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Socioeconomic characteristics of women with substance use disorder during pregnancy and neonatal outcomes in their newborns: A national registry study from the Czech Republic

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ABSTRACT

Background: Maternal substance use can pose a risk to the fetal health. We studied the background characteristics of women with substance use disorders (SUDs) and selected neonatal outcomes in their children.
Material and methods: A database-linkage study was performed. The sample consisted of pregnant women with a SUD during pregnancy (ICD-10 diagnosis F10-F19 except F17, n = 1710), women not diagnosed with a SUD (n = 1,511,310) in Czechia in 2000–2014, and their children. The monitored neonatal outcomes were gestational age, birth weight, preterm birth, and small-for-gestational age (SGA). Binary logistic regression adjusted for age, marital status, education, concurrent substance use, and prenatal care was performed.
Results: Women with illicit SUDs were younger, more often unmarried, with a lower level of education, a higher abortion rate, a higher smoking rate, and lower compliance to prenatal care than women with a SUD related to alcohol, or sedatives and hypnotics (SH). Women with a SUD had worse socioeconomic situations, poorer pregnancy care, and worse neonatal outcomes than women without a SUD. After adjustment, we found no difference in SGA between the illicit SUD groups and the alcohol and the SH groups. The newborns from all SUD groups had a higher risk of SGA when compared to women without a SUD. However after adjustment, the difference remained significant just in the alcohol group (OR = 1.9, 95 % CI = 1.4–2.6).
Conclusion: Mother's SUD during pregnancy increased risk of fetal growth restriction as measured by SGA. The role of maternal socioeconomic and lifestyle factors for the risk of SGA was substantial.

1. Introduction

1.1. Epidemiology of substance use during pregnancy

The use of psychoactive substances (PS) during pregnancy has become a substantial public health problem. Reported drug and alcohol use varies between studies and countries, and it is estimated that up to 30 % of pregnant women use tobacco, 15 % use alcohol, and up to 10 % use cannabis (Hotham et al., 2008; Lamy and Thibaut, 2010); exposure to other PS seems to be much lower. In Europe, women represent up to one quarter of those persons who use drugs, the majority of them being of child-bearing age (European Monitoring Centre for Drugs and Drug Addiction, 2016). The annual pregnancy rate among women with high-risk illicit drug use is estimated to be 6.5–11.0 % (Morrison and Siney, 1995; Weber et al., 2003).

1.2. Impact of maternal psychoactive substance use on the fetus

PS use can affect the fetus through three mechanisms (Ross et al., 2015; Shankaran et al., 2007): (1) Most PS use can directly act on molecular targets in the fetus – they can easily cross the placenta and have a toxic and/or teratogenic effect on the growing tissues, affecting their structure and functions; (2) they can directly affect brain development, with impaired cognitive and motor functions in the long-term; (3) PS use can also act directly on the uterus and/or placenta, affecting, for example, uteroplacental blood flow or influence the mother's

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physiology which can consequently affect the fetus. Alcohol, opioids and nicotine are substances with the best established consequences of their prenatal exposure, however, analogical mechanisms of action can also be assumed in other substances. Moreover, polydrug use pattern is common among people who use PS, including substance-using pregnant women (i.e. Davie-Gray et al., 2013; Delano et al., 2013). Studying PS use during pregnancy presents multiple methodological challenges, and studies are especially vulnerable to confounding from lifestyle and socioeconomic factors. The results from different studies may therefore be difficult to interpret.

Alcohol can produce fetal alcohol spectrum disorders (FASD) with an estimated global prevalence of 0.8 % in the general population, and with 8.0 % of children born to women consuming alcohol during pregnancy (Lange et al., 2017). The most serious form of FASD is fetal alcohol syndrome (FAS) with a typical appearance, growth restriction, neurocognitive and motor deficits, and behavioral disorders (Williams et al., 2015). Heavy alcohol use is associated with negative outcomes such as miscarriage, stillbirth, low birth weight, intrauterine growth restriction, preterm delivery, and infant mortality (Louw, 2018). Taking into account the high teratogenicity of alcohol, no threshold can be established and therefore no dose in pregnancy can be considered safe (Sampson et al., 2000).

Tobacco smoking during pregnancy has been associated with an increased risk of preterm delivery, intrauterine growth restriction, low birth weight, stillbirth and perinatal death (Feng, 1993; Louw, 2018). Furthermore, infections in newborns, cochlear dysfunction or orofacial clefting, and other congenital malformations were reported to be associated with maternal tobacco smoking (Holbrook, 2016).

Cannabis is likely the most prevalent illicit drug used during pregnancy. However, the effects of prenatal exposure to cannabis is unclear, mostly due to the confounding effects of other factors (Hall and Degenhardt, 2009). However, teratogenic effects, anencephaly and neurodevelopmental defects have been reported after prenatal cannabis exposure (Jaques et al., 2014; van Gelder et al., 2009). Negative outcomes which have been reported to be associated with cannabis use during pregnancy include smaller head circumference, low birth weight, intrauterine growth restriction, preterm delivery or stillbirth (Gunn et al., 2016; Louw, 2018).

The use of **opioids** (both illicit and prescription) during pregnancy has been associated with negative consequences. Neonatal abstinence syndrome (NAS) is a well-known and serious adverse event resulting from sudden withdrawal from heroin, an opioid maintenance drug (methadone/buprenorphine), or prescription opioid analgesics (e.g. Kocherlakota, 2014; Stover and Davis, 2015). The use of illicit opioids during pregnancy has been associated with intrauterine growth restriction, preterm delivery and stillbirth (Louw, 2018; Maeda et al., 2014). There are only a few studies specifically about prescription opioid use during pregnancy, and the results have been inconclusive with respect to associations with low birth weight and preterm birth (Yazdy et al., 2015). Opioids have a weak teratogenic effect, although the effect of synthetic opioid analgesics on cardiovascular defects has been described (Källén and Reis, 2016).

Prenatal exposure to **central stimulants** has been studied mostly for cocaine and (meth)amphetamine. Associations with adverse neonatal outcomes of **cocaine** exposure include smaller head circumference, intrauterine growth restriction, preterm birth, low birth weight or stillbirth (Cain et al., 2013; Cressman et al., 2014; Feng, 1993). **(Meth)amphetamine** prenatal exposure has been also associated with an increased risk of placenta-associated syndromes, growth restriction, preterm delivery, low birth weight, low Apgar scores and stillbirth (Good et al., 2010; Gorman et al., 2014; Louw, 2018). The use of central stimulants has been also associated with a teratogenic effect (Bateman et al., 2004; Buehler et al., 1996; Thomas, 1995; Werler et al., 2003), but the effect of other drugs within a polydrug context could not be excluded.

Prenatal exposure to other PS (such as MDMA, LSD or benzodiazepines) has been less studied, however, they seem to pose similar risks to mothers and children as the substances described above (Bellantuono et al., 2013; Ennis and Damkier, 2015; McElhatton et al., 1999; McGlothlin et al., 1970; Scott et al., 2010).

In this epidemiological investigation of a national sample of women with substance use disorders (SUD) during pregnancy, we aimed to:

1) explore maternal background characteristics and selected neonatal outcomes for the different SUD groups, and compare the background characteristics between groups using illicit and licit (alcohol or sedative/hypnotics) PS,
2) compare the growth restriction measured as SGA in newborns of women using illicit and licit PS,
3) compare the SGAs in children of women in different SUD groups with children of women without a SUD, and explore the impact of socioeconomic and lifestyle factors on the association between substance use and SGA.

2. Methods

We used data from nationwide health registries linked on an individual level based on the personal identification numbers assigned to all individuals in the Czech Republic (see also Gabrhelik et al., 2016; Handal et al., 2019; Nechanska et al., 2018; Skurtveit et al., 2019).

2.1. Data sources

2.1.1. The national register of reproduction health (NRRH)

The NRRH includes information collected during prenatal care and delivery: demographic and socioeconomic information, prenatal visits, self-reported substance use during pregnancy in three categories – tobacco, alcohol, and illicit drugs, the course of delivery, as well as pregnancy and neonatal outcomes. The reporting unit is a facility where the delivery took place and information is a mixture of evident (documented) and self-reported (anamnestic) data.

2.1.2. The national register of in-patient treatment (NRIT)

The NRIT includes information on every instance of any type of hospitalization including information on the dates of admission and discharge from hospital, and diagnoses in the discharge summary. The diagnoses are coded according to the International Statistical Classification of Diseases, 10th Revision (ICD-10).

2.2. Study population and study period

The sample was derived from all pregnant women (and their newborns) who gave birth from 2000 to 2014 in the Czech Republic, as reported to the NRRH. The women with SUDs (referred to as the “SUD groups”) were defined as those who were hospitalized for any reason and who received a diagnosis of SUD (ICD-10 diagnosis F10-F19) as recorded in the NRIT during pregnancy. This means that the population is not limited to women seeking treatment for substance use during pregnancy. It should be mentioned that the SUD group of stimulants other than cocaine (F15) is dominated by people who use methamphetamine in the Czech Republic (e.g. Mravčík et al., 2018; Orlíková et al., 2017. The tobacco-related SUD F17 was excluded n = 2678. Women hospitalized with two or more diagnoses of substance use disorder SUD related to different psychoactive substances or who were hospitalized for polydrug use F19 during pregnancy were classified as the polydrug use group n = 505. The group of pregnant women and their newborns without a SUD was defined as women not diagnosed with a SUD during the study period as documented in the same registers and the same period referred to as “non-SUD”.

As regards newborns, the sample was restricted to singleton births (27,750 children from multiple births were excluded) since neonatal parameters are likely different in multiple births (Santana et al., 2018).

2.3. Maternal and prenatal care variables

The maternal demographic and socioeconomic characteristics were age, education, marital status, self-reported substance use during pregnancy (in three categories: alcohol, tobacco and any illicit drug, as pre-defined in NRHH) and the week of enrolment and number of visits during prenatal care. They were also used as the control variables for the analysis of neonatal outcomes.

2.4. Neonatal outcomes

Neonatal outcomes treated as continuous measures were gestational age and birth weight. The binary variables were preterm birth (< 37 weeks of gestation), and small for gestational age (SGA) (Marsal et al., 1996). Gestational age, birth weight and SGA were restricted to live births and birth weight was restricted to term births (≥37 gestational weeks).

2.5. Analysis strategy and statistics

First we explored the mothers' sociodemographic and lifestyle characteristics, data on prenatal care, and neonatal outcomes in different SUD groups and the non-SUD group. Confidence intervals (CI) for proportions were calculated using the continuity-corrected score interval method (Vollset, 1993). The statistical significance level was set to 0.05. Following exploratory analysis we compared the alcohol group and the sedatives and hypnotics (SH) group with all other SUD groups, and then all SUD groups with the non-SUD group. For the multivariable comparison, we selected SGA as a highly relevant parameter of fetal growth restriction and a predictor of adverse postnatal outcomes (Leite and Cecatti, 2019). We performed binary logistic regression and calculated the unadjusted and adjusted odds ratio (OR) with 95 % CI. We adjusted for age, marital status and education, concurrent use of other substances during pregnancy, and the number of visits of prenatal care (as a proxy of a disorganized lifestyle). To show the effects of different types of confounders, we compared SGAs between all SUD groups and the non-SUD group in 3 adjustment scenarios: adjustment for (1) sociodemographic factors (age, education, marital status), (2) sociodemographic factors plus number of controls during prenatal care, (3) and scenario 2 plus smoking (all groups), alcohol (except the alcohol group) and illicit drug use (except the illicit SUD groups). Statistical analysis was conducted using IBM SPSS Statistics for Windows, v. 25.

2.6. Ethics

The study was approved by the Institutional Review Board of the General University Hospital in Prague (IRB00002705).

3. Results

The SUD groups included 383 pregnant women hospitalized with a diagnosis attributed to alcohol (ICD-10 diagnosis F10), 199 to opioids (F11), 69 to cannabis (F12), 216 to sedatives and hypnotics (F13), 28 to cocaine (F14), 258 to stimulants other than cocaine (F15), 29 to hallucinogenic drugs (F16), 23 to inhalants (F18) and 505 to polydrug use (F19 and combination of all other diagnoses). The non-SUD group consisted of 1,511,310 pregnant women.

3.1. Background characteristics of the pregnant women

Maternal sociodemographic and prenatal care characteristics are presented in Table 1. The statistical significance of the differences between the alcohol group, the other SUD groups (*p1*), the SH group, and the other SUD groups (*p2*) is shown.

Overall, women in the various illicit SUD groups (i.e. hospitalized due to opioids, cannabis, cocaine, other stimulants, hallucinogens, inhalants and polydrug use) were younger, larger proportions were not-married, and they had lower levels of education compared to the women in the alcohol and the SH groups. The characteristics of the alcohol and the SH groups were similar to one another, with the exception of the rate of tobacco smoking and illicit drug use, as well as the number of prenatal care visits. Women in the non-SUD group differed in all monitored characteristics from any of the SUD groups. For example, smoking was reported in 38.2 %, 58.0 %, 44.6 % and 50,1% of the opioid, cannabis, other stimulants and polydrug use groups, respectively, compared to 28.2 %, 20.8 % and 5.9 % in the alcohol, SH and non-SUD groups. The mean number of prenatal care visits was 6.5, 6.2, 7.2 and 5.9 in the opioid, cannabis, other stimulants and polydrug use groups, respectively, as compared to 8.8, 10.7 and 11.3 in the alcohol, SH and non-SUD groups (Table 1).

3.2. Neonatal outcomes

Table 2 provides detailed neonatal outcomes information for all the SUD groups and the non-SUD group. The gestational age in illicit SUD groups was shorter by 0.3-0.7 weeks and 1–1.5 weeks when compared with the alcohol and SH groups or the non-SUD group, respectively. Preterm birth was 2–4 times more frequent in the SUD groups when compared to the non-SUD group, and it was more frequent in most illicit SUD groups when compared to the alcohol and SH groups. We also found reduced birth weight in the illicit SUD groups when compared to the alcohol and the SH groups, as well as to the non-SUD group, especially in the opioid, cannabis and inhalants group (approx. minus 400 g as compared to the non-SUD group).

Binary logistic regression models compare SGA in illicit SUD groups with SGA in the alcohol and the SH groups (Table 3) and the non-SUD group (Table 4). We found no significant difference in SGA between the alcohol and illicit SUD groups. No differences were found between the SH group and most of the other SUD groups except alcohol and polydrug use groups, which lost its significance in the adjusted model.

Table 4 shows the effect of adjustment for confounders in models comparing SGA between the SUD groups and the non-SUD group in 3 different adjustment levels. With an increasing level of adjustment, the risk of SGA was reduced. For example, in the polydrug use group, the unadjusted OR was 3.5 (95 % CI = 1.4–2.6 %), and in the first, second and third level of adjustment the OR decreased to 1.9 (1.4–2.4), 1.4 (1.1–1.9) and 1.2 (0.9–1.5), respectively. In the fully adjusted model, the risk of SGA was significantly higher only in the alcohol group (OR = 1.9, 95 % CI = 1.4–2.6 %).

4. Discussion

Women from illicit SUD groups were younger, less frequently married, had lower levels of education, and a higher abortion rate than the women from the alcohol and SH groups. They also started prenatal care later and had fewer prenatal care visits. The alcohol and the SH groups were very similar to each other, except for the higher rate of tobacco smoking and illicit drug use, as well as poorer prenatal care in the alcohol group. The characteristics of the non-SUD group were much better than in all of the SUD groups.

Shorter gestational age, lower birth weight, higher rate of premature birth, and SGA were observed in all of the SUD groups when compared with the non-SUD group. A comparison of SGA within the SUD groups showed no difference between alcohol and any illicit SUD group. However, a higher risk was found in almost all of the SUD groups when compared to the SH group, but the difference was either not significant in the unadjusted analysis or did not remain significant after adjustment.

When compared with the non-SUD group, the risk of SGA was elevated in unadjusted analysis in most SUD groups, however, the difference diminished after adjustment except in the alcohol group. This may indicate the substantial role of prenatal alcohol exposure in fetal growth

Table 1
Socio-economic characteristics of substance use disorder (SUD) groups and non-SUD group in the Czech Republic in 2000-2014.

	alcohol			sedatives and hypnotics				opioids					cannabis		
	n	%	95 % CI	n	%	95 % CI	*p1*	n	%	95 % CI	*p1*	*p2*	n	%	95 % CI
Total number	383			216				199					69		
Age, years															
≤24	134	35.0	30.3-40.0	79	36.6	30.2–43.4	0.137	93	46.7	39.7-53.9	< **0.001**	< **0.001**	31	44.9	33.1-57.3
25-29	99	25.8	21.6-30.6	40	18.5	13.7-24.5		59	29.6	23.5-36.6			29	42.0	30.4-54.5
30-34	92	24.0	19.9-28.7	53	24.5	19.1-30.9		39	19.6	14.5-25.9			7	10.1	4.5-20.4
≥35	58	15.1	11.8-19.2	44	20.4	15.3-26.5		8	4.0	1.9-8.1			2	2.9	0.5-11.0
Marital status															
not married	252	65.8	60.8-70.5	126	58.3	51.4-64.9	0.119	162	81.4	75.2-86.4	< **0.001**	< **0.001**	62	89.9	79.6-95.5
married	121	31.6	27.0-36.5	86	39.8	33.3-46.7		27	13.6	9.3-19.3			7	10.1	4.5-20.4
unknown	10	2.6	1.3-4.9	4	1.9	0.6-5.0		10	5.0	2.6-9.3			0	0.0	0.0-5.2
Education															
primary	142	37.1	32.3-42.2	77	35.6	29.3-42.5	0.070	112	56.3	49.1-63.2	< **0.001**	< **0.001**	45	65.2	52.7-76.0
secondary	203	53.0	47.9-58.1	108	50.0	43.2-56.8		78	39.2	32.4-46.4			20	29.0	19.0-41.3
university	14	3.7	2.1-6.2	19	8.8	5.5-13.6		2	1.0	0.2–4.0			1	1.4	0.1-8.9
unknown	24	6.3	4.1–9.3	12	5.6	3.0-9.7		7	3.5	1.5-7.4			3	4.3	1.1-13.0
Abortions															
induced	97	25.3	21.1-30.0	54	25.0	19.5-31.4	0.342	47	23.6	18.0-30.3	**0.040**	0.292	22	31.9	21.5-44.3
spontaneous	74	19.3	15.6-23.7	35	16.2	11.7-22.0		25	12.6	8.4-18.2			13	18.8	10.8-30.4
Use of addictive substances during pregnancy															
smoking	108	28.2	23.8-33.0	45	20.8	15.7-27.0	**0.047**	76	38.2	31.5-45.4	**0.014**	< **0.001**	40	58.0	45.5-69.6
alcohol	x	x	x	3	1.4	0.4-4.3	**x**	11	5.5	2.9-9.9	**x**	**0.02**	7	10.1	4.5-20.4
illicit drugs	34	8.9	6.3-12.3	6	2.8	1.1-6.2	**0.004**	x	x	x	**x**	**x**	x	x	x
Start of prenatal care (weeks), mean (SD)															
	11.8	7.1		11.4	5.5		0.519	11.8	8.2		0.960	0.563	11.8	7.9	
Number of visits during prenatal care, mean (SD)															
	8.8	4.7		10.7	4.0		< **0.001**	6.5	4.9		< **0.001**	< **0.001**	6.2	5.1	

	cannabis		cocaine					other stimulants					hallucinogens		
	p1	*p2*	n	%	95 % CI	*p1*	*p2*	n	%	95 % CI	*p1*	*p2*	n	%	95 % CI
Total number			28					258					29		
Age, years															
≤24	< **0.001**	< **0.001**	13	46.4	28.0-65.8	0.221	0.150	133	51.6	45.3-57.8	< **0.001**	< **0.001**	11	37.9	21.3-57.6
25-29			8	28.6	14.0-48.9			83	32.2	26.6-38.3			11	37.9	21.3-57.6
30-34			2	7.1	1.2-25.0			33	12.8	9.1-17.6			3	10.3	2.7-28.5
≥35			5	17.9	6.8-37.6			9	3.5	1.7-6.7			4	13.8	4.5-32.6
Marital status															
not married	< **0.001**	< **0.001**	21	75.0	54.8-88.6	0.152	**0.028**	223	86.4	81.5-90.2	< **0.001**	< **0.001**	21	72.4	52.5-86.6
married			5	17.9	6.8-37.6			29	11.2	7.8-15.9			6	20.7	8.7-40.3
unknown			2	7.1	1.2-25.0			6	2.3	0.9-5.2			2	6.9	1.2-24.2
Education															
primary	< **0.001**	< **0.001**	13	46.4	28.0-65.8	**0.008**	**0.006**	145	56.2	49.9-65.3	< **0.001**	< **0.001**	12	41.4	24.1-60.9
secondary			8	28.6	14.0-48.9			103	39.9	34.0-46.2			10	34.5	18.6-54.3
university			1	3.6	0.2-20.2			0	0.0	0.0-1.4			0	0.0	0.0-11.9
unknown			6	21.4	9.0-41.5			10	3.9	2.0-7.2			7	24.1	11.0-43.9
Abortions															

(*continued on next page*)

Table 1 (*continued*)

	cannabis		cocaine					other stimulants					hallucinogens		
	p1	*p2*	n	%	95 % CI	*p1*	*p2*	n	%	95 % CI	*p1*	*p2*	n	%	95 % CI
induced	0.926	0.610	7	25.0	11.4-45.2	0.512	0.794	67	26.0	20.8-31.8	**0.030**	0.291	3	10.3	2.7-28.5
spontaneous			4	14.3	4.7-33.6			33	12.8	9.1-14.6			3	10.3	2.7-28.5
Use of addictive substances during pregnancy															
smoking	< **0.001**	< **0.001**	13	46.4	28.0-65.8	**0.041**	**0.003**	115	44.6	38.4-50.9	< **0.001**	< **0.001**	10	34.5	18.6-54.3
alcohol	**x**	**0.001**	0	0.0	0.0-12.3	**x**	**0.53**	7	2.7	1.2-5.7	**x**	**0.318**	1	3.4	0.2-19.6
illicit drugs	**x**	**x**	x	x	x	**x**	**x**	x	x	x	**x**	**x**	x	x	x
Start of prenatal care (weeks), mean (SD)															
	0.999	0.671	13.0	7.0		0.388	0.17	12.9	8.5		0.081	**0.032**	10.9	7.0	
Number of visits during prenatal care, mean (SD)															
	< **0.001**	< **0.001**	8.2	4.6		0.949	**0.021**	7.2	5.1		< **0.001**	< **0.001**	7.0	4.6	

	hallucinogens		**inhalants**					**polydrug use**					**non-SUD**		
	p1	*p2*	**n**	**%**	95 % **CI**	*p1*	*p2*	**n**	**%**	95 % **CI**	*p1*	*p2*	**n**	**%**	95 % **CI**
Total number			23					505					#######-#		
Age, years															
≤24	0.289	0.059	10	43.5	23.9-65.1	**0.015**	**0.001**	245	48.5	44.1-53.0	< **0.001**	< **0.001**	3,01,014	19.9	19.9-20.0
25-29			11	47.8	27.4-68.9			144	28.5	24.7-32.7			5,54,948	36.7	36.6-36.8
30-34			0	0.0	0.0-14.8			77	15.2	12.3-18.8			4,66,198	30.8	30.8-30.9
≥35			2	8.7	1.5-29.5			39	7.7	5.6-10.5			1,86,150	12.3	12.3-12.4
Marital status															
not married	0.232	0.050	16	69.6	47.0-85.9	0.720	0.512	421	83.4	79.8-86.5	< **0.001**	< **0.001**	5,10,295	33.8	33.7-33.8
married			7	30.4	14.1-53.0			51	10.1	7.7-13.1			9,79,047	64.8	64.7-64.9
unknown			0	0.0	0.0-14.8			33	6.5	4.6-9.1			21,968	1.5	1.4-1.5
Education															
primary	**0.002**	**0.001**	13	56.5	34.9-76.1	0.270	0.173	284	56.2	51.8-60.6	< **0.001**	< **0.001**	1,60,015	10.6	10.5-10.6
secondary			9	39.1	20.5-61.2			171	33.9	29.8-38.2			#######-#	66.7	66.6-66.8
university			0	0.0	0.0-14.8			6	1.2	0.5-2.7			2,68,860	17.8	17.7-17.9
unknown			1	4.3	0.2-24.0			44	8.7	6.5-11.6			74,486	4.9	4.9-5.0
Abortions															
induced	0.232	0.413	2	8.7	1.5-29.5	0.776	0.499	129	25.5	21.8-29.6	0.701	0.144	1,86,193	12.3	12.3-12.4
spontaneous			5	21.7	8.3-44.2			105	20.8	17.4-24.6			2,26,856	15.0	15.0-15.1
Use of addictive substances during pregnancy															
smoking	0.470	0.098	12	52.2	31.1-72.6	**0.014**	**0.001**	253	50.1	45.7-54.5	< **0.001**	< **0.001**	89,225	5.9	5.9-5.9
alcohol	**x**	**0.411**	0	0.0	0.0-14.8	**x**	**0.57**	39	7.7	5.6-10.5	**x**	**0.001**	1,743	0.1	0.1-0.1
illicit drugs	**x**	**x**	6	26.1	11.1-48.7	**0.007**	< **0.001**	x	x	x	**x**	**x**	1,999	0.1	0.1-0.1
Start of prenatal care (weeks), mean (SD)															
	0.496	0.610	10.9	4.8		0.558	0.661	12.7	9.2		0.074	0.059	10.3	3.9	
Number of visits during prenatal care, mean (SD)															
	0.052	< **0.001**	8.1	4.3		0.502	**0.003**	5.9	10.2		< **0.001**	< **0.001**	11.3	3.6	

CI - confidence interval.

p1- statistical signifficance difference versus alcohol.

[p2] - statistical signifficance difference verus sedatives and hypnotics.

Table 2
Neonatal outcomes of substance use disorder (SUD) groups and non-SUD group in the Czech Republic in 2000-2014, singleton pregnancies.

	alcohol		sedatives and hypnotics		opioids		cannabis		cocaine		stimulants		hallucinogens		inhalants		polydrug use		non-SUD	
Total number	377		212		195		67		28		255		29		23		498		14,83,626	
Gestational age[a] (weeks), mean (SD)	38.5	2.9	38.6	2.4	37.9	3	37.8	2.7	38.8	1.6	38.3	9.8	38.5	2.9	37.8	3.2	38.0	2.7	39.2	1.8
Birth weight[b] (g), mean (SD)	3,152	483	3,210	455	2,995	439	2,975	423	3,064	486	3,106	451	3,120	219	2,954	520	3,058	487	3,394	452
Preterm birth[a], n (%; CI)	56	(14.9; 11.6–19.0)	23	(10.9; 7.2–16.1)	38	(20.1; 14.8–26.7)	15	(22.7; 13.7–35.0)	3	(10.7; 2.8–29.4)	42	(16.5; 12.3–21.7)	6	(21.4; 9.0–41.5)	3	(13.0; 3.4–34.7)	110	(22.4;18.8–26.4)	86,356	(5.8;5.8–5.9)
SGA[a], n (%; CI)	47	(12.5; 9.4–16.4)	15	(7.1; 4.2–11.7)	24	(12.7; 8.5–18.5)	8	(12.1; 5.7–23.0)	2	(7.1; 1.2–25.0)	31	(12.2; 8.5–17.0)	0	(0.0; 0.0–12.3)	4	(17.4; 5.7–39.5)	60	(12.2; 9.5–15.5)	58,253	(3.9;3.9–4.0)

[a] live births.
[b] gestational age ≥37 weeks.

restriction. Adjustment for different confounders showed the critical role of sociodemographic factors and prenatal care (a factor representing disorganized lifestyle and poorer access to health care) as well as alcohol and tobacco exposure on fetal development. The most harmful effect of alcohol and tobacco within polydrug use leading to growth restriction was observed in another follow-up research (Janisse et al., 2014).

In contrast to several other studies (e.g. El Marroun et al., 2009; Gunn et al., 2016; Hwang et al., 2017; Maeda et al., 2014) we did not observe an increased risk of growth restriction (as indicated by SGA) in the illicit drugs SUD groups after adjustment. A possible explanation for this finding, which is often discussed among the limitations of various studies, is usually a lack of control over possible confounders, especially alcohol and tobacco use, and other factors such as socioeconomic conditions, lifestyle factors including nutrition, psychological distress, or access to healthcare.

A higher prevalence of multiple risk factors is well documented in people who use PS. These factors include poverty, increased psychiatric and somatic comorbidity, poor coping skills, unemployment, homelessness, transport difficulties, intimate partner violence, legal issues, incarceration, poorer healthcare, stigmatization. In this respect substance use in pregnancy represents a marker for multiple risks affecting the pregnancy and neonatal outcomes (Eyler and Behnke, 1999; Friedman et al., 2009; Gyarmathy et al., 2009; Huber and Seelbach-Gobel, 2014; Metz et al., 2012; Shankaran et al., 2007). This complex context represents a challenge for distinguishing the direct effects of PS alone (Gunn et al., 2015).

In a previous study we analyzed the differences in pregnancy and neonatal outcomes between women using PS and the general population, based only on data registered in the NRRH, without linking them with NRIT. We found adverse neonatal outcomes strongly associated with alcohol; however, the associations with illicit drugs were not found, probably because exposure was not consistently recorded and individual illicit drugs could not be distinguished (Nechanska et al., 2012).

4.1. Methodological considerations

Using registry data allows for the comparing of large unselected populations of pregnant women with and without a SUD. However, as with any registry data, there is the risk of misclassification due to incomplete reports and the control over possible confounders is limited to those present in data.

We were able to distinguish different SUD groups related to individual substances, to distinguish SUD related to misuse of multiple substances and to control for use of other substances use as documented in NRRH. However, even though we aimed to filter out the effects of concomitant use of other substances, we cannot exclude that the use of other PS remained undocumented since (as documented also elsewhere) polydrug use pattern is quite prevalent among people with SUD (Davie-Gray et al., 2013; Delano et al., 2013).

Studies on substance use in pregnant women are mostly based on the maternal self-reported data, which brings information bias to the results (Lamy and Thibaut, 2010). In several studies the authors tried to overcome this limitation by analyzing the mother's blood, hair or the newborn's meconium (e.g. Pichini et al., 2005). In our study, we tried to avoid poor recall by defining exposure as a diagnosis of SUD, and combining information from another register. We can assume that individuals diagnosed with a SUD during in-patient care represent a subgroup with the highest exposure to PS (the most "heavy use over time") and with a higher risk of negative consequences than the undiagnosed (Rehm et al., 2013).

On the other hand, although SUD has a recurrent and relapsing nature (West, 2013), pregnancy is a motivation to stop or reduce PS use throughout gestation. Up to over 52 % of women reported that they made behavioral changes because they wanted a healthy baby (Higgins

Table 3
Binary logistic regresion comparing Small for gestational age (SGA) in all substance use disorder (SUD) groups with the alcohol group and the sedatives and hypnotics (SH) group in the Czech Republic in 2000-2014. singleton pregnancies.

SUD groups	All SUD groups versus alcohol group (ref.)						All SUD groups versus SH group (ref.)					
	unadjusted OR	95 % CI	*p-value*	adjusted OR[a]	95 % CI	*p-value*	unadjusted OR	95 % CI	*p-value*	adjusted OR[a]	95 % CI	*p-value*
opioids	1.0	0.6-1.7	0.973	0.9	0.5-1.6	0.693	1.9	1.0-3.7	0.066	1.3	0.5-3.2	0.587
cannabis	1.0	0.4-2.1	0.926	0.9	0.4-2.2	0.855	1.8	0.7-4.5	0.203	0.9	0.2-3.1	0.814
cocaine	0.5	0.1-2.3	0.407	0.4	0.1-1.9	0.236	1.0	0.2–4.6	0.995	0.2	0.0-2.5	0.196
other stimulants	1.0	0.6-1.6	0.888	0.8	0.4-1.3	0.305	1.8	0.9-3.4	0.072	0.9	0.4-2.1	0.785
innhalants	1.5	0.5-4.5	0.501	1.9	0.5-6.8	0.316	2.8	0.8-9.1	0.098	1.5	0.2-8.6	0.678
polydrug use	0.9	0.6-1.4	0.687	0.7	0.5-1.2	0.226	**1.8**	**1.0-3.3**	**0.045**	1.0	0.5-2.1	0.912
alcohol	–	–	–	–	–	–	**1.9**	**1.0-3.4**	**0.043**	1.8	0.9-3.5	0.081
sedatives and hypnotics	**0.5**	**0.3-1.0**	**0.043**	0.6	0.3-1.1	0.081	–	–	–	–	–	–

CI - confidence interval.
[a] adjusted for age. education. marital status. number of prenatal care visits. smoking and alcohol/illicit drugs.

Table 4
Binary logistic regresion comparing Small for gestational age (SGA) in all substance use disorder (SUD) groups with the non-SUD group with three levels of adjustmen in the Czech Republic in 2000-2014, singleton pregnancies.

SUD groups	All SUD groups versus non-SUD group (ref.)							
	unadjusted OR	95 % CI	1. adjusted OR[a]	95 % CI	2. adjusted OR[b]	95 % CI	3. adjusted OR[c]	95 % CI
opioids	**3.5**	**2.3-5.4**	**2.0**	**1.3-3.1**	1.5	1.0-2.4	1.4	0.9-2.1
cannabis	**3.4**	**1.6-7.1**	1.7	0.8-3.6	1.4	0.6-2.8	1.0	0.5-2.2
cocaine	1.9	0.5-7.9	1.1	0.3-4.7	1.0	0.2–4.3	0.7	0.2-3.2
other stimulants	**3.4**	**2.3-4.9**	**1.8**	**1.3-2.7**	**1.5**	**1.0-2.2**	1.2	0.9-1.8
innhalants	**5.1**	**1.7-15.1**	**3.0**	**1.0-8.9**	2.5	0.8-7.6	2.1	0.7-6.3
polydrug use	**3.4**	**2.6-4.4**	**1.9**	**1.4-2.4**	**1.4**	**1.1-1.9**	1.2	0.9-1.5
alcohol	**3.5**	**2.6-4.7**	**2.4**	**1.8-3.3**	**2.1**	**1.6-2.9**	**1.9**	**1.4-2.6**
sedatives and hypnotics	**1.9**	**1.1-3.2**	1.3	0.8-2.2	1.3	0.8-2.2	1.2	0.7-2.0

CI - confidence interval.
[a] adjusted for age, education, marital status.
[b] adjusted for age, education, marital status and number of prenatal care visits.
[c] adjusted for age, education, marital status, number of prenatal care visits, smoking and alcohol/illicit drugs.

et al., 1995), and this includes also a reduction in PS use with or without external help (Brandon, 2014; Ordean and Kahan, 2011). Findings from the Czech Republic also show that most pregnant women using PS substantially reduce their substance use during pregnancy, and that the biggest reduction was reported during the third trimester (Englcová, 2016; Mravčík et al., 2016; Sudíková, 2014). The risk of prenatal exposure to PS is therefore highest in the early stages of pregnancy, especially when an estimated 40 % of all pregnancies (Singh et al., 2010) and over 80 % of pregnancies in women using PS are unintended (Heil et al., 2011).

We cannot exclude the use of PS in the non-SUD group. Nevertheless, we can assume that this group likely contains a large proportion of women without (heavy) substance use. However, it is also possible that a number of pregnant women with undiagnosed SUD or with less severe forms of SUD not leading to in-patient treatment serve as a 'hidden population' within the non-SUD group.

There are large differences in the sociodemographic and lifestyle characteristics between SUD groups and the non-SUD group. Possible variables to look for in lifestyle characteristics are particularly limited in registers. We have used the number of visits of prenatal care as a proxy for assuming that the lower number of prenatal visits indicates less favorable social, cultural and health-related conditions (Feijen-de Jong et al., 2012; Funkhouser et al., 1993). The reduction of the risk of SGA in SUD groups after adjusting for this proxy indicates the relevance of this assumption.

In this study, the number of pregnant women in the different SUD groups varied. Consequently, the power to detect significant results varied as well, and thus careful interpretation is necessary when comparing the effects in different SUD groups. The alcohol and polydrug use groups were the largest groups and thus statistically significant differences in these groups were more likely to be detected than those in other groups.

5. Conclusions

We observed worse socioeconomic situations, poorer pregnancy care, and a higher risk of fetal growth restriction (as indicated by SGA) among women hospitalized with a SUD during pregnancy when compared to women without a SUD. The rather strong influence of confounders showed the important role of sociodemographic and lifestyle factors acting in complex relationships with substance use. It is clear, however, that SUD represents an important risk factor, which should be screened in pregnant women during prenatal care. If SUD is diagnosed, a range of interventions should be offered targeting not only the substance use itself, but also the unfavorable socioeconomic and lifestyle factors.

Contributions

VM, RG, MH, SS contributed to the design of the study, BM and SS processed the data, all authors contributed to the data analysis, VM drafted the concept of the paper, all authors commented on and contributed to the final form of the paper.

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Declaration of Competing Interest

None declared.

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