

Are oral contraceptive use and pregnancy complications risk factors for atopic disorders among offspring?

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In utero programming of atopic manifestations has been suggested. We investigated the association between oral contraceptive (OC) use before, and complications during pregnancy (CDP) and asthma, along with other atopic manifestations. The study is based on neonates from Kingston and St Andrew, a geographic subcohort from the Jamaican Perinatal Morbidity, Mortality Survey conducted in 1986–1987.

Information on OC use and CDP was extracted from maternal interviews and medical records. In a follow up in 1997–1998, via interviews with mothers, trained nurses collected information on asthma/wheezing, coughing, eczema, and hay fever. Data, specific to this paper, from birth and 11–12 yr of age was available for a total of 1040 of the 1720 members of the geographic subcohort. Using logistic regression, controlling for confounders, we estimated adjusted odds ratio (aOR) and corresponding 95% confidence intervals (CI). For asthma or wheezing, and coughing, aOR for OC use were 1.81 (95% CI: 1.25–2.61), and 2.72 (95% CI: 1.41–5.24), respectively. CDP was only shown to be a significant risk factor for hay fever. Additionally, a higher number of older siblings were protective for hay fever. The results suggest that asthma in childhood may be programmed *in utero*.

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The prevalence of allergies is increasing in many parts of the world, and asthma has become the most common chronic disease of childhood. The etiology of asthma and allergic disease remains poorly understood, despite considerable research (1). Recent work has expanded to include the study of novel factors such as *in utero* and perinatal exposures that may program initial susceptibility (2). Some authors have reported that maternal estrogen levels and maternal health complications during pregnancy (CDP) are associated with asthma and other atopic manifestations later in life (3–6).

The most appropriate design to test an association between perinatal conditions and asthma in offspring is a longitudinal study commencing with mothers in the antenatal period and following their offspring through childhood. The Jamaican Perinatal Mortality and Morbidity

Survey (JPMMS) (7), and the subsequent follow up studies offered a unique opportunity for testing these hypotheses.

The JPMMS, originally designed to ascertain causes of maternal and neonatal mortality and morbidity, obtained detailed information about maternal lifestyle before and during pregnancy, the labor and delivery process. The subsequent follow up studies of the children were designed to identify factors promoting and preventing optimum childhood outcomes, including child health.

Offspring of mothers who participated in the JPMMS in 1986 were re-contacted at 6 wk and again 11–12 yr later. We investigated whether *in utero* and perinatal factors contributed to the development of asthma and other atopic manifestations in children 11–12 yr of age. Specifically, we tested the association between two risk factors:

- 1 Maternal use of oral contraceptives before pregnancy.
- 2 Maternal CDP and the prevalence of four atopic manifestations:
 - (i) asthma/wheezing,
 - (ii) frequent night-time/early morning cough,
 - (iii) eczema, and
 - (iv) hay fever/sinus problems/other allergy.

Methods

Study population

The JPMMS included all pregnant women who had a live or stillbirth during the 2-month period from September 1 to October 31, 1986. Women were interviewed and their babies examined, usually within the first 48 h after delivery. Data were gathered during this phase using the main questionnaire (MQ). A total of 10 392 babies or 94% of the births in the 2-month period were identified and included in the study (main cohort study) (8). The first follow up study of the children occurred at 6 wk of age when 8800 (84.7%) mother-child pair from the main cohort were interviewed. Information on breast-feeding and the infant's health was obtained using the first follow up questionnaire (FFUQ). These 8800 mother-child pairs were used as the baseline cohort (entire island) for the analyses.

Follow up

A geographic subsample of 1720 11–12-yr-old children, representing those residing in Kingston or St Andrew, the two most urban of Jamaica's 14 parishes, was selected for a second follow up study. In a cross-sectional survey of these children, data on health outcomes were collected from participating parents or guardians ($n = 1163$), mostly the mothers, and recorded using a second follow up questionnaire (SFUQ). We linked the three data sets using a unique identification number assigned at birth and dates of birth for both mother and child.

Questionnaires and examinations

During the JPMMS, trained nurse midwives administered face-to-face interviews with mothers and conducted a brief examination of the babies shortly after birth. Babies were also weighed and measured. Hospital delivery notes and maternally held health records were consul-

ted to verify and supplement the data obtained by interview. The MQ provided data on past obstetric history and CDP, labor, and delivery.

Data on the current status of the baby (alive/healthy, alive/ill, dead or don't know) and what the baby was currently being fed (breast, breast and formula or formula only) was extracted from the FFUQ. Information on the presence of asthma or wheezing, coughs, eczema and hay fever/sinus problem/other allergy in the children at 11–12 yr of age was collected from the general health section of the SFUQ. Trained nurse interviewers administered the questionnaire to either the parents or guardians.

Definition of variables

Maternal age at birth was calculated from the mother's date of birth and child's date of delivery. Based on questions from the MQ, a yes, no, or don't know response was used to define the following:

- 1 Did you smoke tobacco regularly at any time during this pregnancy?
- 2 Have you ever used contraception? If yes, which methods have you used? Contraceptive pill was among a list of contraception.
- 3 Were you admitted to hospital or rural maternity center during this pregnancy but before going into labor? - Used to determine maternal hospital admissions.
- 4 Are any of the following services available within 1–2 miles walking distance of where you live? Health center was among a list of services – used to determine access to health care.

Mother's education level was grouped into three categories for the purpose of this study (less than secondary, secondary, and more than secondary education).

Maternal CDP was defined as a positive response to any of the following questions:

- 1 Did you have vaginal bleeding in the first 28 wk of pregnancy?
- 2 Did you have vaginal bleeding after 28 wk (7 months)?
- 3 After starting antenatal care, were you referred during pregnancy for any reason?
- 4 Were you referred during pregnancy for any reason?
- 5 Was the mother diagnosed as having hypertension, pre-eclampsia or eclampsia during this pregnancy?

- 6 Did the mother have any of the following during this pregnancy; epilepsy, eclamptic fits or heart disease and lastly,
- 7 Did the mother have any other complications, disorder or serious illness during this pregnancy?

Responses to the first five questions above were obtained by interview, while the remainder was obtained from health records.

Maternal infection during pregnancy was defined as a positive answer to any of the following question based on information from medical records:

- 1 Did the mother have a vaginal discharge or infection during this pregnancy?
- 2 Did the mother have urinary tract infection, tuberculosis, rubella (German measles), gonorrhea, syphilis, a positive Venereal Disease Research Laboratory test or genital sores or blisters during pregnancy?

The following variables were used to define maternal health complications during labor or delivery (positive if indicated in the medical records):

- 1 Did the mother have eclamptic fits?
- 2 Did she hemorrhage?
- 3 Was labor obstructed?
- 4 Did the uterus rupture?
- 5 Was mother transferred during labor?
- 6 Did the cord prolapse?
- 7 Was there meconium in the liquor?
- 8 Were there any other complications?

The number of preceding live births determined birth order of the index child. The child's birth weight was also recorded during this period (MQ) and grouped into three categories for the purpose of our analyses (< 2.5, 2.5–4.0 and > 4.0 kg).

The variable child's illness or health problems in the first week of life was defined as a positive response to any of the following questions from the FFUQ:

- 1 Was the baby referred to a medical officer?
- 2 Was the baby admitted to hospital or special care baby unit?
- 3 Were any abnormal symptoms noted in the baby?

Outcomes of interest at 11–12 yr of age were ascertained from the SFUQ.

The original question to the parents was, 'Has your child ever had...'. This question was

followed by a list of conditions; including asthma or wheezing, frequent night-time or early morning cough, eczema, and hay fever sinus problem or other allergy.

Statistical analysis

We tabulated the prevalence of the four atopic manifestations for the different ante- and perinatal exposures. Differences in proportions between the different subsamples were assessed. Adjusted odds ratios (aOR) and their 95% confidence intervals (CI) were estimated by logistic regression analysis. Statistically, we controlled for maternal infection, hospital admissions and smoking during pregnancy, as well as maternal complications during labor/delivery, induced labor, anesthetic/analgesic during labor, gender, birth weight, breast-feeding, child's illness in the first week of life, access to health care and mother's level of education. These potential confounders were included based on previous publications and after satisfactorily checking for collinearity between all predictors (risk factors and all confounders) (9). We estimated aOR for all four outcome variables independently.

Further steps were taken to determine whether having both, asthma or wheezing and frequent night-time or early morning cough, was associated with oral contraceptive (OC) use and CDP. All calculations were carried out using SAS for Microsoft Windows (release 8.2) (10).

Results

From the three data sets, we successfully linked 1040 (60.4%) of the 1720 available mother–child pairs from the Kingston and St Andrew subcohort. Compared characteristics between exposure variables from the baseline cohort (entire island) and the linked data set (urban population) are presented in Table 1. Approximately 50% of mothers used OC, and approximately, 50% had CDP. In the baseline sample, maternal education was lower than in our subsample (Table 1: less than secondary level of education – baseline: 35.6%, subsample: 25.4%). The proportion of children born with low-birth weight (< 2.5 kg) was higher in the more urban setting of Kingston and St Andrew (12.2%), where the second follow up cohort originated. A significant rural–urban difference was also indicated by the difference in breast-feeding categories.

When comparing the follow up group for whom health information was available, (n = 1163 of 1720) with the linked sample (n = 1040) there were no substantial difference (asthma or

Table 1. Comparison characteristics of exposure variables in baseline and linked data sets

Factors	Baseline cohort (%) (perinatal and 6-wk follow up) (N = 8800)	Linked data (%) from the subsample in Kingston and St Andrew (n = 1040)
Maternal oral contraceptive use	45.7	49.9
Maternal complications during pregnancy	38.4	49.2
Maternal infections during pregnancy	22.5	25.7
Maternal hospital admission during pregnancy	9.6	12.3
Induced labor	4.3	6.7
Analgesic or anesthetic given during labor	12.0	22.6
Maternal health complications during labor or delivery	11.6	14.5
Maternal education		
Less than secondary	35.6	25.4
Higher than secondary	7.9	15.3
Live within 1–2 miles of health center	78.3	86.1
Feeding		
Breast only	46.2	34.9
Breast and formulae	49.3	59.0
Formulae only	4.5	6.4
Birth weight (kg)		
<2.5	10.7	12.2
2.5–4.0	85.1	83.4
>4.0	4.2	4.4
Child's illness or health problems in first week of life	10.9	20.3

wheezing: 17.0% vs. 16.8%, frequent night-time or early morning cough: 4.8% vs. 5.3%, eczema: 6.5% vs. 6.3%, hay fever or sinus problem: 19.6% vs. 20.1%).

Table 2 presents the extent to which atopic manifestations occur with each other. The proportion of atopic disorders in relation to *in utero* risk factors is presented in Table 3. Children of mothers who used, compared with those who did not use OC before pregnancy, had a higher prevalence of asthma (20% vs. 13.4%), frequent night-time or early morning cough (7.4% vs. 3.6%) and eczema (7.4% vs. 5.5%). Asthma and wheezing, as well as hay fever or sinus problems were more common in children whose mothers had CDP than in those who did not.

Of the perinatal risk factors, induced labor was related to a higher prevalence of eczema (11.4% vs. 6%, Table 4). Children of mothers who had complications during labor or delivery had a greater proportion of frequent night-time or early morning cough (8.1% vs. 4.8%). In children who had illness or health problems in their first week of life, eczema (10.5% vs. 5.3%) and hay fever sinus problem or some other allergy (27.4% vs. 18.3%) were more frequently reported.

Information on breast-feeding was available for only 763 children (Table 4). For this reason, breast-feeding was not considered when testing the hypotheses with a full model. A possible confounding effect of breast-feeding was investigated in additional analyses.

Adjusted odds ratios for asthma or wheeze, and frequent night-time or early morning cough are reported in Table 5 while those for eczema and hay fever, sinus problems or other allergy are reported in Table 6. Maternal OC use before pregnancy was significantly associated with both asthma (aOR = 1.81) and frequent night-time or early morning cough (aOR = 2.72) in the offspring. The association between maternal OC use before pregnancy and asthma was stronger for girls (aOR = 2.02, 95% CI: 1.21–3.37) than for boys (aOR = 1.60, 95% CI: 0.92–2.76). Regarding eczema, and hay fever, sinus problem or other allergy at age 11–12 yr of age, the confidence limits of the aOR for maternal OC use included the null-value (Table 6).

Additionally, it is well-established that ‘all that wheezes is not asthma’ (11), therefore, we conducted further analysis with a combined variable, defined as the conditions asthma or wheezing and frequent night-time or early morning cough occurring concurrently. Of children whose mothers used OC, 5.1% had asthma or wheezing, and coughing compared with 1.9% of children of mothers who did not. This association was then assessed controlling for confounders in the full model. When compared with the two separate effects, the association of the combined outcome was stronger (aOR = 3.32, 95% CI: 1.33–8.32).

Complications during pregnancy gained statistical importance only for hay fever or sinus problems (Table 6). When type of feeding was introduced into the models, analyses were then

Table 2. Proportions of simultaneous occurrence of the different atopic manifestations

	Eczema*		Asthma or wheezing		Frequent night-time or early morning cough		Total group (n = 1040)
	Yes (n = 65)	No (n = 962)	Yes (n = 173)	No (n = 857)	Yes (n = 53)	No (n = 944)	
Asthma or Wheezing	36.9	15.4					16.6
Frequent nighttime or early morning cough	13.8	4.6	16.1	3.1			5.1
Hay fever or sinus problem or some other allergy	50.0	18.0	34.9	17.1	47.0	18.6	19.8

*Total proportions = 6.3.

Table 3. Proportion of atopic disorders in relation to their *in utero* risk factors

Outcome (%)	Gender		Maternal oral contraceptive use		Maternal complications during pregnancy		Maternal infections during pregnancy		Maternal hospital admissions during pregnancy		Smoking during pregnancy	
	Male (n = 488)	Female (n = 547)	Yes (n = 511)	No (n = 509)	Yes (n = 528)	No (n = 512)	Yes (n = 267)	No (n = 773)	Yes (n = 127)	No (n = 907)	Yes (n = 78)	No (n = 962)
Asthma or wheezing	16.7	16.9	20.0	13.4	18.9	14.8	18.9	16.1	18.1	16.7	11.5	17.2
Frequent night-time or early morning cough	4.5	6.0	7.4	3.6	5.5	5.2	5.9	5.1	7.1	5.1	5.3	5.3
Eczema	6.0	6.7	7.4	5.5	7.3	5.4	5.7	6.5	10.2	5.8	6.4	6.3
Hay fever sinus problem or some other allergy	19.1	21.1	20.3	20.0	22.7	17.7	21.0	19.8	15.9	20.8	11.7	20.8

based on 763 children. For CDP, this resulted in an increased OR for hay fever (aOR = 1.72, 95% CI: 1.13–2.63) (data not shown). However, the significant OR for OC use did not change.

A higher number of older siblings (birth order) showed a significant protective effect for hay fever (Table 6). For asthma or wheezing and for coughing, similar association was found although not statistically significant (Table 5).

Discussion

The findings support the hypothesis that children whose mothers used OC before pregnancy, are at a higher risk for developing asthma or wheezing, and frequent night-time or early morning cough at 11–12 yr of age. The data also supported the hypothesis that maternal CDP is a risk factor for atopic manifestations in offspring.

The association between OC use and asthma or wheezing and coughing is in concordance with a suggestion of Wjst et al. who, based on aggregative data on OC sales and hospital discharge data, were the first to hypothesize that maternal use of OC is a risk factor for asthma in the offspring (3). To the best of our knowledge, the present study is the first to prospectively assess the association between, maternal OC use and asthma or wheeze in offspring, using individual data.

The most frequently used OC in Jamaica during the study period was the Pearl®, in which the active components were ethinylloestradiol (30 µg) and levonorgestrel (150 µg), an estrogen and progesterone respectively. It has been suggested that women who use OC have higher estrogens levels after discontinuing its use (12), however, the evidence is not consistent (13).

The OC-atopy association may be explained by endocrine effects on T-helper 2 (Th₂) cells. Th₂ cells produce interleukin (IL)-4, IL-5, and IL-13, which promote the production of immunoglobulin E (IgE) and eosinophil infiltration in the airways and ultimately orchestrate the development of allergy and asthma (14–16). Wjst and coworkers suggest that estrogen might enhance the activity of Th₂ type cytokines (3), predisposing the fetus to atopic disorders later in life. Furthermore, *in vitro* studies suggest that progesterone promotes the preferential development of Th₂-type cells and functions as a potent inducer of the production of the Th₂ type cytokines (17–19). Michel et al. reported that IgE levels in cord blood were significantly increased among neonates whose mothers had taken progesterone during pregnancy (20).

We suggest two possible scenarios for the endocrine mechanism, which may explain our OC-atopy association. Either maternal exposure to estrogen via OC use may trigger an increase Th₂ activity continuing into pregnancy

Table 4. Proportion of atopic disorders in relation to their perinatal potential risk factors

Outcome (%)	Induced labor		Analgesic or anesthetic given during labor		Maternal complications during labor or delivery		Feeding			Birth weight			Child's illness or health problems in first 4 wk of life	
	Yes	No	Yes	No	Yes	No	Breast only	Breast and formulae	Formulae only	<2.5 kg	2.5–4.0 kg	>4.0 kg	Yes	No
	(n = 70)	(n = 970)	(n = 232)	(n = 794)	(n = 522)	(n = 518)	(n = 266)	(n = 449)	(n = 48)	(n = 125)	(n = 852)	(n = 45)	(n = 211)	(n = 829)
Asthma or wheezing	18.6	16.7	18.3	16.6	18.0	16.6	14.8	18.7	17.4	12.8	17.6	17.8	17.7	16.6
Frequent night-time or early morning cough	4.4	5.4	5.0	6.6	8.1	4.8	5.9	6.0	4.6	8.1	5.1	4.4	5.8	5.2
Eczema	11.4	6.0	12.2	4.7	7.3	6.2	6.8	6.1	6.5	3.2	6.7	8.9	10.5	5.3
Hay fever sinus problem or some other allergy	20.3	20.1	28.8	17.2	21.5	19.9	16.5	20.6	24.4	15.5	21.1	15.6	27.4	18.3

(prolonged Th₂ effect), consequently predisposing the fetus to a higher risk of developing atopy later in life, a Th₂-mediated disorder (15, 21, 22). Alternately, women who used OC continuously, discontinuing before becoming pregnant, may have created an environment of higher estrogen or progesterone levels (prolonged endocrine effect), resulting in an increased Th₂ activity impacting the fetus transplacentally.

Evidence for the prolonged Th₂ effect is supported by findings that women exposed *in utero* to the estrogen diethylstilbestrol, were found to have alterations in their T cell-mediated immunity (23). In addition, children of mothers who used OC in the 18 months prior to being pregnant were found to be more likely to have eczema at age 5 (24). This finding was later corroborated by Xu et al. (25).

Evidence in support of a prolonged endocrine effect: Xu et al. reported that atopy in adults was more common among those whose mothers experienced an early age of menarche (4). A likely explanation for the atopy – age at menarche association is that early age of menarche is associated with higher levels of estrogen in adult women (13, 26–28). Hence, the fetus of women with an early age at menarche may experience higher exposure to estrogens. This could then lead to the programming of the immune system of the fetus affecting atopic status later in life (29).

In a cross-sectional study, Frye et al. (30) provided data to support the prevailing OC-atopy association. They, however, downplayed the significance of this finding on the basis that similar results were found in the offspring of women who used OC exclusively after they delivered. It is noteworthy to accentuate the fact that Frye and coworkers used a cross-sectional design wherein OC use was assessed retrospectively. This design will no doubt be plagued with biases. These results may be an artifact of ‘reverse causation’ introduced by behavior modification of the parents. An example of this is; women in the ‘exclusive OC use after birth’ group may have chosen to resume the use of OC after the index child developed atopic eczema. The reason is that a child with eczema will require more attention at nights. Therefore, a mother with a demanding child may decide to delay having another by using OC.

There is a paucity of studies on the relationship between maternal CDP and the risk of having asthma or any atopic disorders. Nafstad et al. in a population-based study estimated the association between pregnancy complication and

Table 5. Odds ratios† and 95% confidence intervals (CI) of antenatal and perinatal risk factors for asthma or wheezing, and frequent night-time or early morning cough

Factors	Asthma or wheezing (n = 976)				Frequent night-time or early morning cough (n = 945)			
	cOR	95% CI	aOR	95% CI	cOR	95% CI	aOR	95% CI
Antenatal outcomes								
Maternal oral contraceptive use	1.62*	1.15–2.26	1.81*	1.25–2.61	2.17*	1.21–3.89	2.72*	1.41–5.24
Maternal complications during pregnancy	1.43*	1.03–1.99	1.27	0.86–1.81	1.30	0.75–2.28	0.90	0.47–1.71
Maternal infections during pregnancy	1.21	0.84–1.74	1.05	0.71–1.56	1.15	0.62–2.14	1.28	0.66–2.47
Maternal hospital admission during pregnancy	1.10	0.68–1.79	1.11	0.65–1.89	1.43	0.68–3.01	1.46	0.62–3.41
Smoking during pregnancy	0.63	0.31–1.28	0.70	0.33–1.46	0.99	0.35–2.82	1.07	0.35–3.20
Perinatal outcomes								
Induced labor	1.14	0.61–2.13	0.97	0.50–1.86	0.81	0.25–2.67	0.39	0.09–1.70
Analgesic or anesthetic given during labor	1.11	0.76–1.64	0.82	0.52–1.30	1.34	0.72–2.48	0.99	0.47–2.10
Maternal complications during delivery	1.10	0.70–1.74	1.10	0.67–1.82	1.74	0.89–3.39	1.70	0.80–3.64
Child's illness or health problems in first week of life	1.08	0.73–1.62	0.97	0.61–1.55	1.13	0.58–2.19	0.83	0.38–1.80
Number of older siblings	0.93	0.80–1.08	0.87	0.71–1.07	0.99	0.77–1.26	0.86	0.60–1.23
Birth weight (<2.5 kg)	0.69	0.39–1.20	0.64	0.36–1.17	1.66	0.81–3.41	1.58	0.72–3.47
Reference (2.5–4.0 kg)	1	1	1	1	1	1	1	1
>4.0 kg	1.01	0.46–2.22	1.07	0.48–2.41	0.87	0.20–3.73	0.50	0.07–3.85

*p-Value ≤ 0.05.

†Adjusted for variables in the table and additionally for gender and maternal age, education and access to health care.

Table 6. Odds ratios† and 95% confidence intervals (CI) of antenatal and perinatal risk factors for eczema, and hay fever or sinus problem or some other allergy

Factors	Eczema (n = 973)				Hay fever or sinus problem or some other allergy (n = 968)			
	cOR	95% CI	aOR	95% CI	cOR	95% CI	aOR	95% CI
Antenatal outcomes								
Maternal oral contraceptive use	1.35	0.81–2.24	1.21	0.69–2.12	0.98	0.72–1.33	1.01	0.71–1.43
Maternal complications during pregnancy	1.43	0.86–2.37	1.22	0.67–2.21	1.29	0.95–1.76	1.50*	1.05–2.16
Maternal infections during pregnancy	0.87	0.48–1.57	0.70	0.36–1.35	1.07	0.76–1.52	1.00	0.68–1.47
Maternal hospital admission during pregnancy	1.85	0.98–3.50	1.76	0.84–3.69	0.72	0.43–1.19	0.62	0.36–1.10
Smoking during pregnancy	1.01	0.39–2.60	1.25	0.42–3.74	0.50	0.25–1.03	0.70	0.33–1.49
Perinatal outcomes								
Induced labor	2.04	0.93–4.46	1.19	0.51–2.80	1.01	0.55–1.86	0.69	0.35–1.35
Analgesic or anesthetic given during labor	2.81*	1.68–4.71	1.54	0.83–2.87	1.96*	1.39–2.75	1.26	0.83–1.90
Maternal complications during delivery	1.19	0.61–2.34	0.78	0.36–1.68	1.10	0.72–1.68	0.82	0.50–1.34
Child's illness or health problems in first week of life	2.12*	1.24–3.63	1.62	0.87–3.02	1.69*	1.19–2.40	1.41	0.92–2.15
Number of older siblings	0.74*	0.58–0.95	0.76	0.55–1.06	0.73*	0.63–0.85	0.70*	0.57–0.86
Birth weight (<2.5 kg)	0.47	0.17–1.31	0.39	0.13–1.14	0.68	0.41–1.14	0.61	0.34–1.09
Reference (2.5–4.0 kg)	1	1	1	1	1	1	1	1
>4.0 kg	1.37	0.47–3.96	1.51	0.49–4.68	0.69	0.30–1.57	0.62	0.25–1.54

*p-Value ≤ 0.05.

†Adjusted for variables in the table and additionally for gender and maternal age, education and access to health care.

asthma by age 4 (5). The authors reported that uterus-related complication (antepartum hemorrhage, preterm contractions, insufficient placenta, and restricted growth of the uterus) increased the risk of having asthma (OR = 3.0, 95% CI: 1.8–5.4) and allergic rhinitis (OR = 2.9, 95% CI: 1.6–5.2). Annesi-Maesano et al. also found maternal CDP to be a risk factor of asthma (OR = 2.01, 95% CI: 1.52–2.67) in the offspring using a large British birth cohort (4065 natural children of 2583 mothers) (6). More recently, two studies have supported these find-

ings (31, 32), one by using data on Norwegian live births (1967–1993, n = 1,548,429) (31). Our study found maternal CDP to be a significant risk factor for hay fever and sinus problems (aOR = 1.5, 95% CI: 1.05–2.16, p = 0.03).

Further analyses for items included in our predictor CDP indicated that only the variable 'have there been any other complications, disorder or serious illness during this pregnancy?' conferred a significantly increased risk for asthma in the child (p < 0.001), but none of the specific items. This finding is in agreement

with a recent report by Nafstad et al. who also found that pregnancy complications in general might present risk factors of stress for the developing fetus (31). It might be that CDP is reflective of factors such as a threatened pregnancy, found to be associated with frequent wheezing (33), which will alter the Th_1/Th_2 balance (34, 35). This hypothesis warrants further investigations with adequate perinatal and breast-feeding information.

Our study adds to the body of evidence, which suggest that the number of siblings, in particular older siblings, is important in the etiology of atopic disorders (28). We found number of older siblings to be protective for hay fever or sinus problems (Table 6). Number of older siblings and OC use were statistically significantly correlated ($r_{\text{Spearman}} = 0.3$, $p = 0.0001$, $n = 1020$).

The lack of association between low-birth weight and asthma is in contrast to some previous studies (6, 36–38) and in agreement with others (39–42). It is worth mentioning that the finding from our Afro-Caribbean cohort is similar to that of an Afro-American (40).

The strengths of the current investigation are in its prospective design, being derived from a large population-based cohort, with all the exposure information collected during pregnancy, at birth and shortly after. This design presents a clear time-order, as outcomes were not assessed until approximately 11 yr after. The impact of recall bias is also reduced. Additionally, controlling for a broad range of confounders minimize the possibility of these findings occurring purely by chance.

A limitation of this study is the follow up proportion of 60.4%. This is largely explained by parental participation in the second follow up study. Although parental consent was obtained for the 1720 children evaluated using the child's completed reports, only 1163 parents provided interview and questionnaire data. The significant differences found between the characteristics of some of the variables from the baseline cohort when compared with those of the linked data set were expected. This we infer is due to the rural–urban difference between these groups.

The difference between reported occurrence of CDP in the baseline cohort (38.4%) and our subsample from Kingston/St Andrew (49.2%) is a possible source of selection bias. The baseline cohort has both rural and urban populations, whereas the subsample is predominantly urban. Different proportions of maternal complications in these samples can be explained by two factors, namely maternal education level and access to health care. For instance, of the women in our

subsample who reported having CDP, 3.6% were characterize as having low level education (less than secondary) and less access to health care compared with 8.9% of those with similar characteristics from the baseline cohort. Recently, McCaw-Binns et al. reported that access to health care in Jamaica differs from rural to urban areas (43). Since these two factors (maternal education level and access to health care) seem to affect the reported proportion of maternal complications, and as the prevalence of asthma, eczema, and sinus problems/allergies increase with level of education, they were included as confounders in our models to minimize the impact of a selection effect (Tables 5 and 6).

Another limitation is the absence of information on how long before pregnancy OC was used and if it was the last method of birth control used. This limitation introduces a non-differential misclassification, which tends to underestimate the association between OC and asthma or wheezing, and coughing. To evaluate, whether the OC hypothesis holds true, we investigated data of children from pregnancies that occurred despite birth control ($n = 90$), 42 with and 35 without using OCs. Asthma was more frequently reported at 11–12 yr of age in children whose mothers used OC, 23.6%, compare with 17.1% in children whose mothers did not use OC when they conceived.

We did not collect information on parental atopy and thus could not adjust for it in our model. While there is data showing parental history of atopy to be a risk factor for atopic disorders in the offspring, data supporting an association between parental history of atopy and OC use is lacking and the plausibility of such an association is questionable. Hence, it is highly unlikely that parental history of atopy would have confounded the association between OC and atopy, since confounding requires both, association with exposure and outcome (44).

The present study was not originally designed to address our hypotheses. However, an advantage of the cohort study design is that data collected can be used to provide answers to newly emerging research questions. We therefore took advantage of the utility and efficiency of this study to test our respective hypotheses. Additionally, the unique nature of this cohort makes this the first study to test perinatal risk factors for asthma in an Afro-Caribbean population.

Regarding coughing, we asked for 'frequent night-time or early morning coughing', but did not include the adjective 'dry'. Nevertheless, the validity of 'early morning coughing' as a marker for asthma has been found to be sufficient

(45, 46). Furthermore, it has been shown that bronchial hyper-reactivity was not related to dry cough or to nocturnal cough (47). According to Chang, coughing and bronchoconstriction may be caused by different mechanisms. Hence, different asthma-like symptoms may indicate different features (48).

The definition or measurement of asthma or wheezing may also be of concern as wheezing is a heterogeneous disorder (49) and not all that wheezes is asthma (11). The impact this misclassification may have, was assessed by combining the variables asthma or wheezing and frequent night-time or early morning cough to create a compound outcome variable. The combined condition was less prevalent and represented a more specific state of bronchial reactivity. The association between the combined variable and maternal OC use before pregnancy was assessed and results showed a stronger association (aOR = 3.15, 95% CI: 1.29–7.71). Additionally, we investigated whether the association with asthma was more likely due to an atopic response. For this purpose, we combined two variables: having both, asthma and allergies. The association between maternal OC and the new combined variable was stronger (aOR = 2.26, 95% CI: 1.18–4.35) compared to the association with only asthma (aOR = 1.81, 95% CI: 1.25–2.61). This strengthening suggests that the association is likely to have been the result of an atopic mechanism.

In summary, this data contributes to existing literature suggesting that maternal OC use may be important in the development of asthma in offspring. In particular, the data helps to address the ongoing question as to whether it is 'hormones or hygiene?' (50) that is responsible for atopy. There are only a few existing studies that allow for the investigation of maternal OC use and the child's risk of atopic manifestation. The hypothesis that OC use may contribute to an increase of asthma in children as put forward by Wjst (3) is very thought provoking. We suggest this hypothesis be tested in future studies with more precise exposure assessment.

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