effect of low-to-moderate PAE on adolescents is consistent with reports from previous studies in younger children (Disney et al., 2008; Pfinder, Liebig, et al., 2014; Sayal et al., 2007; Sood et al., 2001).

An explanation for our findings on the adverse effect of low-to-moderate alcohol intake during pregnancy on behavioral problems in adolescents could be related to the theory of fetal origins of adult diseases, suggesting that the fetal period is highly susceptible to unfavorable conditions, resulting in chronic diseases over the life course (Ben-Shlomo & Kuh, 2002; Graham, 2002; Graham & Power, 2004; Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003). Accordingly, the increased risk of behavioral problems could be due to an alcohol-induced reprogramming of the hypothalamic-pituitary-adrenal (HPA) axis. Animal studies give evidence that HPA axis activity – which regulates stress – is reprogrammed by PAE, resulting in alterations of the neuroendocrine function such as a hyper-activation of the HPA axis (Abel, 1984; Weinberg, Sliwowska, Lan, & Helleman, 2008). Overexposure to glucocorticoids and a hyper-activation of the HPA axis are, in turn, responsible for mood-related disorders, aggressiveness, disruptive behavior, conduct problems and difficult behaviors (French, Hagan, Evans, Mullan, & Newnham, 2004; Maccari & Morley-Fletcher, 2007; McBurnett, Lahey, Rathouz, & Loeber, 2000; Pajer, Gardner, Rubin, Perel, & Neal, 2001; Van Goozen, Matthys, Cohen-Kettenis, Buitelaar, & van Engeland, 2000). Thus, the increased risk of behavioral problems in

Table 1. Sample characteristics (N = 6149).

	% (N)/Mean (SD)
<i>Child characteristics</i>	
Gender (% male)	50.8 (3126)
Age (years)	14.4 (2.0)
Socioeconomic status (%)	26.6 (1630)
Low	48.8 (2988)
Middle	24.5 (1506)
High	15.2 (931)
Ethnicity (non-German%)	3338.5 (528.4)
Birth weight (grams)	
Exposure to smoke at home (% yes)	35.7 (2182)
Victim of sexual harassment (%)	
No	94.0 (5781)
Yes, by youths	1.8 (111)
Yes, by adults	1.7 (106)
No Response	1.5 (94)
<i>Maternal characteristics</i>	
No Response	14.1 (870)
Drinking during pregnancy (% yes, low-to-moderately)	83.3 (5130)
Smoking during pregnancy (%)	12.3 (750)
No	4.0 (242)
Yes, low-to-moderately	26.9 (4.8)
Yes, regularly	
Age at birth of the child (years)	
<i>Behavioral problems</i>	
No	17.0 (1044)
Hyperactivity (% yes)	12.0 (740)
Conduct problems (% yes)	13.8 (850)
Emotional symptoms (% yes)	22.2 (1363)
Peer relationship problems (%yes)	11.9 (730)
Total difficulties score (% yes)	

Data were missing for socioeconomic status (N = 25), ethnicity (N = 40), birth weight (N = 223), exposure to smoke at home (N = 35), victim of sexual harassment (N = 57), smoking during pregnancy (N = 27); maternal age at birth of the child (N = 71). Data: KiGGS Study.

Table 2. Odds ratios (95% CI) and prevalence percentages of hyperactivity, conduct problems, emotional symptoms, peer relationship problems and total difficulties score.

	No PAE N = 5299	Low-to-moderate PAE N = 850	P-value	B (SE)	AIC
Hyperactivity	16.3	20.9	0.001***	0.304 (0.095)	5177.00
Prevalence (%)	1.00	1.36 (1.13, 1.63)	0.001***	0.332 (0.097)	
Unadjusted model	1.00	1.39 (1.15, 1.69)	0.001***		
Model 1					
Conduct problems	11.9	13.0	0.351	0.101 (0.114)	4072.17
Prevalence (%)	1.00	1.11 (0.88, 1.39)	0.376	0.217 (0.118)	
Unadjusted model	1.00	1.24 (0.99, 1.56)	0.066		
Model 1					
Emotional symptoms	13.7	14.5	0.543	0.082 (0.108)	4267.95
Prevalence (%)	1.00	1.09 (0.88, 1.34)	0.448	0.148 (0.113)	
Unadjusted model	1.00	1.16 (0.93, 1.45)	0.191		
Model 1					
Peer relationship problems	22.0	23.2	0.420	0.090 (0.091)	5881.01
Prevalence (%)	1.00	1.09 (0.92, 1.31)	0.323	0.181 (0.093)	
Unadjusted model	1.00	1.20 (1.00, 1.44)	0.052*		
Model 1					
Total difficulties score	11.7	12.9	0.324	0.102 (0.115)	4005.48
Prevalence (%)	1.00	1.11 (0.88, 1.39)	0.374	0.225 (0.119)	
Unadjusted model	1.00	1.25 (0.99, 1.58)	0.058		
Model 1					

Unadjusted model: addition of the independent variable only. Model 1: adjustment for gender, age, birth weight, maternal age at birth of the child, ethnicity, socioeconomic status, exposure to smoke, smoking during pregnancy, at home and victim of sexual harassment. * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. CI = confidence interval; PAE = prenatal alcohol exposure. Data: KiGGS Study.

adolescents might result from prenatal alcohol-induced alterations in the HPA axis.

Exhibiting behavioral problems during adolescence increase the risk for further negative developmental outcomes in later life, such as substance use and abuse, violence and social problems (Disney, Elkins, McGue, & Iacono, 1999; Taylor, Chadwick, Heptinstall, & Danckaerts, 1996). Thus, our findings increase the evidence base for the immense importance of preventing even low-to-moderate alcohol intake during pregnancy.

To our knowledge, this is the first study indicating that tobacco smoking during pregnancy is in the pathway between maternal alcohol intake during pregnancy and hyperactivity and peer relationship problems, respectively.

In line with the review from DiFranza et al. (2004) our results show that fetal smoke exposure is associated with an increased risk of behavioral problems in adolescents (DiFranza et al., 2004). Also in agreement with the review, the results presented in the additional file A1 reveal a dose-response relationship between tobacco smoking during pregnancy and offspring behavioral problems, at least for peer relationship-problems. The results emphasize that both, low-to-moderate tobacco smoking and regular tobacco smoking during pregnancy, respectively, may have severe effects for behavioral problems in adolescent offspring. The underlying biological pathway may be dopaminergic dysregulation in the developing embryo and fetus, caused by fetal tobacco smoke exposure. Dopaminergic activity – which is involved in the pathophysiology of behavioral problems – is modulated by nicotine receptors (Milberger, Biederman, Faraone, Chen, & Jones, 1996).

A limitation in our study is the self-reporting of alcohol intake during pregnancy and tobacco smoking during pregnancy. It is well established that self-reports on alcohol intake and tobacco smoking during pregnancy are likely to be under-reports (Alvik, Haldorsen, Groholt, & Lindemann, 2006;

Ernhart, Morrow-Tlucak, Sokol, & Martier, 1988; Morrow-Tlucak, Ernhart, Sokol, Martier, & Ager, 1989). Thus, our results might be biased by underreports and therefore, the 'real effect' of alcohol intake during pregnancy on behavioral problems in adolescents might be even stronger. Alcohol intake during pregnancy and tobacco smoking during pregnancy was measured in broad categories. Accordingly, both measurements were not recorded numerically, e.g. in terms of glasses per day/week or cigarettes per day/week. However, due to cultural and political conventions in Germany we believe that our derived assumptions on the quantities of alcohol intake and tobacco smoking categories are reasonable (BZgA, 2014). This is in line with previous studies (Cnattingius & Haglund, 1997; Lindley et al., 2000; Lindqvist & Marsál, 1999).

Children born to mothers with an alcohol addiction are mostly raised by other relatives, adoptive- or foster-parents, or at a children's home (Astley, Stachowiak, Clarren, & Clausen, 2002; Miller et al., 2006). The offspring of those women (prevalence in Germany: about 2.2%) are less likely to be included in our study since we excluded all adolescents who were accompanied to the survey by others than their biological parents.

We could not control for current maternal alcohol intake. However, we assume that this will not bias our results as offspring of these women are less likely to be part of the survey for the following reasons: The overall prevalence rate of alcoholic women is relatively low and a higher non-response might have occurred in alcoholic women than in healthy women. Patterns of alcohol intake during pregnancy, in terms of frequency and quantities per occasion, are associated with behavioral problems in offspring (Brown et al., 1991; Kelly et al., 2009; Larkby et al., 2011; Miller, Naimi, Brewer, & Jones, 2007). Reports on the timing of alcohol intake during pregnancy with respect to the fetal vulnerability to alcohol in the different trimesters of pregnancy are inconsistent (Goldschmidt, Richardson, Stoffer, Geva,

& Day, 1996; Ramadoss, Lunde, Pina, Chen, & Cudd, 2007). Our study did not provide information on differences in patterns and timing of alcohol intake during pregnancy to develop behavioral problems in adolescents. Thus, we must take into account that our results may not apply to all trimesters and to all frequencies of alcohol intake equally and they could be biased by the timing and the quantities per occasion of PAE in unknown ways.

Conclusions

In conclusion, our findings demonstrate that investigated life-style-related risk factors during pregnancy increase the risk for behavioral problems in adolescents. Even low-to-moderate levels of alcohol intake during pregnancy are associated with hyperactivity and peer-relationship problems in adolescents. Our results strengthen the urgent need for further intervention and prevention campaigns on alcohol intake during pregnancy as even offspring of low-to-moderate drinkers are at risk of behavioral problems in adolescence. Furthermore, future research should investigate the effect of different drinking patterns (e.g. binge drinking, heavy drinking) and the impact of the timing of PAE on behavioral problems in adolescents.

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Availability of data and materials

The data that support the findings of this study are available from Robert Koch Institute but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Robert Koch Institute.

Authors' Contributions

MP conceived and designed the study and analyzed the data. MP and SL interpreted the results. MP wrote the paper. SL commented on interim drafts of the paper. All have read and approved the submission of the manuscript.

Disclosure of potential conflicts of interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The KiGGS study was approved by the ethics committee of the Charité/Universitätsmedizin Berlin (Germany) and the Federal Office for the Protection of Data on 20 February 2003. Written informed consent according to the Helsinki Declaration was obtained from the participants and their parents or guardians before the subjects entered the study.

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