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Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications

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ABSTRACT

Widespread legalisation of marijuana raises safety concerns for its use in pregnancy. This study investigated the association of marijuana use prior to and during pregnancy with pregnancy outcomes in a prospective cohort of 5588 nulliparous women from the international SCOPE study. Women were assessed at 15 ± 1 and 20 ± 1 weeks' gestation. Cases [278 Preeclampsia, 470 gestational hypertension, 633 small-for-gestational-age, 236 spontaneous preterm births (SPTB), 143 gestational diabetes] were compared separately with 4114 non-cases. Although the numbers are small, continued maternal marijuana use at 20 weeks' gestation was associated with SPTB independent of cigarette smoking status [adj OR 2.28 (95% CI:1.45–3.59)] and socioeconomic index (SEI) [adj OR 2.17 (95% CI:1.41–3.34)]. When adjusted for maternal age, cigarette smoking, alcohol and SEI, continued maternal marijuana use at 20 weeks' gestation had a greater effect size [adj OR 5.44 (95% CI 2.44–12.11)]. Our data indicate that increasing use of marijuana among young women of reproductive age is a major public health concern.

1. Introduction

A 2015 conference on medical use of marijuana indicated that 23 US states have legalised medical marijuana with some also legalising marijuana for recreational use [1]. Although there is moderate evidence for efficacy of cannabinoids for chronic pain and spasticity [2], and some evidence for Multiple Sclerosis and treatment-resistant epilepsy [3–5], there is not good evidence for its use to treat nausea and vomiting associated with chemotherapy, perhaps the best known indication for medical marijuana [6]. Some pregnant women report using marijuana to alleviate nausea and vomiting in pregnancy with success [7] but evidence for its efficacy is mostly anecdotal. However, reports of adverse events for non-pregnant populations using medical marijuana [6] raise concerns for pregnant marijuana users.

According to the National Drug Strategy Household Survey [8] in Australia, 7.6% of females aged ≥14 years used marijuana during 2010 (1% increase compared to 2007), with 34.8% of the female population having used marijuana at least once in their lifetime. A similar trend has also been observed in New Zealand and Europe, with 47.2% of women aged ≥16 years in NZ (from 2007 to 2008) [9,10], 24.6% in the United Kingdom and 17.5% in Ireland having used marijuana at least once [11].

Apart from reported negative impacts on fetal growth and brain development [12–16], marijuana has been associated with

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adverse pregnancy outcomes, including preterm birth (PTB), small for gestational age (SGA), placental abruption and antepartum haemorrhage [17–21]. Specifically, studies have shown that using marijuana during pregnancy is associated with low birthweight and increases the risk of PTB and SGA, with an odds ratio of at least 1.5 when adjusted for age, BMI and smoking [17,20–22].

The association between marijuana use and pregnancy outcomes is often confounded by other known risk factors including cigarette smoking, body mass index (BMI), and socioeconomic index (SEI) [23,24]. Women who use marijuana also tend to smoke cigarettes and are more likely to use other drugs and alcohol, for whom national statistics [25] have shown that amongst Australian women aged ≥14years who used marijuana in 2010, 82.7% also consumed alcohol, and 68.5% were cigarette smokers, with similar patterns of prevalence in New Zealand [10].

There have been inconsistent results reported from American prospective cohort studies, in which associations of marijuana use with adverse pregnancy outcomes were either found [21,26,27] or not found [28–30]. Hence, this study aimed to examine the association of maternal marijuana use (from pre-pregnancy and up to 20 weeks' gestation) in a multi-centre cohort with major pregnancy complications, amongst both cigarette smokers and non-smokers, controlling for well-known risk factors including age, SEI and BMI, as well as its effects on length of gestation.

2. Methods

Data from this analysis were obtained from the SCreening fOr Pregnancy Endpoints (SCOPE) study, which aimed to build a clinical database and pregnancy biobank to screen candidate markers of pregnancy complications. The SCOPE study recruited nulliparous women with singleton pregnancies between November 2004 and February 2011 from one centre in each of Australia, New Zealand, and Ireland, and three centres in the United Kingdom. Ethical approval was obtained from local ethics committees [New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London, Leeds and Manchester 06/MRE01/98 and Cork ECM5 (10) 05/02/08] and all women provided written informed consent.

Women were invited to participate prior to 15 weeks' gestation when attending hospital antenatal clinics, obstetricians, general practitioners or community midwives, and were interviewed and examined by a research midwife at 15 ± 1 and 20 ± 1 weeks of gestation.

The exclusion criteria included women who were considered to be at high risk of PE, SGA or PTB due to underlying medical conditions (e.g. chronic hypertension requiring antihypertensive medication or diabetes), previous cervical knife cone biopsy, three terminations or three miscarriages or if their pregnancy was complicated by a known major fetal anomaly or abnormal karyotype, or if they received interventions that may modify pregnancy outcome (e.g. aspirin, cervical suture).

Details of maternal age, BMI and socioeconomic index[1] (SEI) [31], medical and family history, along with dietary and lifestyle questionnaires with self-reported marijuana and cigarette smoking were recorded at 15 weeks' and 20 weeks' gestation and entered into an internet-accessed, password-protected centralised database with a complete audit trail (MedSciNet^{AB}, Stockholm, Sweden) [32].

The number of episodes of marijuana use over 3 months was also recorded at 15 weeks and 20 weeks of gestation. Other drug use was also recorded, including cocaine, amphetamines, substance P, Ecstasy, opiates, and hallucinogens, with less than 0.6% of women who have taken these drugs 3 months prior to or during pregnancy in SCOPE, but there were insufficient data to be included for analysis.

Self- reported marijuana and cigarette smoking status were classified into five categories (i.e. never, quit prior to pregnancy, quit prior to 15 weeks' gestation, still using at 15 weeks' gestation, and still using at 20 weeks' gestation) in univariable and multivariable analysis, with 'non-smoking' or 'never used marijuana' as the reference categories. The number of reported episodes of marijuana use was included as a continuous variable for frequency effect estimation. Use was self-reported where women provided the number of joints or cones used.

Spontaneous preterm birth (SPTB) was defined as birth at less than 37 weeks of gestation that was not a result of medical or obstetric intervention. Small for gestational age (SGA) was defined as a birthweight of less than the 10th customised centile, adjusted for maternal height, weight, parity, ethnicity, gestational age at delivery and infant sex. Preeclampsia (PE) was defined as gestational hypertension (GHT) (blood pressure of 140/90 or greater on at least 2 occasions 4 h apart after 20 weeks' gestation) accompanied by proteinuria (300 mg/day or greater, or a spot protein creatinine ratio of 30 mg/mmol creatinine or greater). Gestational diabetes mellitus (GDM) was defined as a fasting glucose of 5.5 mmol/L or higher in a Glucose Tolerance Test, a 2 h level of 8 mmol or higher, or a random glucose level of 11 nmol/L or higher. Universal screening was not employed for GDM in the UK and Ireland, where only women identified at risk based on factors such as family history and BMI were screened.

2.1. Statistical analysis

A total of 5588 participants were included in the analysis, with 1155 participants recruited from Australia, 2014 from New Zealand, 1765 from Ireland, and 654 from the United Kingdom. Within the 1514 pregnancies with complications, 278 had PE, 633 had SGA, 236 had SPTB, 470 had GHT, and 143 had GDM (Fig. 1). Details on age, BMI, SEI, as well as marijuana use and cigarette smoking status were complete for all participants.

Marijuana and cigarette smoking status were compared between non-cases and each of the outcomes separately using Fisher's exact test. Although about 4% of women (n = 232) had more than one pregnancy complication, each outcome was analysed separately compared with non-cases. Continuous factors, including maternal age, BMI and SEI were compared using Student's *t*-test.

To investigate the effects of marijuana use between smokers and non-smokers, analysis of marijuana use, stratified by cigarette smoking status for each outcome was performed. Breslow-Day test was used to assess the homogeneity of the odds of marijuana use between cigarette smokers and non-smokers, along with an adjusted common odds estimated from Mantel-Haenszel test [33,34].

Marijuana and cigarette smoking status were then analysed with mixed effects logistic regression to determine the association with pregnancy outcomes, adjusting for maternal age, BMI and SEI, and with recruiting centre differences accounted for as a random effect. Interaction tests were also performed by comparing logistic regression models that included interaction terms. A linear mixed model was also fitted for length of gestation, with quadratic terms for the number of times marijuana was used over the preceding 3 months at 15 and 20 weeks of gestation, age, and BMI, to investigate the dose effect of marijuana and cigarette smoking status on the length of gestation adjusted for other factors in the model. The estimated power of this analysis, involving logistic regression with interaction terms, is 0.99 [35]. All statistical analyses were performed using R version 3.2.0.

[1] a scale between 10 and 90 generated using an algorithm involving age, income and education. A higher score indicates higher socioeconomic status. It is a validated measure of individual socioeconomic status.

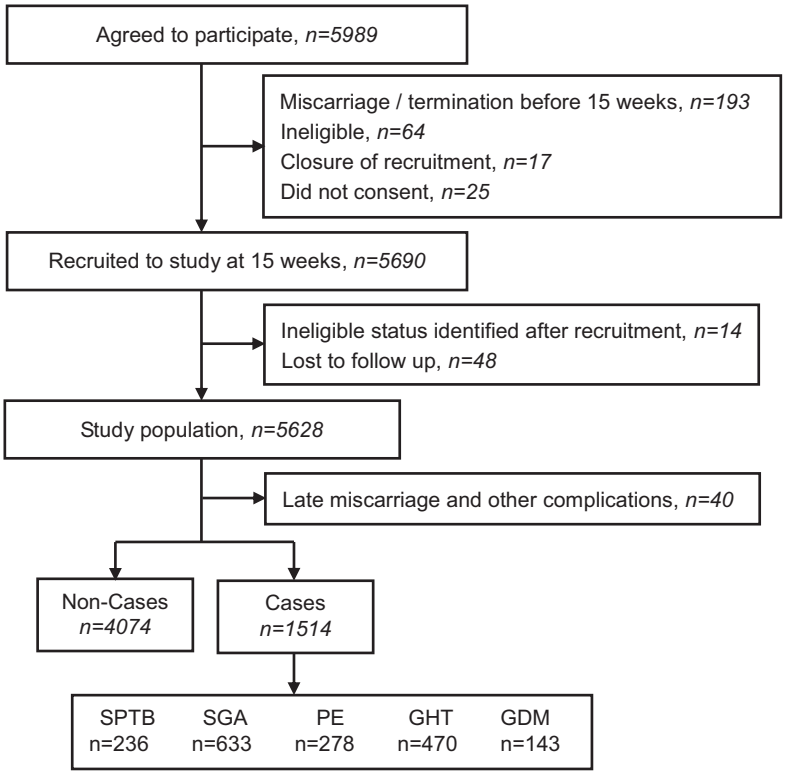

Fig. 1. Participants recruited and study population. Spontaneous preterm birth, SPTB; small for gestational age, SGA; preeclampsia, PE; gestational hypertension, GHT; gestational diabetes mellitus, GDM.

3. Results

Of the 5588 participants, who were predominantly Caucasian (Table 1), the overall proportion of women reporting the use of marijuana before or during pregnancy was 5.6%, with the participating centre in Australia having the highest rate of women using marijuana (11.6%), followed by New Zealand (4.5%), Ireland (3.8%), and United Kingdom (3.7%). Compared to marijuana use, the proportion of cigarette smokers was higher, with an overall 26.4% of women reporting that they smoked cigarettes before or during pregnancy. Amongst Australian participants, 40.8% reported they were cigarette smokers at conception as well as 29.7% of Irish, 29.5% of UK and 14.2% of NZ participants. Country specific demographics are shown in Table 1.

The overall characteristics comparing each of the pregnancy outcomes to non-cases are shown in Table 2. There were significant differences in the average BMI and SEI between non-cases and all outcomes analysed, where BMI was higher in women who developed either PE (27.8 ± 0.38 vs 24.8 ± 0.07 in non-cases; $P < 0.001$), GHT (27.9 ± 0.27; $P < 0.001$), GDM (29.1 ± 0.52; $P < 0.001$), SGA (25.9 ± 0.22; $P < 0.001$) or SPTB (25.4 ± 0.35; $P = 0.035$). Similarly, SEI was lower on average in women with complicated pregnancies including PE (38 ± 0.93 vs 42.5 ± 0.26 in non-cases; $P < 0.001$), GHT (39.7 ± 0.76; $P = 0.001$), GDM (38.9 ± 1.36; $P = 0.011$), and SGA (40.1 ± 0.64; $P = 0.001$). Women who developed PE were also slightly younger on average (27.7 ± 0.34 vs 28.7 ± 0.09 in non-cases; $P = 0.002$), while patients who developed GDM were older (30 ± 0.44; $P = 0.008$).

Marijuana use and cigarette smoking at 20 weeks of gestation were both associated with SGA (18.6% smoking vs only 8.9% in non-cases; $P < 0.001$, and 1.9% marijuana use vs 0.7% in non-cases; $P < 0.005$) and SPTB (16.1% smoking vs 8.9% in non-cases; $P = 0.001$, and 4.7% marijuana use vs 0.7% in non-cases; $P < 0.001$). For both of these outcomes, there was a higher proportion of women who continued to smoke cigarettes or use marijuana at 20 weeks' gestation. In women who delivered a SGA infant, 18.6% continued to smoke cigarettes (compared to 8.9% in non-cases) and 1.9% continued to use marijuana (compared to 0.7% in non-cases), while in women who delivered preterm, 16.1% continued to smoke cigarettes and 4.7% continued to use marijuana at 20 weeks' gestation.

The proportion of women reporting any alcohol consumption (Table 2), from 3 months prior to pregnancy to 20 weeks' gestation, was similar in women who had any complications (less than 77.3%) compared to non-cases (78.6%). Fewer women with SPTB (10.2%; $P = 0.004$), PE (11.5%; $P = 0.002$), and GDM (10.5%; $P = 0.006$) continued to use alcohol at 20 weeks' gestation compared to non-cases (15.2%).

Furthermore, amongst women with SPTB, those who continued to use marijuana at 20 weeks' gestation had a significantly shorter gestation on average of 29.6 ± 1.6 weeks, compared to 34.1 ± 0.3 weeks in those with SPTB who did not use marijuana ($P = 0.005$) (Table 3). The proportion of very early SPTB was also higher, with 36.4% having delivered at less than 28 weeks of gestation and 63.6% at less than 32 weeks in women who continued to use marijuana at 20 weeks' gestation, compared to 4.7% and 15.8% amongst non-users, respectively.

3.1. Interaction between maternal marijuana use and cigarette smoking

It was important to determine whether the association with marijuana use was due to concomitant cigarette smoking. Breslow-Day test showed no evidence of heterogeneity in the association of marijuana use and pregnancy outcomes between smokers and non-smokers ($P = 0.238$), which indicates that the association between marijuana and SPTB was consistent regardless of cigarette smoking status. Hence, when comparing any marijuana use, three months prior to or during pregnancy, between cigarette smokers and non-

Table 1
Country specific demographics.

Variable	Category	Overall (n = 5588)	Australia (n = 1155)	New Zealand (n = 2014)	Ireland (n = 1765)	United Kingdom (n = 654)
		Mean ± SEM N (%)	Mean ± SEM N (%)	Mean ± SEM N (%)	Mean ± SEM N (%)	Mean ± SEM N (%)
Age		28.6 ± 0.1	23.8 ± 0.2	30.4 ± 0.1	29.9 ± 0.1	28.5 ± 0.2
Ethnicity	Caucasian	5061 (89.9)	1067 (91.7)	1707 (84.0)	1733 (97.7)	554 (84.2)
	Maori or Polynesian	116 (2.1)	6 (0.5)	109 (5.4)	0 (0)	1 (0.2)
	Asian	170 (3.0)	42 (3.6)	107 (5.3)	5 (0.3)	16 (2.4)
	Indian	134 (2.4)	4 (0.3)	77 (3.8)	22 (1.2)	31 (4.7)
	Other	147 (2.6)	45 (3.9)	32 (1.6)	14 (0.8)	56 (8.5)
SEI		41.8 ± 0.2	27.8 ± 0.3	47.9 ± 0.3	42.7 ± 0.4	45.4 ± 0.7
BMI		25.3 ± 0.1	27.0 ± 0.2	24.8 ± 0.1	24.9 ± 0.1	25.0 ± 0.2
Alcohol	Yes‡	4387 (78.0)	643 (55.2)	1584 (78.0)	1604 (90.4)	556 (84.5)
	Quit (pre-preg)	877 (15.6)	182 (15.6)	465 (22.9)	154 (8.7)	76 (11.6)
	Quit (<15 wks)	2487 (44.2)	386 (33.2)	886 (43.6)	948 (53.4)	267 (40.6)
	Quit (<20 wks)	178 (3.2)	34 (2.9)	38 (1.9)	90 (5.1)	16 (2.4)
	Yes (at 20 wks)	845 (15.0)	41 (3.5)	195 (9.6)	412 (23.2)	197 (29.9)
Cigarette smoking	Yes‡	1473 (26.4)	471 (40.8)	285 (14.2)	524 (29.7)	193 (29.5)
	Quit (pre-preg)	113 (2.0)	17 (1.5)	40 (2.0)	36 (2.0)	20 (3.1)
	Quit (<15 wks)	699 (12.5)	157 (13.7)	154 (7.7)	294 (16.7)	94 (14.4)
	Quit (<20 wks)	94 (1.7)	41 (3.6)	17 (0.8)	24 (1.4)	12 (1.8)
	Yes (at 20 wks)	567 (10.2)	256 (22.0)	74 (3.7)	170 (9.6)	67 (10.2)
Marijuana	Yes‡	315 (5.6)	134 (11.6)	90 (4.5)	67 (3.8)	24 (3.7)
	Quit (pre-preg)	95 (1.7)	12 (1.0)	45 (2.2)	26 (1.5)	12 (1.8)
	Quit (<15 wks)	145 (2.6)	70 (6.1)	32 (1.6)	35 (2.0)	8 (1.2)
	Quit (<20 wks)	22 (0.4)	14 (1.2)	4 (0.2)	3 (0.2)	1 (0.2)
	Yes (at 20 wks)	53 (1.0)	38 (3.3)	9 (0.5)	3 (0.2)	3 (0.5)
Outcomes	SPTB	236 (4.2)	69 (6.0)	87 (4.3)	56 (3.2)	24 (3.7)
	SGA	633 (11.3)	141 (12.2)	201 (10.0)	190 (10.8)	101 (15.4)
	PE	278 (5.0)	93 (8.1)	85 (4.2)	68 (3.9)	32 (4.9)
	GHT	470 (8.4)	118 (10.2)	114 (5.7)	213 (12.1)	25 (3.8)
	GDM	143 (2.6)	51 (4.4)	38 (1.9)	44 (2.5)	10 (1.5)

‡ Yes = consumed alcohol/smoked cigarette/used marijuana at least once.

smokers, there was a significant independent association between any marijuana use and SPTB (P = 0.001).

While the association between marijuana use and SPTB was independent of smoking status, the Mantel-Haenszel test (Table 5) further indicated that the overall association was also significant (P < 0.001), with an adjusted common odds of 2.28 (95% CI 1.45–3.59). That is, the odds of SPTB for any marijuana use three months prior to or during pregnancy was more than doubled for both cigarette smokers and non-smokers.

Regarding the interaction effect of marijuana in women who ceased cigarette smoking during pregnancy, results from Breslow-Day test on the homogeneity of the odds of any marijuana use (three months prior to or during pregnancy), between women who continued cigarette smoking before 20 weeks' gestation and those who stopped smoking, showed no evidence of heterogeneity (P = 0.541), with a Mantel-Haenszel adjusted odds of 1.97 (95% CI 1.26–3.09). This indicated that the effect of marijuana use was not only independent of any cigarette smoking three months prior to or during pregnancy (as reported above), but was also consistent, with nearly doubled odds, irrespective of whether cigarette smoking ceased prior to 20 weeks' gestation.

Results from Logistic regression with an interaction term between marijuana use and cigarette smoking status also showed no significant interaction effects on SPTB (P = 0.719).

3.2. Interaction between maternal marijuana use and low socio-economic status

Interaction between marijuana use and socio-economic status was also tested, and no significant interaction effect was seen for all pregnancy complications analysed, when added as an interaction term in multivariable models. When comparing low socio-economic status, in the lower quartile (SEI <28), with any marijuana use, Breslow-Day test also showed no evidence of heterogeneity (P = 0.656), indicating that the marijuana association with SPTB was also independent of socio-economic status (adjusted odds 2.17; 95% CI 1.41–3.34).

3.3. Estimated risk

In logistic regression models controlling for maternal age, SEI, cigarette smoking, and alcohol consumption (Table 4), continued

Table 2
Overall demographics for cases vs non-cases.

Variable	Category	Non-Cases (n = 4074) Mean ± SEM N (%)	SPTB (n = 236) Mean ± SEM N (%)	P	SGA (n = 633) Mean ± SEM N (%)	P	PE (n = 278) Mean ± SEM N (%)	P	GHT (n = 470) Mean ± SEM N (%)	P	GDM (n = 143) Mean ± SEM N (%)	P
Age		28.7 ± 0.1	28.3 ± 0.4	0.217	28.6 ± 0.2	0.519	27.7 ± 0.3	***0.002***	28.8 ± 0.3	0.712	30 ± 0.4	***0.008***
SEI		42.5 ± 0.3	40.4 ± 1.1	0.059	40.1 ± 0.6	***<0.001***	38 ± 0.9	***<0.001***	39.7 ± 0.8	***<0.001***	38.9 ± 1.4	***0.011***
BMI		24.8 ± 0.1	25.4 ± 0.4	***0.028***	25.9 ± 0.2	***<0.001***	27.8 ± 0.4	***<0.001***	27.9 ± 0.3	***<0.001***	29.1 ± 0.5	***<0.001***
BMI	<20	310 (7.6)	24 (10.2)	0.054	50 (7.9)	0.138	10 (3.6)	0.362	13 (2.8)	0.116	4 (2.8)	0.509
(cat-	21–25	2187 (53.7)	108 (45.8)	Ref	276 (43.6)	Ref	96 (34.5)	Ref	146 (31.1)	Ref	40 (28.0)	Ref
e-	26–30	1093 (26.8)	68 (28.8)	0.147	188 (29.7)	***0.002***	95 (34.2)	***<0.001***	181 (38.5)	***<0.001***	40 (28.0)	***0.002***
gory)	>30	484 (11.9)	36 (15.3)	***0.040***	119 (18.8)	***<0.001***	77 (27.7)	***<0.001***	130 (27.7)	***<0.001***	59 (41.3)	***<0.001***
Alcohol	Yes	3202 (78.6)	168 (71.2)	–	489 (77.3)	–	192 (69.1)	–	389 (82.8)	–	95 (66.4)	–
	Quit (pre-preg)	639 (15.7)	38 (16.1)	0.195	80 (12.6)	0.063	48 (17.3)	0.147	84 (17.9)	***0.034***	26 (18.2)	0.225
	Quit (<15 wks)	1813 (44.5)	102 (43.2)	***0.044***	278 (43.9)	0.503	104 (37.4)	***0.000***	222 (47.2)	***0.043***	49 (34.3)	***0.001***
	Quit (<20 wks)	130 (3.2)	4 (1.7)	0.075	25 (4.0)	0.519	8 (2.9)	0.216	13 (2.8)	0.814	5 (3.5)	0.454
	Yes (at 20 wks)	620 (15.2)	24 (10.2)	***0.004***	106 (16.8)	0.802	32 (11.5)	***0.002***	70 (14.9)	0.255	15 (10.5)	***0.006***
Smoking	Yes	1024 (25.1)	69 (29.2)	–	213 (33.7)	–	70 (25.2)	–	138 (29.4)	–	34 (23.8)	–
	Quit (pre-preg)	85 (2.1)	3 (1.3)	0.459	7 (1.1)	0.195	4 (1.4)	0.473	16 (3.4)	***0.049***	4 (2.8)	0.597
	Quit (<15 wks)	513 (12.6)	23 (9.8)	0.380	74 (11.7)	0.731	36 (13.0)	0.878	69 (14.7)	0.133	13 (9.1)	0.248
	Quit (<20 wks)	64 (1.6)	5 (2.1)	0.451	14 (2.2)	0.122	6 (2.2)	0.462	9 (1.9)	0.478	2 (1.4)	0.853
	Yes (at 20 wks)	362 (8.9)	38 (16.1)	***<0.001***	118 (18.6)	***<0.001***	24 (8.6)	0.899	44 (9.4)	0.516	15 (10.5)	0.599
Marijuana	Yes	217 (5.3)	27 (11.4)	–	45 (7.1)	–	10 (3.6)	–	21 (4.5)	–	8 (5.6)	–
	Quit (pre-preg)	71 (1.7)	7 (3.0)	0.137	10 (1.6)	0.816	0 (0.0)	0.961	5 (1.1)	0.280	3 (2.1)	0.752
	Quit (<15 wks)	102 (2.5)	7 (3.0)	0.552	18 (2.8)	0.573	8 (2.9)	0.745	14 (3.0)	0.569	3 (2.1)	0.769
	Quit (<20 wks)	14 (0.3)	2 (0.9)	0.202	5 (0.8)	0.104	1 (0.4)	0.979	1 (0.2)	0.637	1 (0.7)	0.492
	Yes (at 20 wks)	30 (0.7)	11 (4.7)	***<0.001***	12 (1.9)	***0.005***	1 (0.4)	0.471	1 (0.2)	0.219	1 (0.7)	0.962

The bold text indicates significant P-values less than 0.05.

Table 3
Gestational age at delivery by marijuana use within SPTB cases.

Marijuana	n	Gestational age (wks) mean ± SEM	P	<28 wks (n = 21)	<32 wks(n = 43)	<37 wks(n = 236)
No	209	34.1 ± 0.3	Reference	16 (4.66%)	33 (15.79%)	209 (100%)
Quit (pre-preg)	7	33.8 ± 1.6	0.934	1 (14.29%)	1 (14.29%)	7 (100%)
Quit (<15 wks)	7	33.8 ± 1.2	0.649	0 (0%)	2 (28.57%)	7 (100%)
Quit (<20 wks)	2	33.4 ± 1.0	0.247	0 (0%)	0 (0%)	2 (100%)
Yes (at 20 wks)	11	29.6 ± 1.6	***0.005***	4 (36.36%)	7 (63.64%)	11 (100%)

The bold text indicates significant P-values less than 0.05.

use of marijuana at 20 weeks' gestation was a significant risk factor for SPTB (OR 5.44; 95% CI 2.44–12.11), but not for any other outcomes analysed. Similarly, as expected, continuing to smoke cigarettes at 20 weeks' gestation was associated with SGA, with an adjusted odds of 3.46 (95% CI 1.31–9.12).

Elevated BMI was a significant risk factor for all outcomes (P < 0.001). By contrast, age was not a significant factor for most pregnancy outcomes assessed except for GDM (OR 1.08; 95% CI 1.05–1.13) and SGA (OR 1.02; 95% CI 1.00–1.04). Consistent with previous studies, higher SEI was a protective factor for PE (OR 0.99; 95% CI 0.98–1.00), with an estimated 1–2% decrease in risk for every unit increase in SEI.

Alcohol consumption after 15 weeks of gestation was a protective factor for SPTB, with an odds of 0.34 (95% CI 0.12–0.97) in women who consumed it after 15 weeks' but quit before 20 weeks' gestation, and an odds of 0.52 (95% CI 0.32–0.86) in women who continued after 20 weeks' gestation. In contrast, alcohol consumption before 15 weeks' gestation was associated with increased risk of GHT, with an odds of 1.80 (95% CI 1.28–2.54) in women who consumed it in the 3 months prior to pregnancy but stopped before pregnancy, and an odds of 1.50 (95% CI 1.11–2.02) when consumed before 15 weeks of gestation. Results from the logistic regression with interaction terms also showed no significant interaction between alcohol consumption and marijuana use for SPTB (P = 0.935).

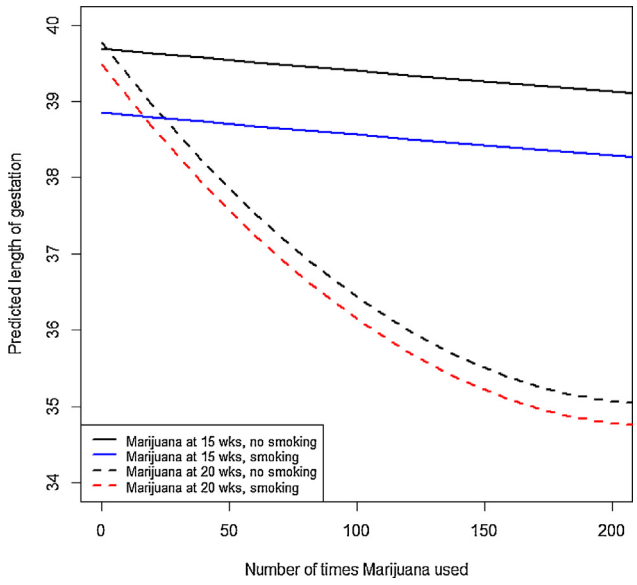

Fig. 2. Predicted length of gestation and number of episodes of marijuana use in women who did or did not also smoke cigarettes in the previous 3 months (adjusted for age, BMI, SEI, cigarette smoking, and alcohol consumption). Note: actual range of marijuana use 0–450 episodes in 3 months.

3.4. Effect on length of gestation

The results from linear mixed modelling showed that marijuana use in first (P = 0.000) or second trimester (P = 0.002) had significant effects on length of gestation, when adjusted for age, BMI, SEI, cigarette smoking status, and alcohol consumption. The predicted length of gestation (Fig. 2) was lower for women who continued to use marijuana at 20 weeks of gestation for both cigarette smokers and non-smokers, with an estimated gestation of less than 37 weeks when more than 100 episodes of marijuana use within the previous three months before 20 weeks' gestation (i.e. more than once per day for the preceding 3 months).

It should be noted that there was a small but significant decrease in the predicted length of gestation for cigarette smokers compared to non-smokers (P = 0.002 at 15 weeks' gestation, and P = 0.006 at 20 weeks' gestation). However, our data show that continued marijuana use at 20 weeks of gestation has a greater effect on gestation irrespective of cigarette smoking status.

Linear mixed modelling (Fig. 2) indicates a modest reduction in gestation in women who ceased marijuana use at 15 weeks' gestation. However, in women who continued to use marijuana at 20 weeks' gestation, there was a much greater decline in gestational age at delivery (Fig. 2; Table 2).

4. Discussion

Marijuana use is increasing in women of reproductive age and its continued use in pregnancy has been of concern for some time [12]. In addition, we have anecdotal evidence to suggest that some pregnant women are using marijuana to reduce nausea in early pregnancy. In this large prospective cohort of nulliparous women we have demonstrated that continued maternal use of marijuana at 20 weeks' gestation is a major contributing risk factor for SPTB. Univariable analysis showed a significant association of marijuana use at 20 weeks' gestation with SPTB and also SGA, but when adjusted for other factors, in particular cigarette smoking, marijuana use was only a significant independent risk factor for SPTB. Furthermore, if marijuana use was continued at 20 weeks' gestation, women were over five times more likely to deliver preterm than nonusers. Of the women who continued to use marijuana at 20 weeks' gestation and delivered preterm, nearly 64% delivered at less than 32 weeks' gestation. Our data do not have sufficient power to determine whether there is a gestational age prior to 20 weeks by which it is advisable to cease marijuana use. Hence, at this stage we recommend that it is prudent to abstain from marijuana use during pregnancy.

Based on the current findings and some earlier reports [17,22,24,36,37], it is likely that maternal marijuana use is an independent risk factor for SPTB. It has been shown that the active compound of marijuana (δ9-tetrahydrocannabinol) and its metabolites are able to cross the placental barrier and thereby have the potential to directly affect perinatal outcomes [38,39]. Whereas the results from this study are in agreement with other studies, it needs to be noted that a few American and a UK prospective cohort studies did not find an association between marijuana use and SPTB [28–30,40]. However, these studies have a higher percentage (>40%) of black race, whereas there are 89.9% Caucasians in this study. Although the studies have also adjusted for ethnicity, age, BMI, and other lifestyle factors, interaction tests were not performed in the analysis to examine the interaction effects of marijuana use and cigarette smoking on pregnancy outcomes.

Table 4
Logistic regression model specifications for SPTB, SGA, PE, GHT, and GDM.

Variable	Category	SPTB Adj Odds‡ (95% CI)	P	SGA Adj Odds‡ (95% CI)	P	PE Adj Odds‡ (95% CI)	P	GHT Adj Odds‡ (95% CI)	P	GDM Adj Odds‡ (95% CI)	P
Age		1.02 (0.99–1.04)	0.307	1.02 (1.00–1.04)	***0.013***	0.98 (0.96–1.01)	0.168	1.01 (0.99–1.03)	0.320	1.08 (1.05–1.13)	***<0.001***
SEI		1.00 (0.99–1.01)	0.555	0.99 (0.99–1.00)	0.052	0.99 (0.98–1.00)	***0.028***	0.99 (0.99–1.00)	0.158	0.99 (0.97–1.00)	0.073
BMI		1.03 (1.00–1.06)	***0.049***	1.04 (1.03–1.06)	***<0.001***	1.10 (1.08–1.13)	***<0.001***	1.12 (1.10–1.14)	***<0.001***	1.13 (1.10–1.16)	***<0.001***
Alcohol	No	Reference		Reference		Reference		Reference		Reference	
	Quit (pre-preg)	0.82 (0.54–1.24)	0.342	0.82 (0.61–1.11)	0.194	0.93 (0.64–1.36)	0.713	1.80 (1.28–2.54)	***<0.001***	0.90 (0.54–1.52)	0.697
	Quit (<15 wks)	0.76 (0.55–1.06)	0.109	0.98 (0.78–1.23)	0.830	0.72 (0.53–0.99)	***0.042***	1.50 (1.11–2.02)	***0.008***	0.60 (0.38–0.94)	***0.026***
	Quit (<20 wks)	0.34 (0.12–0.97)	***0.044***	1.10 (0.68–1.77)	0.710	0.84 (0.39–1.81)	0.652	1.17 (0.62–2.23)	0.629	0.83 (0.31–2.20)	0.703
	Yes (at 20 wks)	0.52 (0.32–0.86)	***0.011***	1.05 (0.78–1.41)	0.762	0.77 (0.49–1.21)	0.254	1.45 (0.99–2.14)	0.058	0.53 (0.28–1.01)	0.055
Smoking	No	Reference		Reference		Reference		Reference		Reference	
	Quit (pre-preg)	0.74 (0.15–3.58)	0.713	0.93 (0.27–3.12)	0.901	0.32 (0.06–1.86)	0.206	7.17 (1.44–35.71)	***0.016***	4.60 (0.43–48.92)	0.206
	Quit (<15 wks)	1.01 (0.31–3.31)	0.982	1.56 (0.58–4.15)	0.378	0.42 (0.10–1.79)	0.242	4.35 (0.94–20.14)	0.060	2.67 (0.29–24.78)	0.387
	Quit (<20 wks)	1.56 (0.36–6.69)	0.548	2.33 (0.76–7.10)	0.138	0.49 (0.10–2.49)	0.389	5.42 (1.02–28.89)	***0.048***	3.53 (0.26–47.74)	0.343
	Yes (at 20 wks)	1.85 (0.58–5.92)	0.302	3.46 (1.31–9.12)	***0.012***	0.32 (0.07–1.35)	0.120	3.73 (0.80–17.36)	0.094	3.62 (0.40–33.11)	0.254
Marijuana	No	Reference		Reference		Reference		Reference		Reference	
	Quit (pre-preg)	2.23 (0.84–5.86)	0.106	1.08 (0.50–2.33)	0.839	–	0.857	0.91 (0.34–2.45)	0.849	2.53 (0.67–9.60)	0.172
	Quit (<15 wks)	1.32 (0.55–3.17)	0.534	0.95 (0.54–1.65)	0.843	0.74 (0.27–2.03)	0.559	1.50 (0.79–2.85)	0.218	1.47 (0.41–5.28)	0.555
	Quit (<20 wks)	2.76 (0.59–13.01)	0.199	1.64 (0.56–4.83)	0.369	0.90 (0.11–7.37)	0.918	0.63 (0.07–5.30)	0.667	2.13 (0.21–21.30)	0.521
	Yes (at 20 wks)	5.44 (2.44–12.11)	***<0.001***	1.84 (0.90–3.76)	0.095	0.44 (0.06–3.35)	0.425	0.43 (0.06–3.31)	0.421	1.48 (0.18–11.89)	0.714
Smoking X Marijuana	Interaction term	1.24 (0.38–4.03)	0.719	1.59 (0.60–4.23)	0.349	0.42 (0.10–1.80)	0.243	4.50 (0.97–20.86)	0.055	3.90 (0.43–35.81)	0.229

The bold text indicates significant P-values less than 0.05.
‡ adjusted for recruitment sites.

Table 5
Risk of pregnancy complications for any marijuana use (3 months prior to or during pregnancy) adjusted for cigarette smoking status.

Outcomes	MarijuanaOdds (95% CI)	P-value‡	Odds (95% CI) adjusted for any Smoking*	P-value	Odds (95% CI)adjusted for Smoking at 20 wks**	P-value
SPTB	2.31 (1.45–3.55)	***<0.001***	2.28 (1.49–3.60)	***<0.001***	1.97 (1.26–3.09)	***0.004***
SGA	1.37 (0.96–1.92)	0.064	1.13 (0.80–1.60)	0.555	1.04 (0.73–1.47)	0.917
PE	0.67 (0.31–1.27)	0.216	0.66 (0.34–1.27)	0.259	0.66 (0.34–1.28)	0.272
GHT	0.74 (0.46–1.19)	0.443	0.25 (0.13–3.54)	0.671	0.81 (0.51–1.30)	0.454
GDM	1.06 (0.44–2.19)	0.877	1.11 (0.52–2.38)	0.949	1.01 (0.48–2.10)	0.986

The bold text indicates significant P-values less than 0.05.
‡ Overall *p*-value comparing marijuana and corresponding outcome.
* Mantel-Haenszel adjusted odds adjusted for any cigarette smoking (3 months prior to or during pregnancy).
** Mantel-Haenszel adjusted odds adjusted for ceased cigarette smoking at 20 weeks' gestation.

While African American ethnicity has been associated with an increased risk of SPTB [41,42], it has also been commonly associated with lower socio-economic status. The relationship of low SEI with pregnancy complications was apparent in this study, where SEI was significantly negatively associated with PE, GHT, GDM, SGA, and SPTB. When adjusted for age, BMI, cigarette smoking, and marijuana use, higher SEI was a protective factor, with a 1–2% decrease in the risk of PE per unit increase in SEI. Similar trends were also seen in previously published SCOPE data [43,44]. However, the results from the current study showed no significant interaction effects between marijuana use and SEI, suggesting that the association between marijuana use and SPTB was also independent of socio-economic status.

Despite a borderline significance for alcohol consumption at 15 weeks' gestation for PE risk, our results are consistent with a study by Klonoff-Cohen et al. [45,46], which showed that maternal alcohol consumption does not appear to have a significant association with preeclampsia. Alcohol consumption during first trimester was not associated with SPTB, consistent with a previous SCOPE publication [46]. However, continued alcohol consumption at 20 weeks' gestation is a protective factor for SPTB, and a recent study by Lundsberg et al. [47] also showed that alcohol consumption during third trimester was associated with a decreased risk of PTB but not when consumed during early pregnancy. The mechanism of this effect is still unknown. However, as maternal alcohol consumption may damage the fetus we cannot recommend it during pregnancy and indeed the National Health and Medical Research Council Guidelines recommend against its use in pregnancy [48].

Maternal cigarette smoking is typically considered to be a risk factor for SPTB and SGA [49–54]. Indeed, maternal cigarette smoking at 20 weeks' gestation was significantly associated with risk of SPTB and SGA in univariable tests, but no longer significant for SPTB when adjusted for other factors, including BMI, SEI, age, and marijuana. Similar results have been found previously in a study by Dekker et al. [55], which incorporated multiple novel risk factors for SPTB. In the current study an association was seen between smoking and SPTB (in univariable analysis), but cigarette smoking was not found to be an independent risk factor for SPTB after adjustment for marijuana use. Nevertheless, continued cigarette smoking is a significant risk factor for many pregnancy complications including stillbirth, placental abruption and SGA and women should be encouraged to quit before or in early pregnancy [56].

The association between smoking and marijuana is often considered as an interaction effect for pregnancy complications, as the majority of women who use marijuana also smoke cigarettes [10,25,57]. In fact, amongst women who used marijuana in the SCOPE cohort, 74% also smoked cigarettes. With a high concurrence rate, the independent effect of marijuana on pregnancy outcomes has generally been unrecognised and just considered to be subsidiary, partly due to the low availability of data on marijuana use compared to cigarette smoking for statistical analysis [36,57]. However, our data from the SCOPE cohort, with 316 participants (5.62%) who were marijuana users, demonstrate that the association of marijuana use with SPTB is consistent across cigarette smokers and non-smokers.

The consistent effect of marijuana use is also apparent when analysing the effect of the estimated number of episodes of marijuana use during pregnancy on the length of gestation. While there was a slight decrease in the predicted length of gestation amongst smokers, the trend for smokers and non-smokers was similar. In contrast, the predicted length of gestation for women who continued to use marijuana at 20 weeks' gestation was significantly decreased compared to those who ceased earlier in gestation, regardless of smoking status. This is consistent with similar studies which showed that marijuana use is associated with a decreased length of gestation [26,27].

Furthermore, apart from a cigarette smoking-marijuana interaction, it is also well recognised that cigarette smoking and illicit drug use are associated with low socio-economic status [57–60], along with a complex inter-relationship with obesity, where smoking cessation may also lead to obesity [57,61–63]. As described in many studies, the prevalence of cigarette smoking and obesity is higher amongst those who are socio-economically disadvantaged, and the incidence of SPTB is higher amongst women with lower income and lower educational status [41,64], which may indicate associations with other lifestyle risk factors.

Furthermore, if there was no maternal marijuana exposure, with an estimated population attributable risk (PAR) of 0.003 for marijuana use, the incidence of SPTB would be expected to decrease by 3 cases per 1000 pregnant women. With an overall rate of SPTB of 4.2% in this study, this represents an estimated 6.2% reduction in the incidence of SPTB in the population, i.e. about 3 out of 50 SPTB cases would be attributed to marijuana use. If we consider the Australian centre only, where any marijuana usage occurred in 11.6% of women compared to 3.6–4.5% in the other centres, the estimated PAR was 0.009 for marijuana use with an expected reduction of SPTB of 9 cases per 1000 pregnant women, and a 11.68% reduction in the incidence of SPTB in this centre if women did not use marijuana. That is, in the Australian study centre, almost 12% of SPTB could be attributable to maternal marijuana use.

4.1. Strengths and limitations

A major strength of this study was its large international multicentre prospective cohort with excellent follow-up and complete data available for this analysis. Women were recruited from a clearly defined population of nulliparous women, with meticulous data monitoring protocols to reduce data entry or transcription errors and ensure the quality of data. While there are other studies that have examined the effect of marijuana use on adverse pregnancy outcomes, interaction tests were not performed. Hence, with complete quality data available from this study, interactions between marijuana use and cigarette smoking status may be examined while also adjusting for potential confounders.

It needs to be noted that the number of SPTB cases amongst women who reported marijuana use at 20 weeks' gestation is small (n = 11) even in this large cohort. The use of self-reported marijuana

use and cigarette smoking status may be a potential limitation, as it may be subject to participant recall bias. Furthermore, this study was undertaken in a nulliparous cohort so it may be the case that our findings apply only to nulliparous women. Although medication for maternal asthma, thyroid disease, and PCOS were recorded, we found no evidence of association with pregnancy outcomes analysed in this study, therefore these were not included in the analysis. Further research is required to confirm these findings, and future studies should include appropriate corrections for the various important confounders (e.g. smoking, BMI, ethnicity).

5. Conclusion

In this large prospective cohort, maternal marijuana use had a major contribution to SPTB and this association was consistent for both cigarette smokers and non-smokers, with doubled odds in women who used marijuana three months prior to or during pregnancy. For women who use marijuana during pregnancy, it should be emphasised that stopping early in pregnancy should be encouraged since continued use of marijuana at 20 weeks of gestation was associated with a five-fold increased risk of SPTB in this study following adjustment for other confounders, including maternal age, BMI, SEI, and cigarette smoking. In this cohort of nulliparous women we estimate there would be an estimated 6.2% reduction in the incidence of SPTB if women were not exposed to marijuana during pregnancy.

Preterm birth is increasing in developed nations, with attendant increases in adverse infant outcomes, as well as psychological and social impacts, and is of great concern to public health. The increasing exposure to marijuana in women of reproductive age and its contribution to the risk for preterm birth make it a modifiable target for intervention. In nations where authorities are considering decriminalisation of marijuana or have already done so, the risks to pregnant women and their babies need much greater consideration.

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Ethics approval

This study was approved by local ethics committees (New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London and Manchester 06/MRE01/98, and Cork ECM5 (10) 05/02/08), and all women provided written informed consent.

Transparency document

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