Journal of Developmental Origins of Health and Disease (2013), **4**(2), 191–199.

doi:10.1017/S2040174412000670

ORIGINAL ARTICLE

Street drug use during pregnancy: potential programming effects on preschool wheeze

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Street drug use during pregnancy is detrimental to fetal development. Although the prevalence of wheeze is high in offspring of substance-abusing mothers, nothing is known about the role of street drug use during pregnancy in its development. We investigated the impact of maternal street drug use and distress during pregnancy on the development of wheeze and allergy in preschool children. Questionnaire data were accessed from the Community Perinatal Care trial of 791 mother–child pairs in Calgary, Alberta. Using logistic regression, the association between maternal substance use and distress during pregnancy, and wheeze and allergy at age 3 years was determined in boys and girls. After adjusting for alcohol use during pregnancy, pre- and postnatal tobacco use, preterm birth, duration of exclusive breastfeeding, daycare attendance and maternal socioeconomic status, maternal street drug use during pregnancy [odds ratio (OR): 5.02, 95% confidence interval (CI): 1.30–19.4] and severe maternal distress during pregnancy (OR: 5.79, 95% CI: 1.25–26.8) were associated with wheeze in girls. In boys, an independent association was found between severe distress during pregnancy (OR: 3.85, 95% CI: 1.11–13.3) and allergies, but there was no association with maternal street drug use. In conclusion, we found an association between maternal street drug use and wheeze in preschool girls that could not be accounted for by maternal distress, smoking or alcohol use during pregnancy. Prenatal programming effects of street drugs may explain this association.

Received 13 January 2012; Revised 30 October 2012; Accepted 31 October 2012; First published online 30 November 2012

Key words: asthma, depression, prenatal, substance use

Introduction

Substance use among women during pregnancy is a significant public health concern worldwide. According to a recent survey in Alberta, Canada, 10% of pregnant women report monthly binge drinking and 2% report use of street drugs, such as cocaine or marijuana.[1] Up to 10% of women in the Community Perinatal Care (CPC) trial in Calgary, Canada reported taking street drugs within a 12-month period before becoming pregnant.[2] According to a recent UK study of recreational drug users, women predominantly smoked marijuana (61%) in the 12 months before pregnancy, followed by ecstasy (37%) and cocaine (35%).[3] The study also noted that use, especially of marijuana, continued well into the first trimester in the majority of women.

Many immediate effects of *in utero* exposure to street drugs, including cocaine, marijuana, opiates and methamphetamine, are well known. Children born to a substance-using mother carry a higher risk of being born prematurely or low birth weight,[4] and more than half will exhibit drug withdrawal symptoms, including respiratory distress, soon after birth.[5–7] Cocaine, opiate and marijuana use in pregnancy have been associated with a number of negative outcomes in infants, such as lower arousal, less self-regulation and higher excitability.[8,9] There is also evidence that street drug use in pregnancy can alter long-term developmental trajectories in offspring via abnormal neuroendocrine and neurotransmitter system development, altered stress responses or epigenetic mechanisms.[10] Language delays, behavior problems and reduced executive function in later childhood have been reported as a result of maternal prenatal drug use.[11,12]

There is building evidence that street drug use in pregnancy has the capacity to program future disease morbidity, including that of a respiratory nature. In the United States, preschool children of mothers admitted for substance abuse treatment have asthma rates at twice the national average.[13] Some of this excess may be attributed to birth complications following street drug use, such as premature birth and respiratory distress syndrome.[14] However, prenatal exposure to substances like marijuana and cocaine have been shown to affect the development of the immune system, as well as the hypothalamic–pituitary axis system.[15–17] Chronic exposure to cannabinoids during the development of the endocannabinoid system in neonates can lead to severe functional impairments in offspring.[18,19] Disruptions to all of these systems may increase the risk of respiratory or allergic disease in childhood. Further, some of these programming effects have been shown to be sex specific.[20]

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Women who use street drugs are more likely to experience stress and mental health problems.[21] Maternal stress during pregnancy is widely regarded as having a major role in the programming of the fetal immune system.[22] Importantly, stress levels in pregnancy predict infant cortisol reactivity in the *postpartum* period.[23] More recently, prenatal maternal stress and depression have been identified as risk factors for elevated pro-inflammatory cytokines and exaggerated allergen response in neonates, and wheeze at 12 months of age.[24,25] Although, street drug use increases the likelihood of stress during pregnancy, as well as alcohol and tobacco use,[21,26,27] it is also conceivable that programming effects of street drugs on the fetal immune or respiratory system may lead to future-development of wheeze and allergic disease in children. As a starting point, we sought to determine whether maternal street drug use during pregnancy, independent of maternal distress, was associated with the outcome of childhood wheeze and allergies at age 3 years. As fetal responses to stress are considered to be sex specific,[28,29] we conducted our analyses separately for boys and girls.

Methods

This was a secondary analysis of the CPC trial, a randomized controlled trial of prenatal nursing or home visitor support conducted from 2001 to 2004 in Calgary, Alberta, Canada. Women from several maternity clinics completed phone interview questionnaires at 7 and 32–34 weeks pregnant, respectively, 8 weeks *postpartum*, and when their children were 3 years old. Approval was received from the Conjoint Medical Bioethics Committee of the University of Calgary and the Calgary Health Region. The CPC trial intervention of prenatal support had no impact on infant or child outcomes, including wheeze or allergies.[2]

The follow-up CPC survey contained 791 mother–child pairs. We used survey data for these pairs on maternal distress and substance use during pregnancy (street drugs, alcohol, tobacco) and related it to child wheeze and allergies reported at age 3 years. Knowing that substance use in pregnancy is underreported,[30] we implemented a measure of probable street drug use during pregnancy that included maternal report of current use in pregnancy, use in the 12 months before the current pregnancy and history of use. We proposed that this measure would capture a larger number of fetuses exposed to street drugs *in utero* because many women do not alter their drug use until after the first trimester.[3] Similar questions have been employed by others to determine street drug use in pregnancy.[31,32] In the CPC surveys, street drugs were referred to as 'street drugs, such as cocaine or marijuana'. Smoking during pregnancy was defined as smoking at least two to three cigarettes per week (moderate to heavy smoking) at either of the two time periods women were surveyed during pregnancy *v.* light smoking (one cigarette per week) or not at all. Smoking after pregnancy was measured in the same manner at 8 weeks *postpartum*.[33] Alcohol use in pregnancy was defined as drinking at least once a month also at either of the same survey periods.[34] The Symptom Questionnaire, consisting of anxiety, depression, somatic and hostility subscales summing to a total distress score, was used to identify maternal distress in pregnancy as severe or moderate.[35]

At 3 years of age, wheeze in the child was recorded as maternal report of a diagnosis of chronic breathing problems made by a healthcare worker. Such problems could include asthma, or bronchopulmonary dysplasia (a chronic lung disease of prematurity), among others. Given that only two children were born at 28 weeks' gestation, when the risk for bronchopulmonary dysplasia is the highest, and that asthma is difficult to confirm in preschool-aged children, we interpreted maternal responses to this question to indicate preschool wheeze.[36] In addition to asthma, this category includes transient or episodic viral wheeze, a well-known phenotype of asthma-like wheeze.[37,38] Mothers also reported allergies in their children at age 3 years based on diagnosis by a healthcare worker. Parent report of breathing problems, such as wheeze and allergy, have been validated in a number of studies,[39,40] including those using phone interviews.[41]

Using SPSS version 18.0, logistic regression was performed to determine crude odds ratios (OR) for child wheeze and allergies and ORs adjusted for the following confounding factors: lower maternal education (no post-secondary education),[42] pre- and postnatal smoking,[43,44] prenatal alcohol use,[7,13] pregnancy stress,[22,24,25] birth weight and preterm birth (<37 weeks' gestation),[45] long-term exclusive breastfeeding (8 weeks or greater), daycare attendance (20 h or greater for out-of-home care)[42] and prenatal vitamin use.[46] Variables were considered significant at a 95% confidence level (CI). Model fit was tested using the Hosmer–Lemeshow test. To account for sex differences in wheeze risk factors[45] and fetal responses to stress,[28,29] an *a priori* decision was made to stratify our analysis by sex. We tested for sex and other variable interactions. With the exception of sex, sample sizes were insufficient to test for interaction effects.

Results

Maternal characteristics

At study intake, 7.4% of women in the follow-up study of the CPC trial were identified as probable users of street drugs during pregnancy according to our definition. A total of 6.6% of pregnant women reported using street drugs in the past 12 months, whereas only 2.2% reported street drug use during their current pregnancy. Of the women reporting use during pregnancy, 94% used street drugs in the previous year or had a history of use. Among women reporting pregnancy or previous use of street drugs, 94% smoked marijuana and 12% used cocaine. With respect to other current substance use during pregnancy, 13.5% of women reported alcohol use and 11.1% reported smoking at least two to three times a week. According to the Symptom Questionnaire,

Table 1. *Prenatal street drug use and distress by maternal characteristics*

% of women	Total number	Street drug Use ($n = 56$)	Any distress ($n = 124$)
Prenatal maternal street drug use			
Yes	56		28.6†
No	701		14.4
Prenatal maternal distress			
Severe	33	18.2†	
Moderate	91	11.9	
No	667	6.3	
Prenatal maternal alcohol use			
Yes	102	14.9†	24.5†
No	654	6	14.1
Prenatal maternal smoking			
Moderate/heavy	84	26.2†	31.0†
Light/none	676	4.9	13.5
Postnatal maternal smoking			
Moderate/heavy	62	22.6†	13.7†
Light/none	684	5.7	6.3
Maternal education level			
High school or lower	141	16†	21.3*
Any post-secondary	636	5.5	14.8
Prenatal maternal vitamin use			
Yes	727	7.2	15.5
No	19	5.3	21.1
Preterm birth			
Yes	51	8.2	15.7
No	694	6.9	15.6
Exclusive breastfeeding			
Breastfed for <8 weeks	146	10.3*	20.5*
Breastfed for ⩾8 weeks	600	6.4	14.5
Child in out-of-home care			
Yes	278	11.3†	16.9
No	512	5.3	15

*$P < 0.1$.
† $P < 0.05$.

11.5% of women had scores that revealed moderate distress at study intake, and 4.2% had severe distress during pregnancy.

Substantially, more women had taken street drugs if they smoked during their current pregnancy (26.2%) or reported drinking alcohol (14.9%; Table 1). Moderate or severe distress during pregnancy was significantly more likely in women with probable street drug use, as well as in those reporting alcohol or tobacco use during their current pregnancy. Women with no post-secondary school education were more likely to have used street drugs or be distressed during pregnancy. Distress during pregnancy was more likely in women reporting shorter-term exclusive breastfeeding. Women who were distressed or used street drugs were more likely to smoke after pregnancy. The children of mothers who reported street drug use were more likely to attend daycare.

Child health outcomes

Almost half of the study children were boys. Consistent with rates from previous studies using validated methods of doctor-diagnosed wheeze in preschool children,[44,48] a reported 7.7% of all children had wheeze at age 3 years. Wheeze was noted in 10% of boys and 5% of girls. Allergies were reported in 9.7% of all children at age 3 years, which represented 12% of the boys and 8% of the girls in the sample. Seven percent of children were born preterm and 35% had attended child care outside of the home. Wheeze was two to three times more prevalent among boys born to mothers who smoked during or after pregnancy (Table 2). Allergies were three times more common in boys if their mothers reported distress during pregnancy. In girls, both wheeze and allergies were more prevalent in girls whose mothers reported distress during pregnancy. Independent of other factors (Table 3), severe maternal distress during pregnancy elevated the risk for wheeze and allergies in all children, although statistical significance was not achieved for wheeze. Preterm birth increased the likelihood of preschool wheeze, whereas prenatal vitamin use diminished it. Despite elevated ORs, maternal street drug use during pregnancy was not found to be statistically associated with either outcome.

Evidence of an interaction between sex and maternal street drug use ($P < 0.11$) and between sex and prenatal smoking ($P < 0.04$) was found for preschool wheeze, justifying our *a priori* decision to proceed with stratified analyses. Indeed, sex-specific analyses uncovered associations with *in utero* street drug exposure. Among girls, severe distress in pregnancy (crude OR: 4.41, 95% CI: 1.15–16.9) and prenatal vitamin use (crude OR: 0.14, 95% CI: 0.04–0.58) were the only univariate determinants of wheeze (Table 4). However, when adjusted for alcohol use in pregnancy, smoking during and after pregnancy, prenatal maternal distress, preterm birth, prenatal vitamin use, maternal education level and out-of-home child care, wheeze was fivefold more likely in girls born to women with probable street drug use (95% CI: 1.30–19.4). Severe maternal distress during pregnancy (OR: 5.79, 95% CI: 1.25–26.8), and prenatal vitamin use (OR: 0.14, 95% CI: 0.04–0.58) also retained statistical significance in this model. Wheeze was fourfold higher among girls born preterm but this association was not statistically significant. Subsequent to the small cell size, we verified our results by performing exact logistic regression for street drug use; it remained significant ($P < 0.04$).

Smoking during (crude OR: 2.41, 95% CI: 1.02–5.69) and after pregnancy (crude OR: 3.38 95% CI: 1.32–8.57) were the only individual pregnancy exposures to be associated with preschool wheeze in boys (Table 4). Prenatal smoking lost statistical significance in the final model when adjusted for pregnancy distress, as well as following adjustment for postnatal smoking, but not street drug or alcohol use during pregnancy. Similarly, postnatal smoking lost statistical significance in the final model only when adjusted for smoking during pregnancy.

https://doi.org/10.1017/S2040174412000670 Published online by Cambridge University Press

Table 2. *Sex-specific child outcomes at age 3 years by maternal and child characteristics*

	Girls at age 3 years			Boys at age 3 years		
% with outcome	Total number	Wheeze ($n = 22$)	Allergies ($n = 31$)	Total number	Wheeze ($n = 39$)	Allergies ($n = 46$)
Prenatal maternal street drug use						
Yes	37	10.8	10.8	19	10.5	21.1
No	354	4.8	7.1	347	10.1	10.7
Prenatal maternal alcohol use						
Yes	55	1.8	5.5	47	6.4	6.4
No	336	6.0	7.7	318	10.7	12.6
Prenatal maternal smoking						
Moderate/heavy	42	2.4	11.9	42	19.0†	19.0
Light/none	350	5.7	6.9	326	8.9	10.7
Postnatal maternal smoking						
Moderate/heavy	34	2.9	8.8	28	25.0†	21.4
Light/none	351	5.4	7.4	333	9.0	11.1
Prenatal maternal distress						
Severe	17	17.6†	17.6*	16	12.5	31.3†
Moderate	46	6.5	13	45	15.6	11.1
No	345	4.6	6.4	322	9.3	11.2
Maternal education level						
High school or lower	76	7.9	5.3	65	9.2	10.8
Any post-secondary	328	4.9	8.2	308	10.7	12.3
Prenatal maternal vitamin use						
Yes	373	4.6†	7.2	354	10.2	11.9
No	12	25.0	16.7	7	14.3	14.3
Preterm birth						
Yes	23	13.0*	8.7	28	17.9	7.1
No	362	4.7	7.5	332	9.6	12.3
Exclusive breastfeeding						
Breastfed for <8 weeks	70	2.9	8.6	76	11.8	11.8
Breastfed for ⩾8 weeks	315	5.7	7.3	285	9.8	11.9
Childcare outside of the home						
Yes	149	6.7	8.7	129	10.1	13.2
No	259	4.6	6.9	253	10.3	11.1

*$P < 0.1$.
†$P < 0.05$.

Prenatal smoking retained statistical significance in a model without postnatal smoking. Probable street drug use was unrelated to wheeze in boys in unadjusted and adjusted models.

Severe pregnancy distress was associated with allergy in boys in unadjusted analyses (crude OR: 3.61, 95% CI: 1.19–11.0, Table 5). In the final model that included drug use, alcohol and tobacco use and other confounding factors, severe maternal distress during pregnancy continued to be a statistically significant risk factor for allergies in boys (OR: 3.85, 95% CI: 1.11–13.3). Despite ORs near 2.0, no significant associations were found between street drug use and allergy in boys in any model. Among girls, probable street drug use during pregnancy, pregnancy distress and smoking showed substantially elevated risk for allergies in crude and adjusted analyses. However, none of these associations were statistically significant (Table 5). The OR for moderate pregnancy distress approached statistical significance in adjusted models: 2.72 (95% CI: 0.98–7.56).

Discussion

This follow-up study of 791 preschool children in a prenatal care trial found that probable maternal street drug use, along with severe distress during pregnancy, were individually associated with an increased risk of wheeze in preschool girls. Severe maternal distress during pregnancy increased the risk of wheeze nearly sixfold. Independent of this strong association with prenatal stress, as well as alcohol use during pregnancy, tobacco use during and after pregnancy, prenatal vitamin use, maternal socioeconomic status and other confounding

https://doi.org/10.1017/S2040174412000670 Published online by Cambridge University Press

Table 3. *Risk of wheeze and allergies in relation to prenatal street drug use in all children*

	Wheeze at age 3 years		Allergies at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Prenatal street drug use (reference: none)	1.50 (0.61–3.66)	1.76 (0.66–4.70)	1.72 (0.78–3.79)	1.75 (0.72–4.27)
Prenatal alcohol use (reference: none)	0.45 (0.16–1.28)	0.41 (0.14–1.19)	0.56 (0.23–1.32)	0.45 (0.18–1.12)
Smoking, prenatal (reference: light)	1.54 (0.73–3.25)	0.82 (0.20–3.38)	1.91 (1.00–3.66)	1.91 (0.65–5.60)
Smoking, postnatal (reference: light)	1.92 (0.86–4.26)	1.95 (0.45–8.49)	1.67 (0.79–3.55)	0.97 (0.29–3.27)
Prenatal distress				
Severe	2.41 (0.89–6.54)	2.62 (0.92–7.43)	3.36 (1.45–7.79)	3.57 (1.48–8.65)
Moderate (reference: none)	1.67 (0.81–3.43)	1.52 (0.69–3.34)	1.44 (0.73–2.87)	1.69 (0.82–3.46)
Prenatal vitamin use (reference: none)	0.29 (0.09–0.92)	0.28 (0.09–0.92)	0.56 (0.16–1.97)	0.59 (0.16–2.17)
Preterm birth (reference: term)	2.45 (1.09–5.50)	2.75 (1.19–6.35)	0.78 (0.27–2.24)	0.88 (0.30–2.59)

*Adjusted for prenatal maternal alcohol use, smoking, distress and vitamin use, postnatal smoking, preterm birth, duration exclusive breastfeeding, maternal education level and out-of-home childcare.

Table 4. *Sex-specific risk of preschool wheeze in relation to prenatal street drug use*

	Girls at age 3 years		Boys at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Prenatal street drug use (reference: none)	2.40 (0.76–7.56)	5.02 (1.30–19.4)	1.05 (0.23–4.73)	1.17 (0.23–6.03)
Prenatal alcohol use (reference: none)	0.29 (0.04–2.23)	0.19 (0.02–1.67)	0.57 (0.17–1.93)	0.55 (0.15–1.95)
Smoking, prenatal (reference: light)	0.40 (0.05–3.08)	0.21 (0.01–4.59)	2.41 (1.02–5.69)	1.07 (0.16–7.02)
Smoking, postnatal (reference: light)	0.53 (0.07–4.08)	0.84 (0.04–18.7)	3.38 (1.32–8.57)	2.96 (0.42–20.7)
Prenatal distress				
Severe	4.41 (1.15–16.9)	5.79 (1.25–26.8)	1.39 (0.30–6.41)	1.21 (0.24–6.03)
Moderate (reference: none)	1.44 (0.40–5.13)	2.09 (0.53–8.20)	1.79 (0.74–4.36)	1.47 (0.54–3.95)
Prenatal vitamin use (reference: none)	0.14 (0.04–0.58)	0.10 (0.02–0.50)	0.68 (0.08–5.80)	0.64 (0.07–5.66)
Preterm birth (reference: term)	3.04 (0.82–11.3)	4.03 (0.90–18.0)	2.04 (0.63–5.73)	1.67 (0.55–5.09)

*Adjusted for prenatal maternal alcohol use, smoking, distress and vitamin use, postnatal smoking, preterm birth, duration exclusive breastfeeding, maternal education level and out-of-home childcare.

factors, the likelihood of wheeze was fivefold higher (95% CI: 1.30–19.4) in girls born to women with probable street drug use during pregnancy. Our research also revealed a fourfold increased risk for allergies in young boys following severe maternal distress in pregnancy. No associations were found between probable prenatal maternal street drug use, and childhood allergy or wheeze in boys. Our research builds on a growing body of evidence for the association between

https://doi.org/10.1017/S2040174412000670 Published online by Cambridge University Press

Table 5. *Sex-specific risk of preschool allergies in relation to prenatal street drug use*

	Girls at age 3 years		Boys at age 3 years	
	Crude OR (95% CI)	Adjusted OR (95% CI)*	Crude OR (95% CI)	Adjusted OR (95% CI)*
Prenatal street drug use (reference: none)	1.60 (0.52–4.86)	1.68 (0.47–5.99)	2.23 (0.70–7.09)	2.47 (0.65–9.40)
Prenatal alcohol use (reference: none)	0.69 (0.20–2.36)	0.53 (0.14–1.95)	0.47 (0.14–1.60)	0.43 (0.11–1.60)
Smoking, prenatal (reference: light)	1.84 (0.66–5.10)	2.62 (0.55–12.6)	1.96 (0.84–4.56)	1.22 (0.23–6.42)
Smoking, postnatal (reference: light)	1.21 (0.35–4.23)	0.39 (0.05–2.84)	2.18 (0.83–5.73)	2.28 (0.38–13.5)
Prenatal distress				
Severe	3.15 (0.84–11.8)	3.47 (0.87–13.8)	3.61 (1.19–11.0)	3.85 (1.11–13.3)
Moderate (reference: none)	2.20 (0.84–5.76)	2.72 (0.98–7.56)	0.99 (0.37–2.68)	1.18 (0.42–3.34)
Prenatal vitamin use (reference: none)	0.39 (0.08–1.87)	0.42 (0.08–2.24)	0.81 (0.10–6.87)	0.64 (0.07–5.69)
Preterm birth (reference: term)	1.18 (0.26–5.31)	1.43 (0.29–6.94)	0.55 (0.13–2.39)	0.53 (0.11–2.51)

*Adjusted for prenatal maternal alcohol use, smoking, distress and vitamin use, postnatal smoking, preterm birth, duration exclusive breastfeeding, maternal education level and out-of-home childcare.

wheeze and allergy in children, and caregiver stress in key developmental stages *in utero* and after birth.[22,41,49,50] Although links between prenatal substance use and respiratory distress in newborn infants have been reported,[5,7] we are the first to find a link between maternal street drug use in pregnancy and the development of wheeze in young girls at age 3 years.

Several possible biological mechanisms *in utero* may explain the results of our research. Findings related to pregnancy stress contribute evidence to the concept of prenatal programming with respect to wheeze and allergic disease. Stress has been found to elevate maternal IgE levels in pregnant women, sensitizing the fetus to allergens.[22,51] Moreover, stress exposure is also posited to alter the programming of the hypothalamic–pituitary–adrenal (HPA) axis function in the fetus, which impacts the immune system and subsequently lung function.[25,52] Although prenatal stress and depression have also been associated with infant wheeze,[24] our findings associating prenatal street drug use with wheeze in girls were independent of prenatal distress. The risk from street drug use was also independent of an association with preterm birth, a birth outcome that has been linked to maternal street drug use, as well as childhood allergy and respiratory morbidity.[42,45] It is conceivable then that street drug use in pregnancy can have programming effects on lung development and subsequent wheeze in young children. We return to this hypothesis later in the discussion.

Other competing hypotheses for our results include the effects of smoking and poor maternal diet in pregnancy, both of which are more common among women who use street drugs.[27,53] *In utero* exposure to alcohol, as well as pre- and postnatal exposure to tobacco smoke, can lead to the development of early childhood wheeze or low birth weight, a strong determinant of wheeze.[43,44,54] Expectedly, we found associations between pre- and postnatal smoking and wheeze. However, as models controlled for maternal smoking and alcohol use, these exposures are not an adequate explanation for our findings. Poor nutrition during pregnancy and subsequent vitamin D deficiency may also contribute to the development of preschool wheeze.[46,55] Prenatal vitamin use, a major source of Vitamin D intake during pregnancy,[56] had an independent inverse association with wheeze in our models, providing further evidence for possible protective properties, but it did not explain the association between maternal street drug use and distress on preschool wheeze. A final explanation for our results centers on socioeconomic status. Financial difficulties cause distress in pregnant women with addiction problems and they are often barriers to good prenatal care.[57,58] Respiratory conditions are often observed in the offspring of low-income women.[42,47,59] However, the inclusion of maternal education, our measure of socioeconomic status, did not change the results for street drug use or distress during pregnancy.

We now return to the potential programming effects of street drugs, such as cocaine and marijuana, on fetal development and propose reasons for the programming of wheeze in preschool girls. The use of such drugs in pregnancy has been shown to affect the developing fetal endocannabinoid system, as well as to alter regulation of the immune system and suppress T-lymphocyte response, all of which can impact later lung function.[16–18] In particular, chronic interference with the

https://doi.org/10.1017/S2040174412000670 Published online by Cambridge University Press

developing endocannabinoid system *in utero* has been shown to have significant disease programming effects in childhood,[60] potentially impacting development of the pulmonary system. Street drug use in pregnancy also alters fetal development of the hypothalamic–pituitary axis system, which can lead to impaired cortisol regulation later in childhood, and subsequent respiratory problems.[61]

There are a number of explanations for the differential effects of drug use in preschool girls. Exposure in key developmental periods to substances such as cocaine and cannabinoids has shown sex-specific effects across a variety of health outcomes; this has been attributed to the earlier maturation of many physiologic systems in female fetuses and greater exposure to drugs during their development.[62,63] Little is known about the determinants of preschool wheeze in girls because of greater research interest in the persistent wheeze that progresses to asthma in boys.[37,64] In both genders, lower lung function is seen before 1 year of age in children with transient or persistent wheeze during their preschool years.[37] However, at birth, girls have greater lung maturity and lower IgE levels, which may explain their lower prevalence of preschool wheeze and allergies to begin with.[65] On the other hand, the placental enzyme 11β-hydroxysteroid dehydrogenase 2 (11β-HSD 2), which prevents transplacental passage of cortisol, is more sensitive to changes in maternal catecholamines in the female *v.* the male placenta.[28] Cocaine and marijuana alter maternal catecholamine levels, such as noradrenaline, with the potential to downregulate 11β-HSD 2 production and increase fetal cortisol levels.[66,67] This places the female fetal lung at greater risk for the HPA axis programming effects of cortisol.[25] Moreover, prenatal cocaine exposure causes periodic breathing in newborns and is postulated to play a role in fetal programming of respiratory control.[68] Fetal breathing is also critical to the development of lung function.[64] As modulation of respiration is sex specific, it is plausible that cocaine has a greater inhibitory affect on breathing movements of female fetuses.[68]

The strengths of this hypothesis-generating study include the use of validated instruments for maternal distress during pregnancy,[69,70] the longitudinal design and the large sample size, which was sufficient to run separate models in boys and girls that were adjusted for essential confounding factors. However, the limitations of our study must not go without mention. The longitudinal design of the CPC trial resulted in a loss to follow-up from 1324 to 791 participants,[2] meaning that we only were able to analyze information on the women who participated in all four surveys. Dropouts in the trial were more likely to use drugs, smoke, have a history of depression and have adverse life events. Further, a higher proportion of unreachable women reported street drug use within 12 months of pregnancy.[71] Given that our sample size was small, if these participants had been retained in analysis it is possible that our results may have been strengthened. We have discussed the potential for underreporting of street drug use during pregnancy, and our rationale for combining pregnancy and recent use to identify actual use. Recent studies of recreational drug use in UK women show that first trimester use is similar to the year before pregnancy; after the first semester, it drops off for cocaine (30%) and ecstasy (5%), but remains high for alcohol (75%) and marijuana (65%).[3] It is important to note, however, that we were not able to examine the effects of individual illicit drugs, which have different pharmacological actions. We also did not have comprehensive data on nutrition during pregnancy. Instead, we relied on a measure of prenatal supplement use but this measure is a very good estimate for Vitamin D intake. The measure of wheeze in our research was based on parent report of a diagnosis for a chronic breathing problem like asthma, made by a healthcare worker. As noted under our research methods, this measure has been validated and likely identifies many children with transient or episodic viral wheeze, the most common wheezing condition at this age next to asthma.[37,44,48] In further support of this measure, rates of wheeze prevalence in our study are similar to rates in US children. Finally, parents were not asked about their own atopic status. Although this is a well-known determinant of childhood atopic disease,[72] family history of atopy is not a risk factor for transient wheeze, our main outcome of interest.[37,38]

Prevalence rates of wheeze are strikingly high in preschool children of mothers who have substance abuse problems.[13] We have uncovered evidence that maternal street drug use may have independent, sex-specific programming effects on the development of wheeze in young children. Mental health disorders and substance abuse are commonly found together.[73] As rates of substance use in pregnancy, in particular multi-substance use, continue to rise,[74] prenatal street drug use may become a more common determinant of childhood wheeze. Further research with larger study populations needs to be done in order to verify the veracity of our findings and to explore possible programming mechanisms in this pathway. In the interim, akin to smoking cessation during pregnancy,[75] treatment of drug addiction and stress during pregnancy has multiple benefits for long-term health of children.

Acknowledgments

Funding for this project provided by the Norlien Foundation and the Women & Children's Health Research Institute (WCHRI). Funding for the CPC Trial provided by the Calgary Children's Initiative, the Physician Partnership Steering Committee and the Child and Women's Health Portfolio of the Calgary Health Region. Salary for M.A. provided by the Faculty of Medicine and Dentistry at the University of Alberta. Salary for AK's Research Chair, Maternal-Child Health and the Environment provided by WCHRI/Stollery Children's Hospital. The authors thank Sheila McDonald, postdoctoral fellow, University of Calgary and statistician Yiye Zeng for their help with data extraction and analysis.

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