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Cannabis Use during Pregnancy and Risk of Adverse Birth Outcomes: A Longitudinal Cohort Study

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Abstract
Background: With recent changes in legislation regulating recreational and medical cannabis use around the globe, increased use in pregnancy is to be expected. ***Objectives:*** To investigate the association between cannabis use during pregnancy and birth outcomes. ***Method:*** Data from the Norwegian Mother and Child Cohort Study (MoBa), a prospective pregnancy cohort, were used. Participants were recruited from all over Norway between 1999 and 2008: 9,312 women with 10,373 pregnancies who reported use of cannabis before or in pregnancy. Women reported on their illegal drug use before pregnancy and at pregnancy weeks 17/18 and 30 and at 6 months postpartum. Linear regression was used to estimate crude and adjusted effects of prenatal cannabis exposure on birth outcomes. ***Results:*** In 10,101 pregnancies, women had used cannabis before pregnancy but not during pregnancy. In 272 pregnancies, women had used cannabis during pregnancy, and among these, in 63 pregnancies, women had used cannabis in at least 2 periods. In adjusted analyses for potential confounders, only cannabis use during at least 2 periods of pregnancy showed statistically significant effects on birth weight. The effect was observed in the complete cohort ($B = -228$ g, 95% CI = −354 to −102, $p < 0.001$) and for the subgroup where information about the child's father was available ($B = -225$ g, 95% CI = −387 to −63, $p = 0.01$). Our results may indicate that prolonged use causes more harm, whereas short-term use did not indicate adverse effects on birth outcomes. ***Conclusions:*** There was a statistically significant and clinically relevant association between the use of cannabis during pregnancy and reduced birth weight. Clinicians should screen not only for cannabis use but also for the length and intensity of use as part of a comprehensive substance use screening.

Introduction

Cannabis is one of the most frequently used recreational drugs in the world, with a yearly prevalence from 1 to 9% in different countries, with highest use in adolescents and young adults [1]. While men tend to use the drug more frequently and become addicted more often

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than women [2], female use is increasing [3]. Rates of cannabis use among pregnant women are increasing just as fast as among nonpregnant women of reproductive age [4]. In 2015, the American College of Obstetricians and Gynecologists issued a committee opinion discouraging physicians from suggesting use of cannabis during preconception, pregnancy, and lactation.

With changes in legislation regulating recreational cannabis use around the globe in the last decade, increased use is to be expected [5, 6]. The changing public discourse may also support the tendency to view cannabis as a relatively safe drug [7]. Furthermore, cannabis is also used as a medication to pregnant women [8, 9], which might contribute to the drug seeming more harmless and to increased use [10]. Contemporary cannabis products contain more Δ-9-tetrahydrocannabinol than the products previously studied [11] and may infer a higher risk of adverse effects. With the increasing use of higher potency cannabis, there is a need for new research for public health policies to provide evidence-based advice about risks associated with cannabis use during pregnancy.

Most women quit using cannabis when they get pregnant [12], but about 3–4% of pregnant women in the US and southern Europe have reported cannabis use in pregnancy [13, 14]. In general, women who do not abstain from cannabis in pregnancy are also engaged in other risky behaviors such as alcohol and tobacco use [12]. Cannabis use during pregnancy raises concerns because prenatal cannabis exposure may be associated with adverse birth outcomes [15–19]. Some studies have demonstrated decreased birthweight and/or fetal growth after cannabis exposure while others have failed to find such differences [13, 18]. Referring to another systematic review and meta-analysis [20], adverse birth outcomes associated with maternal cannabis use appear to be attributable to concomitant tobacco use and other confounding factors. Adjustment for tobacco and other confounding factors was not performed in the meta-analysis by Gunn et al. [15]. In the "Generation R" Study, data on fetal growth obtained by ultrasounds showed that cannabis use during pregnancy was associated with growth restrictions in mid- and late pregnancy [21]. Furthermore, a meta-analysis [15] concluded that infants exposed in utero to cannabis had lower birth weight, but not shorter birth length or smaller head circumference. Similarly, studies of the association between cannabis use and preterm birth have shown mixed results [17, 22]. Current evidence does not suggest an association between cannabis exposure and any specific congenital birth defect, while data regarding the association between stillbirth and cannabis use are still scarce [17].

Most of the studies mentioned above have limitations. Earlier studies on cannabis and birth outcomes have been retrospective and did not possess information about important confounders such as mental health problems, socioeconomic and educational factors and have not been able to adjust for use of other substances including tobacco, alcohol, other illicit or prescribed drugs [19]. Further, in most studies, information about paternal characteristics or relevant comparison groups is not included. However, recent research suggests that regular use of cannabis in men causes epigenetic changes in sperm cells [23], and paternal cannabis use during pregnancy has, potentially, further epigenetic effects [24]. Studying effects of paternal cannabis use during pregnancy is encouraged [25].

When studying the possible adverse effects of prenatal cannabis use on children, it is an advantage to include a relatively large and homogeneous population and to be able to control for polysubstance use and other confounding factors. In the current study, we used data from the Norwegian Mother and Child Cohort Study (MoBa), a large prospective population-based pregnancy cohort with information from both parents [26, 27]. We aimed to describe the sociodemographic characteristics of women who used cannabis during pregnancy and assess if there is an association between cannabis use during pregnancy and adverse birth outcomes. We compared children of women who used cannabis during pregnancy with children of previous users of cannabis in unadjusted analyses and models adjusted for important confounders.

Materials and Methods

The Norwegian Mother and Child Cohort Study

MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 41% of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers, and 75,200 fathers. The invited women reported by responding to questionnaires at gestational weeks 17/18 and 30 and 6 months postpartum. Information from fathers was obtained at week 17/18 of pregnancy. Some of the information in MoBa was obtained from the Medical Birth Registry of Norway (MBRN), a national health registry containing information about all births in Norway [28]. It includes information on pregnancy, delivery, and neonatal health. The attending physician and midwife collected medical information during delivery, which is recorded in the MBRN. All MoBa questionnaires are available at the Norwegian Institute of Public Health's website (https://www.fhi.no/en/sys/search-result/?term=MoBa+questionnaires#).

Study Population

This study was based on data from pregnant women who participated in MoBa and their children (data file version 8). Children from pregnancies with multiple fetuses and pregnancies with incomplete questionnaires when cannabis use in pregnancy was to be reported were excluded. After exclusion, the population consisted of 74,641 pregnancies in 65,412 women. Women who had a history of cannabis use may differ from women who never used cannabis regarding many risk factors. A comparison between "use during pregnancy" versus "never use" could thus be biased due to unmeasured confounding. In order to reduce this problem, in our analyses, we included only pregnancies where women reported use of cannabis before pregnancy and/or during pregnancy. The study population hence consisted of 9,312 women with 10,373 pregnancies. The study was approved by the Regional Committee for Medical Research Ethics (2015/1343).

Self-Report of Cannabis Use

The women answered questions regarding illegal drug use at pregnancy weeks 17/18 and 30 and 6 months postpartum. The 3 questionnaires covered use earlier in life, use during the last month before pregnancy, use during 3 time periods during pregnancy (before week 17/18, between weeks 17/18 and 30, and after week 30), and use after birth. The women provided information about their hashish, amphetamine, ecstasy, cocaine, and heroin use during these time periods. The use of cannabis was defined as use of hashish since in Norway hashish was traditionally the only cannabis product available.

The use of cannabis during 1 period was defined as curtailed use, and the use of cannabis during 2 or more periods was defined as prolonged use. The use of cannabis earlier in life or last month before pregnancy but not during pregnancy was defined as previous use.

Birth Outcomes

Information on birth weight, birth length, head circumference, preterm birth (<37 weeks of gestation), malformations, and Apgar score after 1 and 5 min was obtained from the MBRN. Small for gestational age was calculated after Marsál et al. [29]. The length of pregnancy was mainly determined from the estimated pregnancy start date based on ultrasound. For pregnancies in which no ultrasound was performed, the start of pregnancy was set to the first day of the last menstrual period.

Possible Confounders, Mediators, and Effect Modifiers

Information on factors that could be associated with cannabis use during pregnancy, for example, maternal age, marital status, parity, and body mass index (kg/m^2), was retrieved from the MBRN. Information about the level of education, whether the pregnancy was planned, and the working status during pregnancy was retrieved from the first pregnancy questionnaire. The 5-item version of the Hopkins Symptom Checklist (HSCL-5 of the HSCL-90) was used to assess symptoms of anxiety or depression. A description of the assessment has been described elsewhere [30]. Symptoms of anxiety or depression were assessed during pregnancy weeks 17/18 and 30. In the first questionnaire, mothers also reported on their lifetime history of major depression by answering the lifetime occurrence of 5 key depressive symptoms from the symptomatic criteria for Major Depression in the Diagnostic and Statistical Manual of Mental Disorders [30]. The two pregnancy questionnaires and the 6-month postpartum questionnaire also included questions on other substance use during pregnancy: tobacco smoking, alcohol intake, and use of prescribed opioids and benzodiazepines and illegal drugs other than cannabis. The mothers' answer on all the 3 questionnaires were used to categorize all these variables. Tobacco smoking during pregnancy was categorized as no, sometimes, and daily. To fall into the no tobacco use group, the woman had to respond not smoking in all three questionnaire periods. Similarly, to be considered a daily smoker, the woman had to answer daily smoking in all three questionnaire periods. All remaining women who responded smoking at any time comprised the sometimes group. Alcohol intake during pregnancy was categorized as never, sometimes, and regular/binge. To be defined as a pregnant woman who never used alcohol, the woman must have answered never using alcohol in all three questionnaire periods. To be defined in the regular/binge group, the woman had to report drinking regularly or drinking 5 units or more on one occasion in at least one of the three questionnaire periods. The rest of the women reporting some alcohol use comprised the sometimes group.

The Child's Father

Information about the father's age was retrieved from the MBRN [31]. Information about education was self-reported by the mother, and information about symptoms of anxiety and depression was retrieved from the father questionnaire. Fathers also reported on illegal drug use earlier in life, during the last 6 months before their partner became pregnant, and during the first 17/18 weeks of the pregnancy. Fathers' smoking during pregnancy was reported by both the father and the mother. The information was coded as "yes" if any of them reported smoking.

Analysis Strategy and Statistical Methods

The study population of pregnant women was divided into 3 mutually exclusive groups according to self-reported use of cannabis:

1. Previous use: cannabis before pregnancy (lifetime and/or the last month before pregnancy, but not during pregnancy).
2. Curtailed use: cannabis during 1 period in pregnancy.
3. Prolonged use: cannabis during at least 2 periods in pregnancy.

Groups 2 and 3 could also include the use of cannabis before pregnancy. Potential confounders were identified a priori based on the published literature. We summarized and analyzed (χ^2 analysis) maternal and paternal characteristics for each of the 3 groups (Table 1). Mean values, standard deviations, and proportions for different birth outcomes for each of these 3 groups were calculated (Table 2). Descriptive analysis (linear regression and χ^2 analysis) showed that there were statistically significant differences in the neonatal growth parameters (weight [$p < 0.001$], length [$p = 0.008$], and head circumference [$p = 0.031$]) between the 3 cannabis groups.

Based on the results from these analysis, linear regression was used to estimate adjusted effects of prenatal cannabis exposure on weight, length, and head circumference (Table 3). We adjusted for the following covariates: maternal age, education, parity, alcohol use during pregnancy, presence of symptoms of anxiety/depression, tobacco smoking in pregnancy, use of illicit drugs, use of prescribed medications during pregnancy (opioids and benzodiazepines), work situation, planned pregnancy, and sex. We did not include depression before pregnancy because of the high correla-

Table 1. Parental characteristics by maternal use of cannabis before and during pregnancy. Participants of the Norwegian Mother and Child Cohort Study (*N* = 10,373 singleton pregnancies)

	Group 1 previous use of cannabis, but not used during pregnancy *n* (%)	Group 2 cannabis use 1 period in pregnancy (short-term users) *n* (%)	Group 3 cannabis use at least 2 periods in pregnancy (long-term users) *n* (%)	*p* value
n	10,101 (97.4)	209 (2.0)	63 (0.6)	
Maternal education, higher[a] (*N* = 10,326)				
No	3,567 (35.5)	119 (56.9)	37 (60.7)	<0.001
Yes	6,579 (65.4)	90 (43.1)	24 (39.3)	
Paternal education, higher (*N* = 9,991)				
No	4,616 (47.4)	129 (67.2)	44 (73.3)	<0.001
Yes	5,123 (52.6)	63 (32.8)	16 (26.7)	
Maternal age in years (*N* = 10,316)				
<25	1,608 (16.0)	77 (37.0)	20 (31.7)	<0.001
25–29	3,477 (34.6)	70 (33.7)	24 (38.1)	
30–34	3,604 (35.9)	39 (18.8)	12 (19.0)	
≥35	1,356 (13.5)	22 (10.6)	7 (11.1)	
Paternal age in years (*N* = 10,223)				
<25	796 (8.0)	36 (17.6)	10 (15.9)	<0.001
25–29	2,650 (26.6)	63 (30.7)	22 (34.9)	
30–34	3,748 (37.7)	56 (27.3)	22 (34.9)	
≥35	2,761 (27.7)	50 (24.9)	9 (14.3)	
Planned pregnancy (*N* = 10,277)				
No	2,895 (28.9)	113 (55.7)	35 (57.4)	<0.001
Yes	7,118 (71.1)	90 (44.3)	26 (42.6)	
Maternal tobacco smoking in pregnancy (*N* = 8,038)				
No	6,315 (80.6)	81 (54.4)	15 (27.3)	<0.001
Sometimes	1,039 (13.3)	46 (30.9)	20 (36.4)	
Daily	480 (6.1)	22 (14.8)	20 (36.4)	
Paternal tobacco smoking in pregnancy (*N* = 9,991)				
No	6,015 (59.6)	64 (30.6)	13 (20.6)	<0.001
Yes	4,086 (40.5)	128 (61.2)	47 (74.6)	
Maternal use of illegal drugs (other than cannabis) (*N* = 6,106)				
No	3,374 (57.0)	21 (14.7)	2 (4.4)	<0.001
Yes, earlier to pregnancy	2,522 (42.6)	80 (55.9)	38 (84.4)	
Yes, in pregnancy	22 (0.4)	42 (29.4)	5 (11.1)	
Paternal use of illegal drugs (*N* = 7,662)				
No	3,154 (42.1)	28 (22.4)	3 (6.4)	<0.001
Yes, earlier	3,406 (45.5)	31 (24.8)	8 (17.0)	
Yes, last 6 months before pregnancy	782 (10.4)	56 (44.8)	25 (53.2)	
Yes, in pregnancy	148 (2.0)	10 (8.0)	11 (23.6)	
Maternal alcohol intake in pregnancy (*N* = 10,183)				
Never	2,997 (30.2)	41 (20.3)	12 (19.0)	<0.001
Sometimes	4,373 (44.1)	82 (40.6)	23 (36.5)	
Regularly/binge	2,548 (25.7)	79 (39.1)	28 (44.4)	
Maternal analgesic opioids use in pregnancy (*N* = 10,373)				
No	9,846 (97.5)	197 (94.3)	56 (88.9)	<0.001
Yes	255 (2.5)	12 (5.7)	7 (11.1)	
Maternal benzodiazepines[b] use in pregnancy (*N* = 10,373)				
No	9,924 (98.3)	193 (92.3)	57 (90.5)	<0.001
Yes	177 (1.8)	16 (7.7)	6 (9.5)	
Parity (*N* = 10,316)				
0	5,753 (57.3)	156 (75.0)	35 (55.6)	<0.001
1	3,156 (31.4)	33 (15.9)	19 (30.2)	
≥2	1,136 (11.3)	19 (9.1)	9 (14.3)	

Table 1 (continued)

	Group 1 previous use of cannabis, but not used during pregnancy *n* (%)	Group 2 cannabis use 1 period in pregnancy (short-term users) *n* (%)	Group 3 cannabis use at least 2 periods in pregnancy (long-term users) *n* (%)	*p* value
Marital status (*N* = 10,316)				
Married or living with partner	9,235 (91.9)	161 (77.4)	55 (87.3)	<0.001
Others	810 (8.1)	47 (22.6)	8 (12.3)	
Maternal BMI (*N* = 10,133)				
<25	7,304 (74.0)	147 (73.9)	54 (85.7)	0.530
25–29	1,834 (18.6)	36 (18.1)	7 (11.1)	
30–34	528 (5.4)	12 (6.0)	2 (3.2)	
≥35	205 (2.1)	4 (2.0)	0 (0)	
Maternal depression before pregnancy[c] (*N* = 10,001)				
No	8,529 (87.7)	178 (89.0)	45 (73.8)	<0.001
Yes	1,201 (12.3)	22 (11.0)	16 (26.2)	
Maternal symptoms of anxiety and depression during pregnancy[d] (*N* = 9,216)				
No	7,100 (79.1)	112 (63.3)	31 (50.0)	<0.001
Yes, short term	1,381 (15.4)	43 (24.3)	17 (27.4)	
Yes, long term	496 (5.5)	22 (12.4)	14 (22.6)	
Paternal symptoms of anxiety and depression during pregnancy[c] (*N* = 8,643)				
No	8,092 (95.5)	111 (88.1)	39 (86.7)	<0.001
Yes	380 (4.5)	15 (11.9)	6 (13.3)	
Working status (*N* = 10,322)				
Working	9,022 (89.8)	159 (76.4)	48 (77.4)	<0.001
Not working	718 (7.1)	35 (16.8)	10 (16.1)	
Disability pensioner	143 (1.4)	7 (3.4)	4 (6.5)	
Others	169 (1.7)	7 (3.4)	0 (0)	

[a] Completed or on-going college or university degree. [b] Benzodiazepines and benzodiazepines-like (a class of drugs with similar pharmacodynamics and different chemical structures to benzodiazepines) drugs. [c] Assessment was done in week 17–18. [d] Symptoms of anxiety and depression were assessed in pregnancy weeks 17–18 or 30 (short term) or 17–18 and 30 (long term) by the 5-item version of the Hopkins Symptom Checklist. Cutoff 2.0 was chosen.

tion between this variable and maternal symptoms of anxiety and depression during pregnancy. Neither did we include marital status because the distribution between the two categories of this variable was not consistent throughout the three cannabis groups. We used clustered robust variance estimators for 95% confidence intervals to account for clustering among mothers with multiple pregnancies.

We examined the robustness of our findings in a set of additional analyses:

1. 41.1% of information about maternal use of other illegal substances and 22.5% of smoking information were missing. To account for missingness of these important confounders, we have performed multiple imputation using chained equations (mi impute chained command in STATA) and included the following covariates as potential predictors of the missing values: maternal age, education, parity, alcohol use during pregnancy, presence of symptoms of anxiety/depression, tobacco smoking in pregnancy, use of illicit drugs, use of prescribed medications during pregnancy (opioids and benzodiazepines), work situation, planned pregnancy, and sex. Combined results from 10 imputation sets are presented.
2. We used propensity scores to address imbalances in baseline confounder distributions between prolonged users and discontinuers, and curtailed users and previous users, separately. In logistic regression models, we estimated the probability of using cannabis in pregnancy (separately for short- and long-term use), conditional on the confounders used in adjusted models described above. We used inverse probability of treatment weighting (IPTW) approaches based on the propensity score to estimate the average effect of cannabis and assessed the balance of baseline characteristics in the weighted population using the standardized mean difference, with 0.15 as a cutoff for evidence of imbalance. In a rare case, when we were not able to achieve <0.15 standardized mean difference between covariates in weighted populations, the covariates were added to a final weighted model.
3. Not all pregnancies had information from both parents. Additional analyses were performed in the pregnancies, which also included paternal information. In these analyses, the characteristics of the father were also included as confounders in the adjusted analysis.

Statistical analyses were conducted using SPSS for Windows, 20.0; SPSS Inc., Chicago, IL, and STATA 14.

Table 2. Descriptive statistics for cannabis use and birth outcome among participants in the Norwegian Mother and Child Cohort Study (MoBa)

	Use of cannabis		
	group 1 previous use of cannabis, but not used during pregnancy, *n* = 10,101	group 2 cannabis use 1 period in pregnancy only (curtailed use), *n* = 209	group 3 cannabis use at least 2 periods in pregnancy (prolonged use), *n* = 63
Birth weight, g, mean (SD)	3,564 (588)	3,449 (560)	3,377 (438)
Birth length, cm, mean (SD)	50.2 (2.8)	49.7 (2.7)	49.7 (2.9)
Head circumference, cm, mean (SD)	35.2 (1.9)	35.0 (1.9)	34.7 (1.2)
Gestational length, week, mean (SD)	39.5 (2.3)	39.3 (2.7)	39.2 (1.6)
Apgar score, 1 min, mean (SD)	8.6 (1.3)	8.5 (1.8)	8.6 (1.5)
Apgar score, 5 min, mean (SD)	9.4 (1.0)	9.3 (1.4)	9.4 (1.0)
Placements in neonatal intensive care unit, *n* (%)	764 (7.9)	23 (11.9)	5 (8.1)
Preterm birth, *n* (%)	528 (5.3)	18 (8.7)	4 (6.3)
Malformation, *n* (%)	524 (5.2)	11 (5.3)	4 (6.3)
Small for gestational age, *n* (%)	218 (2.2)	4 (1.9)	1 (1.6)

SD, standard deviation.

Table 3. Linear regression models for birth weight, head circumference, and birth length outcomes predicted by cannabis exposure during pregnancy

	Curtailed use versus previous use of cannabis, but not used during pregnancy[a]			Prolonged use versus previous use of cannabis, but not used during pregnancy[b]		
	B	95% CI	*p* value	*B*	95% CI	*p* value
Birth weight						
Cannabis in pregnancy – unadjusted[c]	−57	−166 to 53	0.31	**−334**	**−507 to −160**	**<0.001**
Cannabis in pregnancy – adjusted[d]	12	−88 to 112	0.82	**−228**	**−354 to −102**	**<0.001**
Birth length						
Cannabis in pregnancy – unadjusted[c]	−0.5	−0.9 to 0.0	0.07	**−1.0**	**−1.8 to −0.2**	**0.01**
Cannabis in pregnancy – adjusted[d]	−0.1	−0.7 to 0.5	0.75	−0.5	−1.6 to 0.6	0.41
Head circumference						
Cannabis in pregnancy – unadjusted[c]	−0.1	−0.4 to 0.3	0.74	**−0.6**	**−1.2 to −0.1**	**0.03**
Cannabis in pregnancy – adjusted[d]	0.2	−0.2 to 0.5	0.30	−0.4	−0.8 to 0.1	0.07

[a] *N* = 4,981 for birth weight; *N* = 4,797 for birth length; *N* = 4,895 for head circumference. [b] *N* = 4,922 for birth weight; *N* = 4,736 for birth length; *N* = 4,838 for head circumference. [c] The crude regression analyses were restricted to the same study sample as in the adjusted analysis. [d] Adjusted for a set of confounders: maternal age, education, parity, alcohol use during pregnancy (never, sometimes, and regular/binge), presence of symptoms of anxiety/depression, tobacco smoking in pregnancy (never, sometimes, and daily), use of illicit drugs, use of prescribed medications during pregnancy (opioids and benzodiazepines), work situation, planned pregnancy, and sex.

Results

Table 1 shows baseline maternal characteristics according to cannabis use before and during pregnancy. In total, 10,101 women reported cannabis use before pregnancy (previous use) and 272 women reported cannabis use during pregnancy. In 209 of pregnancies, the woman had used cannabis during only 1 period (curtailed use), while use in at least 2 periods was reported in 63 pregnancies (prolonged use).

Table 4. Linear regression models for birth weight, head circumference, and birth length outcomes predicted by cannabis exposure during pregnancy

	Prolonged use versus previous use of cannabis, but not used during pregnancy		
	B	95% CI	*p* value
Birth weight			
Cannabis in pregnancy – adjusted	**−153**	**−262 to −42**	**0.01**
Birth length			
Cannabis in pregnancy – adjusted	−0.3	−1.1 to 0.5	0.47
Head circumference			
Cannabis in pregnancy – adjusted	**−0.3**	**−0.7 to 0.0**	**0.05**

Multiple imputation on variables tobacco smoking and use of illicit drugs during pregnancy used. $N = 8{,}652$ for birth weight; $N = 8{,}332$ for birth length; $N = 8{,}509$ for head circumference. Adjusted for a set of confounders: maternal age, education, parity, alcohol use during pregnancy (never, sometimes, and regular/binge), presence of symptoms of anxiety/depression, tobacco smoking in pregnancy (never, sometimes, and daily), use of illicit drugs, use of prescribed medications during pregnancy (opioids and benzodiazepines), work situation, planned pregnancy, and sex.

Parental Characteristics

The proportion of women with higher education was markedly higher in the group of women who only used cannabis before pregnancy (65.4%) and a similar pattern was seen for fathers (52.6%) (Table 1). In addition, the majority (71.1%) of pregnancies in this group were planned, in contrast to low proportions of planned pregnancies among women with curtailed cannabis use (44.3%) and with prolonged cannabis use (42.6%) during pregnancy.

Women who used cannabis during pregnancy were more likely to use other illegal and prescribed drugs during pregnancy and to have partners with a similar pattern of drug use. These women were also more likely to smoke while pregnant, a lower proportion who abstained from drinking during pregnancy, and the proportion of binge drinking was higher, compared to women who used cannabis before pregnancy.

The proportion of women who reported depression before to pregnancy was high in all the cannabis groups. Women who used cannabis during pregnancy were more likely to report long-term symptoms of depression or anxiety during pregnancy than women who did not (12.4–22.6% vs. 5.5%, respectively).

Birth Outcomes

In Table 2 we present descriptive statistics of birth outcomes according to different cannabis groups. There was a gradual reduction in mean values of birth weight, head circumference, and birth length from the group of women who only used cannabis before pregnancy to the group with curtailed use and further to the group with prolonged use (Table 2). There were no clear patterns for the other birth outcomes.

Table 3 shows the results of linear regression analysis on the growth parameters for short-term and long-term cannabis use during pregnancy. Unadjusted and adjusted analyses suggest unlikely effects of short-term exposure on birth weight, length, and head circumference. For long-term use, our data support the effect on all growth parameters in unadjusted analyses, but after adjustment, the only statistically significant effect was on birth weight ($B = -228$ g, $p < 0.001$).

The observed effects of prolonged cannabis use on the birth weight of the newborn stayed consistent where we accounted for missingness (Table 4) and when we used IPTW approaches (Table 5). Results were also similar for the subgroup of women where information about the child's father was available (Table 6). When information about the father was included in combination with maternal characteristics in the analysis, prolonged cannabis use showed effects on birth weight in the same order of magnitude as when only maternal characteristics were included in the adjusted analysis ($B = -225$ g, $p = 0.01$). An effect on birth length was also observed in children of women with prolonged use ($B = -1.4$, $p = 0.01$) (Table 6).

Table 5. Linear regression models for birth weight, head circumference, and birth length outcomes predicted by cannabis exposure during pregnancy

	Prolonged use versus previous use of cannabis, but not used during pregnancy		
	B	95% CI	*p* value
Birth weight			
Cannabis in pregnancy – adjusted	**−369**	**−517 to −220**	**<0.001**
Birth length			
Cannabis in pregnancy – adjusted	2.9	−3.3 to 9.2	0.93
Head circumference			
Cannabis in pregnancy – adjusted	−0.6	−1.5 to 0.4	0.25

The propensity score based on maternal characteristics, IPTW approaches used. *N* = 4,922 for birth weight; *N* = 4,736 for birth length; *N* = 4,838 for head circumference. Adjusted for a set of confounders: maternal age, education, parity, alcohol use during pregnancy (never, sometimes, and regular/binge), presence of symptoms of anxiety/depression, tobacco smoking in pregnancy (never, sometimes, and daily), use of illicit drugs, use of prescribed medications during pregnancy (opioids and benzodiazepines), work situation, planned pregnancy, and sex. IPTW, inverse probability of treatment weighting.

Table 6. Linear regression models for birth weight, head circumference, and birth length outcomes predicted by prolonged cannabis exposure during pregnancy

	Prolonged use versus previous use of cannabis, but not used during pregnancy		
	B	95% CI	*p* value
Birth weight			
Cannabis in pregnancy – adjusted[a]	**−225**	**−387 to −63**	**0.01**
Birth length			
Cannabis in pregnancy – adjusted[a]	**−1.4**	**−2.3 to −0.4**	**0.01**
Head circumference			
Cannabis in pregnancy – adjusted[a]	−0.5	−1.1 to 0.2	0.14

Adjustment based on maternal and paternal characteristics. *N* = 3,710 for birth weight; *N* = 3,573 for birth length; *N* = 3,648 for head circumference. [a]Adjusted for a set of confounders: maternal and paternal age and education, parity, alcohol use during pregnancy (never, sometimes, and regular/binge), presence of symptoms of anxiety/depression, maternal (never, sometimes, and daily) and paternal tobacco smoking in pregnancy, maternal and paternal use of illicit drugs, use of prescribed medications during pregnancy (opioids and benzodiazepines), work situation, planned pregnancy, and sex.

Discussion

In this study, children of mothers reporting curtailed cannabis use during pregnancy did not display any of the studied adverse birth outcomes when compared to previous users of cannabis and after adjustment for relevant confounders. However, after maternal prolonged cannabis use, children had a lower mean birth weight of approximately 200 g, even after adjusting for important confounders as for instance smoking.

The association between prolonged maternal use of cannabis during pregnancy and lower birth weight is in accordance with the recent meta-analysis [15]. The reduction in birthweight observed in the present study linked with cannabis use was estimated to be approximately 200 g, which was in the same order of magnitude

as what has been reported in tobacco smoking women [32].

Previous reviews regarding birth length have shown conflicting results [15–17]. Our results were not in line either. We only observed reduced birth length in the smaller subgroup of pregnant women who had a partner who filled in and returned the father's questionnaire making it possible to include paternal characteristics in the analysis. Probably, this population has a better socioeconomic status than women living without partners, and we would expect this group to have fewer other unmeasured confounders that could contribute to reduced birth length. Since this is a smaller and more selected group of individuals, it might, however, be problematic to generalize this finding. Another possible explanation of a smaller effect on length could be that measurement error might be a greater problem when measuring length than weight. Thus, we cannot rule out a possible effect of cannabis also on birth length.

Less than 1% of the women in the study reported cannabis use during pregnancy. Studies from other countries find higher figure [4, 14]. Norwegian women were less likely to use cannabis during pregnancy, or they may have underreported their use. There is, however, the possibility that the participants represent a selected group with higher socioeconomic status and more health-literate behavior compared to pregnant women in Norway in general [33].

Women reporting cannabis use during pregnancy had lower socioeconomic status, used more alcohol, tobacco, and prescribed drugs, and had more psychiatric symptoms compared to women using cannabis before but not during pregnancy. This illustrates the importance of adjusting for all possible confounders that could influence outcome. Clustering of risk by concurrent tobacco, alcohol, and cannabis use in pregnancy is in agreement with previous studies [12, 34, 35]. Specifically, concomitant tobacco use with maternal cannabis use may be attributable to increased adverse birth outcomes and less attributable to cannabis alone [20].

Methodological Consideration

A major strength of this population-based study is the size of the cohort and that the risk of recall bias is minimized by the prospective design. Response to detailed questions regarding lifestyle and health-related and sociodemographic factors allowed adjusting for important potential confounders. We could adjust for paternal characteristics in the analysis. Information about cannabis use both before and during pregnancy was particularly important since this made it possible to distinguish between effects of cannabis use during pregnancy as such and the effects of unmeasured characteristics of the women using cannabis.

The findings should, however, be interpreted with some caution. Firstly, the data on cannabis use were based on self-report, and the questions on illegal drug use have not been validated. In other cohorts, the correspondence between pregnant women's self-reporting of cannabis use and samples of their urine or meconium of their children varies [36–39]. However, any underreporting is expected to have a marginal effect on the risk estimates, as high specificity is more important than sensitivity when the prevalence is low [40]. Underreporting of tobacco smoking is common [41] and may have bias association. A validation study of MoBa compared plasma cotinine with self-reported tobacco smoking and concluded that self-reported tobacco use is a valid marker for use [42]. This also suggests that MoBa participants in fact report risk behavior, suggesting the validity of the cannabis use measures as well.

We lack information on potency/dose and frequency of cannabis use as well as precise information on the duration of cannabis use. Pregnant women reporting curtailed cannabis use (in one period) might, in theory, have used more cannabis or over a more extended period than those who report prolonged use, that is, use in two or more periods. However, women reporting prolonged use during pregnancy are more likely to report using cannabis to manage mood, stress, and morning sickness [38, 39], supporting the idea that they were likely to have consumed more cannabis over time.

The selection of individuals into the MoBa cohort may have introduced bias. Participants in MoBa have been shown to have a healthier lifestyle than the general pregnant population in Norway [33]; for instance, they report lower use of prescribed drugs with abuse potential compared to the whole pregnant population [43, 44]. This may also suggest that MoBa participants are less likely to use cannabis than the general pregnant population. However, a relatively homogeneous population with a healthy lifestyle may prove an advantage when assessing associations since unmeasured confounding is probably reduced.

Cannabis is the most commonly used illegal psychoactive substance, and many young adults have experience with the drug. Rates of cannabis use among pregnant women are increasing [4]. Healthcare providers have an important opportunity to address prenatal cannabis use in the prenatal care setting.

Future research on long-term outcomes is necessary. A challenge to such studies is attrition, and thus cohorts need to heavily invest in reducing participant loss. A possible solution to this challenge is using nationwide registries that are well suited for longitudinal studies [45–47].

Implications

This study indicates that long-term cannabis use in pregnancy results in reduced birth weight of the newborn, a worrying effect since low birth weight may have negative at-birth as well as long-term consequences for the child, such as a risk factor of neonatal and infant death, development of chronic disease, and growth and cognitive disorders [48, 49]. Pregnant women and those considering becoming pregnant should be advised to avoid using cannabis. Clinicians should screen not only for cannabis use but also for the length and intensity of use as part of a comprehensive substance use screening. In addition, pregnant women should be advised that cutting down the use of cannabis during pregnancy is beneficial as opposed to continuous use of cannabis while pregnant.

Conclusion

This study provides evidence of a clinically relevant association between prolonged maternal use of cannabis during pregnancy and reduced birth weight of the newborn. The weight reduction observed was in the same order of magnitude as what has been reported for tobacco smoking during pregnancy. The results may indicate that use over time is necessary to cause harm. These results add to the growing body of evidence of reduced birth weight following cannabis use in pregnancy.

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Statement of Ethics

The establishment and data collection in MoBa was based on a license from the Norwegian Data Protection Agency and approval from the Regional Committee for Medical Research Ethics, and it is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by the Regional Committee for Medical Research Ethics (2015/1343). Written informed consent was obtained from each MoBa participant upon recruitment.

Conflict of Interest Statement

The authors have nothing to declare.

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Author Contributions

Study conception and design: S.S. and M.H. Acquisition of data: S.S. Analysis and interpretation of data: S.S., R.G., R.S., M.M., M.H., J.B., I.L., and E.S. Drafting of the manuscript: R.G., S.S., M.H., and M.M. Critical revision: R.S., E.S., J.B., M.H., M.M., and I.L.

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