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Adolescents' Use of Alcohol, Tobacco and Illicit Drugs in Relation to Prenatal Alcohol Exposure: Modifications by Gender and Ethnicity

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Abstract — Aims: The study aimed to investigate (a) the association between low to moderate prenatal alcohol exposure (PAE) and the use of alcohol, tobacco and illicit drugs in adolescence and (b) whether the associations are modified by gender and ethnicity. **Methods:** The subjects of the study were 5922 children and adolescents, aged from 11 to 17 years, enrolled in the cross-sectional German Health Interview and Examination Survey for Children and Adolescents (the KiGGS study). Information on PAE is based on parental self-report questionnaires. Use of alcohol, tobacco and illicit drugs was assessed through self-report questionnaires for adolescents. **Results:** Low to moderate PAE was associated with an increased risk of drinking alcohol (adjusted odds ratio (OR) 1.73, 95% confidence interval (CI) 1.34, 2.18) and also of illicit drug use (adjusted OR 1.62, 95% CI 1.23, 2.14). The associations between PAE and the use of alcohol, tobacco and illicit drugs differed according to gender and ethnicity. Gender-stratified analyses resulted in adverse effects of PAE on drinking alcohol, smoking and illicit drug use in females; however, in German males, the associations disappeared. Stronger associations between PAE and the outcome measures were found in non-Germans. **Conclusions:** Our findings indicate that low to moderate levels of maternal alcohol intake during pregnancy are a risk factor for use of alcohol, tobacco and illicit drugs by the offspring, with stronger associations in females and non-Germans.

INTRODUCTION

The prevalence of drinking, smoking and illicit drug use among adolescents is at a precarious level (Bauman and Phongsavan, 1999; Young *et al.*, 2002; Foster *et al.*, 2003; Lampert and Thamm, 2007). The use of psychoactive substances during one's youth has long-term consequences due to the adverse effects of drugs on the brain, since several areas of the brain—especially the frontal lobe and the temporal lobe (hippocampus, amygdala)—continue to develop into early adulthood (De Bellis *et al.*, 2000; Hickie and Whitwell, 2009). Furthermore, drug use in adolescence is associated with a range of negative outcomes such as dropping out of school, unsafe sexual behaviours, depression, anxiety, unintentional injuries, diverse illegal activities, physical and sexual violence, suicide and an increased risk of drug dependence in adulthood (Grant and Dawson, 1998; Bonomo *et al.*, 2004; Metzner and Kraus, 2008). This emphasizes not only the urgent need for prevention of adolescents' use of alcohol, tobacco and illicit drugs but also the need to explore, examine and act on the causal factors involved.

One of the causal factors of adolescent drug use may be prenatal alcohol exposure (PAE). There is evidence from animal models that PAE results in an altered sensitivity to drugs and an increased alcohol preference (Bond and Giusto, 1976; Phillips and Stainbrook, 1976; Abel *et al.*, 1981; Randall *et al.*, 1983; Sulik *et al.*, 1984; Molina *et al.*, 1987; Chotro and Molina, 1990; Dominguez *et al.*, 1998; Akers *et al.*, 2011). A human study in patients diagnosed with foetal alcohol syndrome (FAS) reported a high prevalence of alcohol and drug problems (Streissguth *et al.*, 2004). Further human studies with small sample sizes reported an association between heavy and/or episodic PAE and offspring drinking (Baer *et al.*, 1998, 2003; Griesler and Kandel, 1998). Research on the association between PAE and adolescents' use of psychoactive substances is rare and there has been no research carried out on the effect of low to moderate levels of PAE on adolescents' use of alcohol, tobacco and illicit drugs. To our knowledge, this is the first study investigating research on the association between PAE and illicit drug use and smoking.

There is evidence that the adverse effects of PAE differ by gender and ethnicity (Sokol *et al.*, 1986; Abel and Hannigan, 1995; Griesler and Kandel, 1998; O'Connor, 2001; Sood *et al.*, 2001; Rasmussen *et al.*, 2007, 2011; Herman *et al.*, 2008; Willoughby *et al.*, 2008). Animal models suggest that females with PAE exhibit stronger responses to drugs and to diverse stressors (Weinberg, 1988, 1992; Lee and Rivier, 1996). Also, a human study reports that heavy PAE has an effect on adolescent drinking in females only (Griesler and Kandel, 1998). Therefore, we hypothesize that the effect of low to moderate PAE on the use of alcohol, tobacco and illicit drugs could be stronger in females.

Studies suggest that the adverse effects of alcohol are more prevalent in ethnic minority groups (Sokol *et al.*, 1986; Abel and Hannigan, 1995). A review of ten studies from the USA, Canada and Alaska reported on a substantially increased prevalence of FAS among American Indians and Canadian Aborigines (Burd and Moffat, 1994). Abel and Hannigan (1995) suggest ethnicity being a key permissive factor for the creation of a biological milieu within which alcohol develops its major effects as ethnic groups differ according to biological conditions with specific groups having a higher susceptibility to alcohol-induced cellular changes, which in turn augment alcohol's toxic effects. And a study from the USA (Sokol *et al.*, 1986) reports that being of black race (compared with white) is a concomitant risk factor for susceptibility to the effects of PAE and the development of FAS. Ethnicity, too, is associated with specific drinking patterns and dietary habits

that exacerbate or attenuate the toxic effect of alcohol (Abel and Hannigan, 1995; Abel, 1998). Thus, we hypothesize that the effect of foetal alcohol exposure on adolescents' drug behaviour could vary across ethnic groups, even on low to moderate levels of maternal alcohol intake during pregnancy.

The present study, with a large sample size, examined the relation between low to moderate levels of PAE and the use of alcohol, tobacco and illicit drugs in 11–17 year-olds and—due to the increasing evidence of gender- and ethnicity-specific effects on the offspring as an outcome of maternal alcohol intake during pregnancy—it also examined possible effect modification by gender and ethnicity.

METHODS

KiGGS study

This study makes use of data from the 'German Health Interview and Examination Survey for Children and Adolescents' (KiGGS). The KiGGS study is the first German nationwide representative study on the health of 0–17 year-old children and adolescents. The study was designed and conducted by the Robert Koch-Institute and commissioned by the German Federal Ministry of Health. Details on the survey are found elsewhere (Kurth *et al.*, 2008). Briefly, between May 2003 and May 2006, four study teams followed a random route plan of 167 study locations across the whole of Germany. Invitations to participate in the study were sent to the parents of eligible children and adolescents. To maximize the number of participants, several strategies were applied: The survey was advertised in local media, incentives were offered and in order also to reach migrant families, the questionnaires were translated into six different languages. The children and adolescents were born between 1985 and 2006 with their main residence being in Germany. Age-appropriate questionnaires were designed to be filled in by the parents, and by the children and adolescents from 11 years old and above. The questionnaires cover topics of general mental and somatic health, sense of well-being, social environment, living conditions, family structures and socio-demographics. Physical examinations and tests were performed and blood and urine samples were carried out at central laboratories. A computer-assisted personal interview was performed by a physician. Of the total sample of 28,299 participants, 17,641 children and adolescents in the age group between 0 and 17 years and their parents were able to be surveyed (response rate: 66.6%).

Ethics approval for the KiGGS study was obtained from the ethics committee of the Charité/Universitätsmedizin Berlin (Germany) and the Federal Office for the Protection of Data on 20 February 2003 (authorization number: EA2/058/09).

Dependent variables

Alcohol intake

Alcohol intake in adolescence was measured using self-report questionnaires. Subjects aged 11 and above were asked within the questionnaire 'Have you ever consumed alcohol?'. Possible answer categories were yes and no. In cases where they gave a positive answer on alcohol intake they were additionally asked how many times they had drunk (a) beer, (b) wine, fruit wine, and sparkling wine and (c) liqueur within the previous month. For each of the three categories (a), (b) and (c), respondents selected one of the seven answer categories: (1) one or more glasses per day, (2) five to six glasses per week, (3) two to four glasses per week, (4) one glass per week, (5) one to three glasses per month, (6) less than one glass per month and (7) not at all. A binary variable on a 1 week prevalence of drinking was derived, comparable with that used in a previous study on youth drinking (Barnes and Farrell, 1992). The dummy variable, drinking at least one glass per week, was constructed by combining answers from the three categories (a), (b) and (c) with the categories on the amount (1)–(4) as a positive answer and (5)–(7), with 'never consumed alcohol before' as a negative answer.

Smoking

Tobacco smoking was measured through adolescent self-reporting, questioning whether they smoke or not (yes/no).

Illicit drug use

Illicit drug use was measured through questions on the use of marijuana, ecstasy, amphetamines/speed, medications and glue-sniffing in the last 12 months (no/once/a few times/often/I do not know this substance). Adolescents who responded on each of the five substances with 'no' or 'I do not know this substance' were classified as non-users.

Independent variable

Prenatal alcohol exposure

PAE was measured through retrospective parental self-reports, questioning whether the mother drank alcohol during pregnancy. Possible answer categories were regular, moderate or no alcohol intake during pregnancy. The number of self-reported regular drinkers during pregnancy was very low in the baseline sample (16/5922 = 0.0%). Additionally, we must take into consideration that self-reports on 'moderate' and 'regular' alcohol intake during pregnancy are affected by the respondents' subjective estimation of the quantities 'moderate' and 'regular'. In order to avoid bias through subjective estimates on 'moderate' and 'regular' alcohol intake, we created a variable with the categories 'no PAE' and 'PAE'.

Covariates

Covariates were selected on the basis of a theoretical approach (Hawkins *et al.*, 1992; Poikolainen *et al.*, 2001) and defined a priori. The following covariates were measured:

- Gender (categorical variable: male/female).
- Age (continuous variable).
- As a proxy of ethnicity we used country of birth of the individual and both parents. If at least one parent was born abroad, the person was considered as non-German. In cases of mixed origin, the mother's country of birth prevailed (Bos *et al.*, 2005; Stirbu *et al.*, 2006). The non-German group is composed of Slavic ($n = 355$), Turkish ($n = 293$) and other ethnic groups ($n = 459$). To increase statistical power, as the prevalence of PAE is very low in the single ethnic groups (Slavs: $n = 33$, Turks: $n = 7$; others: $n = 61$), we created a dichotomous

variable on ethnicity (categorical variable: German/non-German).

- The socioeconomic status (SES) was measured using 'Winkler's index', which was readjusted for the KiGGS study (Winkler and Stolzenberg, 2009). Winkler's index is a widely used social class index, based on the validated 'Scheuch index' (Scheuch, 1970) and is defined and measured by the net income, the basic and the vocational education and the profession. Each of the three dimensions scores between one and seven points. The index can range between three and twenty-one points. Three to eight points were attributed to the low SES group, nine to fourteen points were ascribed to the middle SES group and fifteen to twenty-one points were assigned to the high SES group (Winkler and Stolzenberg, 1999, 2009). The variable is derived from the main wage earner in the household and categorized into 'high, middle and low'. Further details of the measurement and classification are found elsewhere (Winkler and Stolzenberg, 2009).
- Parental smoking was measured via parental self-reports, questioning whether the father and/or the mother smoke (yes/no).
- Quality of life within the family was measured through adolescent self-reports on the KINDL-R questionnaire. The KINDL-R questionnaire is a 24-item 5-point Likert scale on 6 dimensions of the quality of life. We used the dimension on family, measured by four items with a sum score of 0–100. In our sample, quality of life within the family was a reliable measurement with a Cronbach's $\alpha = 0.715$. We divided the scale score by 10 to increase statistical power, resulting in scores between 0 and 10. Higher scores indicate a high quality of life within the family (continuous variable).
- School failure (repeated a year/did not repeat a year).
- Friends who smoke were measured by questioning the adolescents as to whether their friends smoke (yes/no).
- Exposure to tobacco smoke during pregnancy was measured through parental self-reports on whether the mother smoked during pregnancy (regularly/moderately/not at all).

Study population

For the baseline sample, all subjects without information on PAE, alcohol intake, smoking, illicit drug use and younger than 11 years old were excluded, leaving a study population of 5922 children and adolescents in the age group between 11 and 17 years.

Statistical analysis

Frequency analyses were applied in order to examine the sample characteristics and multiple logistic regression analyses were performed to examine the association between PAE and the use of alcohol, tobacco and illicit drugs. Model 1 was adjusted for gender, age, ethnicity, SES, quality of life within the family, paternal smoking, school failure, friends who smoke and maternal smoking during pregnancy.

To test whether the effect of PAE on the use of alcohol, tobacco and illicit drugs is modified by gender or ethnicity, we added two-way interactions to model 1 (model 2). To test whether the association between PAE and the use of alcohol, tobacco and illicit drugs is moderated by both, gender and ethnicity, we added all three pairs of two-way interactions and the three-way interaction to model 1 (model 3). By means of these terms we assessed whether an interaction could be demonstrated with conventional levels of significance ($P < 0.05$). We performed regression models with adjustment for confounders for drinking, smoking and illicit drug use in stratified analyses according to gender, and ethnicity, and both together. The stratified analyses were performed to describe effect modifications in terms of their dimension and direction, and not only by means of statistical significance. The Statistical Package of Social Sciences (SPSS) version 19.0 was used for all statistical analyses.

RESULTS

The sample characteristics of the young people and their parents are shown in Table 1. Of the 5922 children and adolescents, 50.5% were male and 49.5% were female. The mean age was 14.3 years. Of the adolescents in the sample, 26.2% had a low SES, 48.2% had a middle SES, 25.0% had a high SES and 18.7% had a non-German ethnic background. The prevalence of paternal smoking was 52.5% and 43.8% of the children and adolescents reported having friends who smoke. The need to repeat a class was experienced by 15.3%. Exposure to tobacco smoke during pregnancy was reported by 16.1%, with 4.1% smoking regularly during pregnancy. PAE was reported by 14.2%. The prevalence of psychoactive

Table 1. Sample characteristics ($n = 5922$)

	% (n)/mean (SD)
Demographics	
Gender (% male)	50.5 (2990)
Age (years)	14.3 (2.0)
Socioeconomic status (%)	
Low	26.2 (1549)
Middle	48.2 (2854)
High	25.0 (1483)
Ethnicity (non-German%)	18.7 (1107)
Family drug behaviour	
Parental smoking (% yes)	52.5 (3012)
Family conflict/bonding	
Quality of life within the family	8.2 (1.5)
School failure	
Repeat a class (% yes)	15.3 (900)
Association with drug-using peers	
Friends who smoke (% yes)	43.8 (2529)
Prenatal substance exposure	
Tobacco smoke exposure during pregnancy (%)	
Regularly	4.1 (242)
Moderately	12.0 (708)
None	83.5 (4942)
Prenatal alcohol exposure (% yes)	14.2 (838)
Use of addictive substances	
Drinking (% yes)	20.1 (1191)
Smoking (% yes)	18.1 (1069)
Illicit drugs (% yes)	7.4 (439)

Data were missing for socioeconomic status ($n = 36$), ethnicity ($n = 45$), parental smoking ($n = 183$), family-related quality of life ($n = 73$), school failure ($n = 38$), friends who smoke ($n = 147$), tobacco smoke exposure during pregnancy ($n = 30$).

substance use was the following: 21.1% reported drinking, 18.1% smoking and 7.4% illicit drug use.

Both the univariate and multivariate results showed an increased risk of regular drinking (at least once a week) (adjusted odds ratio (OR) 1.73; 95% confidence interval (CI) 1.34, 2.18) and illicit drug use (adjusted OR 1.62; 95% CI 1.23, 2.14) in relation to PAE. The regression models on smoking showed a significant association with PAE only after inclusion of the interaction terms (adjustment including a three-way interaction: OR 1.49; 95% CI 1.05, 2.11 adjustment including two-way interactions: OR 1.49; 95% CI 1.06, 2.08). The two-way interaction term between PAE and gender was highly significant for drinking ($P = 0.007$) and smoking (0.002). We found a significant *P*-value for interaction between PAE and ethnicity for drinking ($P = 0.021$). For illicit drug use, none of the *P*-values for interaction was significant. After including the three-way interaction between PAE, ethnicity and gender and the three pairs of two-way interactions, the *P*-value for interaction between PAE and gender remained significant for drinking ($P = 0.010$) and smoking ($P = 0.003$). None of the three-way interactions showed statistical significance ($P \leq 0.05$) (Table 2). Associations between drinking, smoking and illicit drug use and PAE and the covariates are shown in the appendix.

Table 3 shows gender-stratified analyses for drinking, smoking and illicit drug use. The analyses resulted in no association between PAE and drinking, smoking and illicit drug use in males. A strong association between PAE and all measures of psychoactive substance use was found in females: the adjusted OR for drinking alcohol was 2.22 (95% CI 1.61, 3.07), the adjusted OR for smoking was 1.58 (95% CI 1.14, 2.19) and the adjusted OR for illicit drug use was 1.91 (95% CI 1.29, 2.82).

Table 4 shows ethnicity-stratified analyses for drinking, smoking and illicit drug use. The analyses resulted in stronger associations between PAE and the use of alcohol, tobacco and illicit drugs in non-Germans compared with Germans. In non-Germans, the adjusted OR for drinking at least once a week was 3.18 (95% CI 1.63, 6.20) and the adjusted OR for illicit drug use was 2.61 (95% CI 1.23, 5.56). In Germans, there was no association between PAE and smoking, but in non-Germans, the adjusted OR for smoking was 1.96 (95% CI 1.00, 3.83).

Table 5 shows stratified analyses by ethnicity and gender for drinking, smoking and illicit drug use. In relation to PAE, the analyses resulted in increased risks of drinking in females with stronger associations in non-Germans (adjusted OR 4.56; 95% CI 1.69, 12.27) than in Germans (adjusted OR 2.07; 95% CI 1.47, 2.92). In German males, we found a positive effect of PAE on smoking (adjusted OR 0.66; 95% CI 0.45, 0.97), which disappeared in non-German males. Stronger effects of PAE on smoking were found in females than in males and in non-Germans than in Germans, with statistical significance in German females (adjusted OR 1.48; 95% CI 1.04, 2.10). Significant associations between PAE and illicit drug use were found in German females (adjusted OR 1.90; 95% CI 1.25, 2.89) and non-German males (adjusted OR 3.74; 95% CI 1.27, 10.99).

DISCUSSION

Key findings

The current study shows that PAE is associated with an increased risk of regular drinking and illicit drug use in children and adolescents aged from 11 to 17 years. Smoking did not show an association with PAE in the general sample. However, stratified analyses showed that the associations between PAE and the use of alcohol, tobacco and illicit drugs differed according to gender and ethnicity, resulting in stronger effects of PAE on drinking, smoking and illicit drug use in females and in non-Germans.

Evaluation of potential limitations

First, reporting bias may have occurred as PAE and the use of alcohol, tobacco and illicit drugs were measured using self-reports, and information on alcohol intake during pregnancy was measured up to 17 years retrospectively. It is also true that self-reports on alcohol intake during pregnancy are likely to be underreports (Ernhart *et al.*, 1988; Morrow-Tlucak *et al.*, 1989; Jacobson *et al.*, 1991; Alvik *et al.*, 2006); however, retrospective reports on alcohol intake during pregnancy were reported to be more reliable than antenatal reports (Ernhart *et al.*, 1988; Morrow-Tlucak *et al.*, 1989; Jacobson *et al.*, 1991; Alvik *et al.*, 2006; Hannigan *et al.*, 2010). Although several studies showed a high validity of self-reports among young people (Mensch and Kandel, 1988; Winters *et al.*, 1990), we have to consider that information on drinking, smoking and the use of illicit drugs could also be underreported here. If either one or both of alcohol intake during pregnancy and use of psychoactive substances were underreported, the association between PAE and the use of alcohol, tobacco and illicit drugs in children and adolescents could be biased in unknown ways.

Second, selective participation could have occurred, with a higher non-response in alcoholic women and heavy drinkers. Therefore, our results apply to low to moderate levels of PAE only and the results cannot be applied to heavy PAE. Replication of this study is therefore suggested in a sample including heavy drinkers and alcoholic women.

Third, we lack information on the timing of alcohol intake during pregnancy. Reports on the vulnerability to alcohol for the developing embryo with respect to the trimesters of pregnancy are inconsistent (Goldschmidt *et al.*, 1996; Schneider *et al.*, 2001; Ramadoss *et al.*, 2007) and we cannot give information on differences in vulnerability to the use of alcohol, tobacco and illicit drugs in relation to PAE with respect to the timing of alcohol exposure during pregnancy. Thus, we must take into account that our results may not apply to all trimesters equally and they could be biased by the timing of PAE in unknown ways.

Fourth, although we could control for a large number of confounders, confounding bias might have occurred as we could not control for family history of drinking, illicit drug use and mental health problems or for peer use of alcohol and illicit drugs. Parents' use of psychoactive substances and their mental health problems, and peers' use of alcohol and illicit drugs could confound the relationship between alcohol intake during pregnancy and a subject's use of psychoactive substances, possibly resulting in an overestimation of the effect of PAE on adolescent drinking and use of illicit drugs (Kandel and Andrews, 1987; Ary *et al.*, 1993; Van der Vorst *et al.*, 2005). However, sensitivity analyses on the effect of parental smoking on the association between PAE and smoking behaviour in offspring resulted in slight decreases of the ORs after removing parental smoking from the adjusted models. The

Table 2. Odds ratios (95% CI) and prevalence percentages of drinking, smoking and illicit drug use and PAE

	No PAE ($n = 5084$)	PAE ($n = 838$)	*P*-value	B (SE)	Nagelkerkes R^2	*P*-value for PAE * gender * ethnicity	*P*-value for PAE * gender	*P*-value for PAE * ethnicity	*P*-value for ethnicity * gender
Drinking									
Prevalence (%)	19.3	25.3	<0.001						
Unadjusted model	1.00	1.42 (1.20, 1.68)	<0.001	0.351 (0.087)	0.004				
Model 1	1.00	1.73 (1.37, 2.18)	<0.001	0.547 (0.120)	0.492				
Model 2	1.00	2.17 (1.54, 3.05)	<0.001	0.733 (0.174)	0.494		0.007	0.021	
Model 3	1.00	2.18 (1.53, 3.10)	<0.000	0.780 (0.180)	0.495	0.775	0.010	0.151	0.237
Smoking									
Prevalence (%)	17.9	19.1	0.397						
Unadjusted model	1.00	1.08 (0.90, 1.31)	0.398	0.081 (0.095)	0.000				
Model 1	1.00	1.11 (0.88, 1.42)	0.375	0.108 (0.122)	0.437				
Model 2	1.00	1.49 (1.06, 2.08)	0.022	0.396 (0.172)	0.440		0.002	0.066	
Model 3	1.00	1.49 (1.05, 2.11)	0.026	0.396 (0.178)	0.440	0.939	0.003	0.202	0.620
Illicit drug use									
Prevalence (%)	6.9	10.6	<0.001						
Unadjusted model	1.00	1.61 (1.26, 2.05)	<0.001	0.474 (0.125)	0.005				
Model 1	1.00	1.62 (1.23, 2.14)	0.001	0.483 (0.143)	0.222				
Model 2	1.00	1.91 (1.27, 2.86)	0.002	0.644 (0.208)	0.223		0.164	0.446	
Model 3	1.00	1.99 (1.31, 3.02)	0.001	0.686 (0.214)	0.224	0.413	0.118	0.908	0.792

Unadjusted model: addition of the independent variable only.
Model 1: adjustment for gender, age, ethnicity, socioeconomic status, quality of life within the family, parental smoking, school failure, friends who smoke and maternal smoking during pregnancy.
Model 2: Model 1 + PAE*gender and PAE*ethnicity.
Model 3: Model 1 + PAE*gender + PAE*ethnicity + ethnicity*gender and PAE *ethnicity*gender.
P-values for interaction are derived from the fully adjusted model.
CI, confidence interval; PAE, prenatal alcohol exposure.

Table 3. Odds ratios (95% CI) and prevalence percentages of drinking, smoking, illicit drug use and PAE, separated by gender

	PAE	Prevalence (%)	Model 1 OR (95% CI)	*P*-value	B (SE)	Nagelkerkes R^2
Drinking						
Male	No ($n = 2571$)	23.1	1.00			
	Yes ($n = 419$)	26.7	1.32 (0.94, 1.86)	0.180	0.279 (0.175)	0.559
Female	No ($n = 2513$)	15.3	1.00			
	Yes ($n = 419$)	23.9	2.22 (1.61, 3.07)	<0.001	0.799 (0.165)	0.412
Smoking						
Male	No ($n = 2571$)	17.7	1.00			
	Yes ($n = 419$)	16.0	0.75 (0.52, 1.07)	0.109	–0.292 (0.183)	0.459
Female	No ($n = 2513$)	18.0	1.00			
	Yes ($n = 419$)	22.2	1.58 (1.14, 2.19)	0.006	0.458 (0.166)	0.425
Illicit drug use						
Male	No ($n = 2571$)	7.8	1.00			
	Yes ($n = 419$)	10.7	1.40 (0.94, 2.08)	0.102	0.334 (0.204)	0.259
Female	No ($n = 2513$)	5.9	1.00			
	Yes ($n = 419$)	10.5	1.91 (1.29, 2.82)	0.001	0.645 (0.201)	0.189

Model 1: adjustment for age, ethnicity, socioeconomic status, quality of life within the family, parental smoking, school failure, friends who smoke and maternal smoking during pregnancy.
CI, confidence interval; OR, odds ratio; PAE, prenatal alcohol exposure.

Table 4. Odds ratios (95% CI) and prevalence percentages of drinking, smoking, illicit drug use and PAE, separated by ethnicity

	PAE	Prevalence (%)	Model 1 OR (95% CI)	*P*-value	B (SE)	Nagelkerkes R^2
Drinking						
German	No ($n = 4038$)	20.9	1.00			
	Yes ($n = 732$)	25.4	1.60 (1.24, 2.05)	<0.001	0.467 (0.128)	0.499
Non-German	No ($n = 1006$)	13.4	1.00			
	Yes ($n = 101$)	24.8	3.18 (1.63, 6.20)	<0.001	1.156 (0.341)	0.461
Smoking						
German	No ($n = 4038$)	19.0	1.00			
	Yes ($n = 732$)	19.1	1.03 (0.79, 1.33)	0.840	0.026 (0.131)	0.446
Non-German	No ($n = 1006$)	13.9	1.00			
	Yes ($n = 101$)	18.8	1.96 (1.00, 3.83)	0.050	0.672 (0.342)	0.395
Illicit drug use						
German	No ($n = 4038$)	6.9	1.00			
	Yes ($n = 732$)	10.4	1.53 (1.13, 2.07)	0.006	0.424 (0.154)	0.226
Non-German	No ($n = 1006$)	6.9	1.00			
	Yes ($n = 101$)	11.9	2.61 (1.23, 5.56)	0.013	0.960 (0.386)	0.234

Model 1: adjustment for gender, age, socioeconomic status, quality of life within the family, parental smoking, school failure, friends who smoke and maternal smoking during pregnancy.
CI, confidence interval; OR, odds ratio; PAE, prenatal alcohol exposure.

analyses did not, therefore, suggest an overestimation of the effect of PAE when parental smoking history is missing and thus, we assume that the lack of information on parental drinking and parental use of illicit drugs might not cause a substantial effect on the ORs for adolescent behaviour of drinking and illicit drug use. Also, Baer *et al*. (1998) reported that the effect of a family history of drinking on the association between PAE and adolescent drinking is negligibly small and therefore we believe that the reported associations might hold. Further analyses showed that adolescent smoking is correlated with drinking ($\rho = 0.404$, $P < 0.001$) and illicit drug use ($\rho = 0.365$, $P < 0.001$), and therefore we believe that the variable on peers' smoking behaviour also captures a large part of the confounding factor of peers' drinking and illicit drug use on a subject's use of alcohol and illicit drugs. Thus, the lack of information on peers' drinking and illicit drug use should not have a substantial impact on the results.

Discussion of the main findings

We found the risk of drinking at least once a week and the risk of illicit drug use to be significantly increased in adolescents from the ages of 11–17 years whose mothers consumed alcohol during pregnancy. Our findings are comparable with the findings of animal studies that report on an increased risk of substance use in those exposed to alcohol intrauterine (Bond and Giusto, 1976; Phillips and Stainbrook, 1976; Abel *et al.*, 1981; Randall *et al.*, 1983; Sulik *et al.*, 1984; Molina *et al.*, 1987; Chotro and Molina, 1990; Dominguez *et al.*, 1998; Akers *et al.*, 2011). Streissguth *et al*. (2004) reported that the prevalence of alcohol and drug problems was 35% in their sample of children and adolescents aged 12 years and older, diagnosed with FAS. We also report on an increased risk due to PAE of regular drinking and use of illicit drugs, but our results suggest that this applies not only to the offspring of heavy drinkers or to subjects with the diagnosis 'FAS'; even low to moderate levels of PAE were found to be associated with increased risks. We cannot compare our results with a study in a more general sample as to our knowledge this is the first study in humans reporting on associations between low to moderate levels of PAE and the risks of drinking and using illicit drugs.

One explanation for our findings could be linked to the theory of foetal origins of adult diseases, which suggests that

Table 5. Odds ratios (95% CI) and prevalence percentages of drinking, smoking, illicit drug use and PAE, separated by ethnicity and gender

	PAE	Prevalence (%)	Model 1 OR (95% CI)	*P*-value	B (SE)	Nagelkerkes R^2
Drinking						
German						
Male	No (*n*=2030)	24.7	1.00			
	Yes (*n* = 366)	26.5	1.19 (0.83, 1.73)	0.347	0.178 (0.189)	0.581
Female	No (*n* = 2008)	17.0	1.00			
	Yes (*n* = 366)	24.3	2.07 (1.47, 2.92)	<0.001	0.730 (0.175)	0.409
Non-German						
Male	No (*n* = 519)	17.9	1.00			
	Yes (*n* = 50)	28.0	2.12 (0.84, 5.37)	0.114	0.750 (0.475)	0.474
Female	No (*n* = 487)	8.6	1.00			
	Yes (*n* = 51)	21.6	4.56 (1.69, 12.27)	0.003	1.517 (0.505)	0.423
Smoking						
German						
Male	No (*n* = 2030)	18.8	1.00			
	Yes (*n* = 366)	15.8	0.66 (0.45, 0.97)	0.036	–0.412 (0.197)	0.470
Female	No (*n* = 2008)	19.2	1.00			
	Yes (*n* = 366)	22.4	1.48 (1.04, 2.10)	0.028	0.392 (0.179)	0.434
Non-German						
Male	No (*n* = 519)	14.5	1.00			
	Yes (*n* = 50)	18.0	1.52 (0.54, 4.29)	0.439	0.417 (0.529)	0.430
Female	No (*n* = 487)	13.3	1.00			
	Yes (*n* = 51)	19.6	2.45 (0.97, 6.18)	0.058	0.896 (0.472)	0.374
Illicit drug use						
German						
Male	No (*n* = 2030)	7.8	1.00			
	Yes (*n* = 366)	10.1	1.22 (0.78, 1.89)	0.189	0.196 (0.224)	0.261
Female	No (*n* = 2008)	6.0	1.00			
	Yes (*n* = 366)	10.7	1.90 (1.25, 2.89)	0.003	0.641 (0.215)	0.197
Non-German						
Male	No (*n* = 519)	8.1	1.00			
	Yes (*n* = 50)	16.0	3.74 (1.27, 10.99)	0.017	1.319 (0.550)	0.297
Female	No (*n* = 487)	5.5	1.00			
	Yes (*n* = 51)	7.8	1.89 (0.58, 6.19)	0.294	0.636 (0.606)	0.182

Model 1: adjustment for age, socioeconomic status, quality of life within the family, parental smoking, school failure, friends who smoke and maternal smoking during pregnancy.
CI, confidence interval; OR, odds ratio; PAE, prenatal alcohol exposure.

the intra-uterine phase is a critical period of life. Poor conditions for the embryo and foetus could programme the biological mechanism, resulting in chronic diseases in adulthood and later life (Ben-Shlomo and Kuh, 2002; Graham, 2002; Kuh *et al.*, 2003; Graham and Power, 2004). Thus, the increased risk of drinking and illicit drug use could be due to an alcohol-induced reprogramming of the hypothalamic–pituitary–adrenal (HPA) axis. There is evidence from animal studies that PAE reprogrammes the activity of the HPA axis, leading to an altered neuroendocrine function such as a hyper-responsiveness to stress (Weinberg *et al.* 2008). Hypo- and hyper-function of the HPA axis, which in turn is responsible for stress regulation, increase the vulnerability to drug dependence (Piazza *et al.*, 1991; Piazza and Le Moal, 1996; Schluger *et al.*, 2001; O'Malley *et al.*, 2002; Kreek *et al.*, 2005; Lovallo, 2006). Thus, the vulnerability to use of alcohol and illicit drugs might result from an altered HPA axis activity, caused by maternal alcohol intake during pregnancy.

Another explanation for the increased risk of regular drinking and illicit drug use could be alcohol-induced antenatal disorders of the olfactory bulbs and the basal olfactory cortex, which persist until adulthood and have been suggested as resulting in an increased preference for alcohol (Sulik *et al.*, 1984; Akers *et al.*, 2011).

We found the association between PAE and the risk of smoking to be apparent in females only. Among females, we found strong associations between PAE and all three adverse outcomes we measured. This association was even evident in ethnicity-stratified analyses, resulting in stronger effects of PAE on the use of psychoactive substances in both German and non-German females. These associations were less clear in males. Our findings suggest that females are more vulnerable to the adverse effects of low to moderate PAE with respect to their susceptibility to use of alcohol, tobacco and illicit drugs. The finding on increased risks from PAE of regular drinking in females is in line with the findings reported from Griesler and Kandel (1998), suggesting an effect of heavy PAE on adolescent drinking in females only. As this is the first study in humans to investigate an interaction between PAE and gender on the use of illicit drugs and smoking, we cannot compare our results with those in other human studies. But our results are in accordance with animal models which showed that females with PAE exhibit stronger responses to drugs and to diverse stressors (Weinberg, 1988, 1992; Lee and Rivier, 1996).

An explanation for the findings of a stronger effect of PAE on the use of alcohol, tobacco and illicit drugs in females could be gender-specific differences in the alcohol-induced foetal programming of the HPA axis (Zhang *et al.*, 2005). Studies in animals showed that females with PAE exhibited higher levels of corticosterone (Weinberg, 1988, 1992; Lee and Rivier, 1996). However, data on gender-specific HPA axis

hyper-responsiveness in PAE animals are inconsistent (Weinberg, 1992; Weinberg *et al.*, 1996; Kim *et al.*, 1999). The inconsistency may be due to different conditions in the laboratories and the application of different species of animals as HPA axis activity was reported to differ between species (Matthews, 2002; Beishuizen and Thijs, 2003).

In agreement with our initial hypothesis, there was an interaction between PAE and ethnicity. PAE was associated with adverse effects on the use of alcohol, tobacco and illicit drugs in non-Germans. This association was even apparent after additional stratification by gender, resulting in stronger effects in non-German males and females than in German males and females. The non-German group was composed of 32.1% Slavs, 26.5% Turks and 41.5% other ethnic groups. Stronger effects of PAE in ethnic minority groups have also been reported previously (Sokol *et al.*, 1986; Burd and Moffat, 1994); however, to our knowledge, this is the first study investigating an interaction between PAE and ethnicity on the use of alcohol, tobacco and illicit drugs in adolescence and thus, further research is needed to elucidate the interaction between PAE and ethnicity on the use of psychoactive substances in young people. As the number of subjects with PAE was too low in the single ethnic groups of Slavs, Turks and others to conduct multiple regression analyses and stratifications according to these groups, we suggest replication of the analyses in a multiethnic study to detect diversities across different ethnic groups.

Slavic, Turkish and other ethnic minority groups differ from the Germans with respect to their drinking patterns and the social acceptance of drinking in their cultures, and they also show variations in metabolism (Lex, 1987; Abel, 1998). The diverse genetic and enzymatic variants across ethnic groups and their response to alcohol are unclear (O'Leary, 2004), but we can confirm that within our sample all ethnic minority groups show a strong relation to a low SES. Therefore, one reason for the stronger effect of foetal alcohol exposure in ethnic minorities could be an intrauterine interaction between alcohol and the correlates of poverty that exacerbate the toxic effect of alcohol, such as a poor nutrition, stress and environmental pollution (Abel and Hannigan, 1995; May *et al.*, 2004, 2005).

Another reason for the stronger effects of PAE on the use of alcohol, tobacco and illicit drugs in Slavic, Turkish and other ethnic groups than in Germans could be ethnic differences in foetal programming with respect to altered neuroendocrine responses in the HPA axis due to ethnic differences in maternal cortisol levels during pregnancy (Lu and Halfon, 2003; Wadhwa, 2005; Glynn *et al.*, 2007). Further research should investigate the effects of PAE on the HPA axis across different ethnic groups to confirm this hypothesis.

A further, more socio-cultural, explanation could be culturally determined patterns in the use of alcohol, tobacco and illicit drugs. An in-depth analysis showed that a high prevalence of PAE is especially evident in the offspring of parents (mother, father or both) from several Latin-American countries (Uruguay, Paraguay, Brazil, Argentina, Costa Rica and Mexico), France, Russia, Belarus, Poland, Kyrgyzstan, the UK, Hungary, Austria and Switzerland. All of these countries have permissive to over-permissive tobacco and drinking cultures with utilitarian drinking manners (Mäkelä 1975, 1983; O'Connor, 1975; Room, 1976; Solms, 1976; Coombs and Globetti, 1986; Room and Mäkelä, 2000; Mäkinen and Reitan, 2006) and that might determine the usage of psychoactive substances in the younger generations. Therefore, a more general pattern could also serve as the explanation, since the potential explanation above also indicates that alcohol and smoking varies by culture and thus, cultural aspects could determine drinking and smoking patterns.

CONCLUSIONS

Our findings suggest that maternal alcohol intake during pregnancy is associated with an increased risk in offspring of using illicit drugs and drinking, regardless of gender and ethnic origin. Females are more vulnerable to the adverse effects of low to moderate PAE with respect to the susceptibility to use of alcohol, tobacco and illicit drugs. We observed adverse effects of PAE on the use of alcohol, tobacco and illicit drugs in females and in non-Germans, even after stratification by ethnicity and gender together. Further studies in multiethnic populations are needed to detect diversities across different ethnic groups.

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Appendix Table A1. Detailed results of Model 1 (table 2) – Odds ratios (OR) and 95% confidence interval (CI) of drinking, smoking and illicit drug use and its association with PAE and the covariates

	Drinking			Smoking			Illicit drug use		
	OR (95 % CI)	B (SE)	P-value	OR (95 % CI)	B (SE)	P-value	OR (95 % CI)	B (SE)	P-value
PAE									
No	1.00			1.00			1.00		
Yes	1.73 (1.37, 2.18)	0.547 (0.120)	<0.001	1.11 (0.88, 1.42)	0.108 (0.122)	0.375	1.62 (1.23, 2.14)	0.483 (0.143)	0.001
Gender									
Female	1.00			1.00			1.00		
Male	2.53 (2.12, 3.01)	0.927 (0.089)	<0.001	1.06 (0.90, 1.26)	0.060 (0.086)	0.486	1.36 (1.09, 1.69)	0.306 (0.112)	0.006
Age (years)	2.35 (2.20, 2.51)	0.854 (0.033)	<0.001	1.68 (1.58, 1.77)	0.516 (0.029)	<0.001	1.53 (1.42, 1.64)	0.423 (0.038)	<0.001
SES									
High	1.00			1.00			1.00		
Middle	1.20 (0.97, 1.47)	0.179 (0.105)	0.087	1.17 (0.95, 1.45)	0.159 (0.110)	0.147	0.82 (0.63, 1.07)	−0.199 (0.135)	0.142
Low	1.07 (0.83, 1.38)	0.070 (0.129)	0.585	1.36 (1.05, 1.75)	−0.212 (0.025)	0.010	0.73 (0.52, 1.00)	−0.322 (0.166)	0.053
Ethnicity									
German	1.00			1.00			1.00		
Non-German	0.55 (0.43, 0.70)	−0.600 (0.121)	<0.001	0.62 (0.49, 0.79)	−0.472 (0.119)	<0.001	1.07 (0.80, 1.42)	0.064 (0.146)	0.663
Parental smoking									
No	1.00			1.00			1.00		
Yes	0.84 (0.70, 1.00)	−0.179 (0.093)	0.054	2.09 (1.74, 2.52)	0.738 (0.095)	<0.001	1.24 (0.97, 1.58)	0.214 (0.123)	0.082
Quality of life within the family School failure	0.84 (0.80, 0.88)	−0.176 (0.025)	<0.001	0.81 (0.77, 0.85)	−0.214 (0.025)	<0.001	0.80 (0.75, 0.85)	−0.225 (0.029)	<0.001
No	1.00			1.00			1.00		
Repeat a class	0.82 (0.65, 1.02)	−0.204 (0.112)	0.069	1.55 (1.26, 1.91)	0.438 (0.105)	<0.001	1.43 (1.11, 1.85)	0.356 (0.131)	0.006
Friends who smoke									
No	1.00			1.00			1.00		
Yes	3.89 (3.20, 4.72)	1.357 (0.099)	<0.001	7.12 (5.69, 8.91)	1.963 (0.114)	<0.001	2.79 (2.11, 3.71)	1.028 (0.144)	<0.001
Tobacco smoke exposure during pregnancy									
No	1.00			1.00			1.00		
Moderately	0.93 (0.71, 1.22)	−0.073 (0.226)	0.605	1.47 (1.15, 1.89)	0.386 (0.126)	0.002	1.56 (1.14, 2.13)	0.444 (0.158)	0.005
Regularly	0.98 (0.63, 1.53)	−0.020 (0.226)	0.930	1.29 (0.87, 1.91)	0.251 (0.202)	0.214	1.36 (0.82, 2.28)	0.309 (0.260)	0.234
Constant B (SE)	−14.269 (0.558), $p < 0.001$			−9.594 (0.496), $p < 0.001$			−8.185 (0.630), $p < 0.001$		
Nagelkerkes R^2	0.492			0.437			0.222		
N	5403			5403			5403		

PAE = prenatal alcohol exposure; SES = socioeconomic status.