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# Self-Reported Parental Exposure to Pesticide during Pregnancy and Birth Outcomes: The Mecoxpo Cohort Study

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## Abstract

The Mecoxpo study was performed in the Picardy region of northern France, in order to investigate the putative relationship between parental exposures to pesticides (as reported by the mother) on one hand and neonatal parameters on the other. The cohort comprised 993 mother-newborn pairs. Each mother completed a questionnaire that probed occupational, domestic, environmental and dietary sources of parental exposure to pesticides during her pregnancy. Multivariate regression analyses were then used to test for associations between the characteristics of parental pesticide exposure during pregnancy and the corresponding birth outcomes. Maternal occupational exposure was associated with an elevated risk of low birth weight (odds ratio (OR) [95% confidence interval]: 4.2 [1.2, 15.4]). Paternal occupational exposure to pesticides was associated with a lower than average gestational age at birth (−0.7 weeks;  $p = 0.0002$ ) and an elevated risk of prematurity (OR: 3.7 [1.4, 9.7]). Levels of domestic exposure to veterinary antiparasitics and to pesticides for indoor plants were both associated with a low birth weight (−70 g;  $p = 0.02$  and −160 g;  $p = 0.005$ , respectively). Babies born to women living in urban areas had a lower birth length and a higher risk of low birth length (−0.4 cm,  $p = 0.006$  and OR: 2.9 [1.5, 5.5], respectively). The present study results mainly demonstrate a negative correlation between fetal development on one hand and parental occupational and domestic exposure to pesticides on the other. Our study highlights the need to perform a global and detailed screening of all potential physiological effects when assessing in utero exposure to pesticides.

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## Introduction

Human exposure to pesticides is a very complex phenomenon, since it involves many different compounds, sources of exposure and exposure pathways (i.e. respiratory, cutaneous and intestinal pathways). Once pesticides have been applied, the primary compounds and their degradation products are dispersed into the air, water and soil. Human exposure to pesticides can be occupational (through agriculture, floristry, municipal maintenance, etc.), dietary (through the consumption of food contaminated by pesticide residues), domestic (through the spraying of houseplants or garden plants, the eradication of domestic insect pests (such as mosquitoes, flies, etc.) and the use of antiparasitics in humans or in domestic pets) or environmental (i.e. the inhalation of volatilized pesticides of agricultural or non-agricultural origin) [1–2]. Although occupational exposure has been extensively investigated, there are few studies of domestic exposure [2].

Pesticide exposure during pregnancy is becoming an increasingly important public health issue because it may affect the development of the exposed fetus. The association between

pesticide exposure in pregnant women and fetal growth has [11,14]. However, this topic is still subject to debate because the various studies did not reach consistent conclusions - probably because of differences in location, exposure assessment methods and the type and number of compounds investigated [3–12]. Furthermore, most of these epidemiological studies focused on a very specific population, such as farmers or other populations with high levels of pesticide exposure (e.g. those living near to crop-farming areas or other areas with intensive pesticide use). To the best of our knowledge, very few studies [9,10,13,14] have studied the relationship between “routine” domestic/dietary parental exposure on one hand and birth outcomes on the other. There are few data on the need for prevention of these types of exposure, and these data can only be gathered in general population cohorts.

The primary objective of the present Mecoxpo study was to assess the different types of prenatal exposure to pesticides in the Picardy region of northern France (a region which is characterized by a high birth rate (13.1‰, according to the French National Institute of Statistics and Economic Studies (*Institut National de la*

*Statistique et des Études Économiques*), relative to the national average. A secondary objective was to investigate the relationship between the different modes of exposure on one hand and birth outcomes on the other. Prenatal exposure to pesticides was assessed via a self-questionnaire filled out by the mother; this is the only method that can simultaneously gather information on all the various sources of intrauterine exposure to pesticides (i.e. occupational, domestic, environmental and dietary exposure) in a sample of the general population.

## Methods

### 2.1 Study participants

The Mecoxpo cohort (comprising 993 mother-newborn pairs) was recruited between January 2011 and January 2012. Eleven of Picardy's 16 maternity clinics agreed to participate in the study. Unfortunately, the region's neonatal intensive care units (which treat newborns suffering from a severe neonatal disease or with a gestational age <32 weeks at birth) did not participate.

To be included in the Mecoxpo cohort, the mother had to be had to be (i) 18 years of age or older and (ii) fluent enough in French to understand the study's objectives and procedures. Mothers aged under 18 and mothers who did not have full parental authority over their child (such as incarcerated persons) were excluded from the study. Multiple births were also excluded from the present study.

The study and both maternal and neonatal data collection (questionnaire, medical records) were approved by the local investigational review board (*Comité de Protection des Personnes dans la Recherche Biomédicale de Picardie*). Potential participants were given a verbal presentation of the study by their attending pediatrician in the maternity clinic. All mothers signed an informed consent giving us permission to enroll them and their infants in the study. A study information sheet was given to the women prior to their completion of the study questionnaire. During completion of the self-administered questionnaire, an investigating physician was always on hand to provide explanations but did not influence the answers. In view of the many different aspects of possible exposure probed by the questionnaire and in order to shorten and facilitate the questionnaire's completion, the respondent was instructed not to answer a given question if in any doubt. Most of the questions were "yes"/"no" or multiple choice questions. Open questions were used to gather additional information, when necessary. None of the data collected during the study enabled the direct identification of participants.

### 2.2 Characteristics of intrauterine exposure to pesticides in a questionnaire-based survey

Mothers from the cohort completed the questionnaire during their stay in the maternity clinic (4 to 5 days after giving birth). The questionnaire addressed occupational, domestic, environmental and dietary sources of pesticide exposure. Prior to use in the study, the questionnaire was validated in a sample of 25 women (aged between 25 and 45 and from various socio-professional categories). It was then modified by taking account of the women's answers, comments and questions. The final questionnaire comprised 44 items and took respondees about 15 minutes to read and complete.

**2.2.1 Occupational exposure to pesticides.** The mother was asked to state (i) whether she had ever worked during the pregnancy (and, if so, the duration), (ii) whether her occupation and/or that of the father involved exposure to pesticides (e.g. in agriculture, animal husbandry, gardening, etc.) and (iii) the modalities of maternal exposure to pesticides (the duration and

location of exposure, the type of compound and the use or not of protective equipment).

**2.2.2 Domestic exposure to pesticides.** The questionnaire probed possible uses of pesticides in the mother's home during her pregnancy (whether applied directly by the mother or indirectly by another person). The mother was asked to report use of (i) antiparasitics for human administration (to treat lice, scabies, ticks, etc.), (ii) antiparasitics for domestic pets (to treat fleas, ticks, etc.) and the number and type of treated animals, (iii) insecticides, herbicides, fungicides and plant growth regulators for treating houseplants or garden plants and (iv) pesticides for eradicating domestic insect pests (such as flies, mosquitoes, etc.).

**2.2.3 Environmental exposure to pesticides.** The mother was asked to state whether she lived within 1 km of (i) green areas (a park, a sports field, etc.), (ii) a crop field, (iii) a highway, a railway or an airport. The mother was also asked to state the locality in which she had lived during her pregnancy. We then queried a database (produced by the French National Institute of Statistics and Economic Studies) to obtain the population density for each locality. The localities were then arbitrarily divided into rural localities (<2 000 inhabitants/km<sup>2</sup>) and urban localities (≥2 000 inhabitants/km<sup>2</sup>).

**2.2.4 Questions on dietary exposure.** The mother was asked to state (i) her total dietary intake of the main food categories (fruits and vegetables, cereals, milk products and meat) during pregnancy (possible answers were "never or almost never", "not every day", "every day", "several times a day") and (ii) the frequency with which the consumed fruits and vegetables, milk products and meat were organic foods (with possible answers of "never", "sometimes", "most of the time").

### 2.3 Birth outcomes

Neonatal data - gestational age (weeks of amenorrhea), birth weight (g), birth length (cm) and head circumference at birth (cm) - were extracted from medical records by the maternity clinic's pediatrician. Prematurity was defined as birth before 37 weeks of amenorrhea. Low birth weight or length was defined as a birth weight or length (adjusted for the mother's age, weight, and height, the rank of pregnancy, the gestational age and the baby's gender) below the 5<sup>th</sup> percentile (relative to normative data for France) [15–16]. Small head circumference was defined as a measurement (adjusted for gestational age and the baby's gender) below the 5<sup>th</sup> percentile (relative to normative data for France) [15]. Infants with missing neonatal or maternal data on adverse birth outcomes were not considered in these analyses.

### 2.4 Confounding factors

Factors known or suspected (on the basis of the scientific literature) to have an effect on fetal development were considered as confounding factors, i.e. the mother's age and body mass index (BMI), parity, diabetes, hypertension, tobacco use, alcohol use, drug abuse, socioprofessional category (educational level and type of work), and the baby's gender.

### 2.5 Data processing

The study data (questionnaire data, birth outcomes and covariates) were recorded using Sphinx plus<sup>2</sup> software (version 5.1.0.6, Le Sphinx Développement, Chavanod, France). Some questionnaire answers were combined, in order to obtain new, composite variables that were more relevant than those obtained from single questions. Thus, the composite variables used in the assessment of intrauterine exposure to pesticides included maternal or paternal occupational exposure, maternal domestic exposure to human antiparasitics, veterinary antiparasitics, and

**Table 1.** Maternal characteristics in the MecoExpo cohort (n = 993).

| Variables                               | Mean (SD)  |
|---|------------|
| Age (year)                              | 29 (5.2)   |
| Parity:                                 | n(%)       |
| Primiparous                             | 409 (41.7) |
| Multiparous                             | 573 (58.3) |
| Missing data                            | 11         |
| Maternal diabetes during pregnancy:     | n(%)       |
| Yes                                     | 62 (6.2)   |
| No                                      | 931 (93.8) |
| Maternal hypertension during pregnancy: | n(%)       |
| Yes                                     | 47 (4.7)   |
| No                                      | 946 (95.3) |
| Maternal smoking during pregnancy:      | n(%)       |
| Yes                                     | 293 (29.5) |
| No                                      | 700 (70.5) |
| Maternal educational level:             | n(%)       |
| ≤High school completed                  | 504 (53.7) |
| >High school completed                  | 434 (46.3) |
| Missing data                            | 55         |
| Working during pregnancy:               | n(%)       |
| Yes                                     | 671 (67.6) |
| No                                      | 322 (32.4) |
| Place of residence during pregnancy:    | n(%)       |
| Rural locality                          | 774 (85.9) |
| Urban locality                          | 127 (14.1) |
| Missing data                            | 92         |

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**Table 2.** Newborn characteristics in the MecoExpo cohort (n = 993).

| Variables                        | Mean (SD)  | n (%)      |
|----------------------------------|------------|------------|
| Gestational age (weeks)          | 39.3 (1.3) | 924 (93.1) |
| Missing data                     |            | 69 (6.9)   |
| Birth weight (g)                 | 3340 (492) | 932 (93.9) |
| Missing data                     |            | 61 (6.1)   |
| Birth length (cm)                | 49.5 (2.1) | 922 (92.8) |
| Missing data                     |            | 71 (7.2)   |
| Head circumference at birth (cm) | 34.4 (1.4) | 911 (91.7) |
| Missing data                     |            | 82 (8.3)   |
| Gender:                          |            |            |
| male                             |            | 508 (51.2) |
| female                           |            | 485 (48.8) |
| Prematurity:                     |            |            |
| Yes                              |            | 24 (2.6)   |
| No                               |            | 900 (97.4) |
| Missing data                     |            | 69         |
| Low birth weight:                |            |            |
| Yes                              |            | 788 (94.9) |
| No                               |            | 42 (5.1)   |
| Missing data                     |            | 163        |
| Low birth length:                |            |            |
| Yes                              |            | 56 (6.8)   |
| No                               |            | 764 (93.2) |
| Missing data                     |            | 173        |
| Small head circumference:        |            |            |
| Yes                              |            | 34 (4.0)   |
| No                               |            | 822 (96.0) |
| Missing data                     |            | 137        |

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domestic pesticides for houseplants or garden plants, environmental exposure (the home’s proximity to a crop fields, green areas, highways, railways or airports) and dietary exposure (consumption of fruits and vegetables, cereals, milk products and meat; consumption of organic fruits and vegetables, etc.).

### 2.6 Statistical analyses

The MecoExpo cohort’s demographics and intrauterine exposure to pesticides were first characterized in a descriptive analysis. Quantitative parameters (gestational age, birth weight, etc.) were expressed as the mean and the standard deviation (SD). Qualitative parameters (prematurity, low birth weight, maternal occupational exposure to pesticides, etc.) were expressed as the number and the percentage of the study population.

Multivariate linear regression and logistic regression analyses were used to study the putative associations between birth outcomes and the characteristics of *in utero* exposure to pesticides. Using forward selection, covariates with a p-value<0.20 in a univariate analysis were fed into the multivariate analyses. The risk of an adverse birth outcome (prematurity, small head circumference, and low birth weight and low birth length) was expressed as an odds ratio (OR) [95% confidence interval (CI)]. The 95% CI was calculated according to Woolf’s method, with an

alpha risk of 0.05. All statistical analyses were performed with SPSS software (V.20.0, Chicago, IL, USA).

## Results

### 3.1 Characteristics of the study population

A total of 993 mother-newborn pairs were included in the MecoExpo cohort. Given that some questionnaire answers or clinical values were missing, the total n for some variables was below 993 and so the corresponding missing data rates are also reported.

The characteristics of the MecoExpo study population are summarized in Table 1 and Table 2. The mean (SD) maternal age was 29 (5.2) and the mean pre-pregnancy BMI was 24.4 (5.5) kg/m<sup>2</sup>. Six percent of the mothers were diabetic and less than 5% had arterial hypertension during pregnancy. Forty-two percent of the women were primiparous, 46% had completed high school and 68% had been working during their pregnancy. About 30% of the mothers stated smoking during pregnancy; the corresponding values for drinking alcohol and illicit drug use were 3% and 1%, respectively. Overall, 86% of the women lived in rural localities (<2 000 inhabitants/km<sup>2</sup>).

**Table 3.** Characteristics of prenatal exposure to pesticides (n = 993).

| Variables  | n (%)      |
|--|------------|
| <b>Occupational exposure to pesticides</b>           |            |
| Mother:  |            |
| Yes  | 43 (4.3)   |
| No   | 950 (95.7) |
| Father:  |            |
| Yes  | 86 (8.7)   |
| No   | 907 (91.3) |
| <b>Maternal domestic exposure to pesticides</b>      |            |
| Human antiparasitics:                                |            |
| Yes  | 328 (33.0) |
| No   | 665 (67.0) |
| Veterinary antiparasitics:                           |            |
| Yes  | 215 (21.7) |
| No   | 776 (78.3) |
| Missing data   | 2          |
| Pesticides against insects:                          |            |
| Yes  | 127 (13.0) |
| No   | 850 (87.0) |
| Missing data   | 16         |
| Pesticides for indoor plants:                        |            |
| Yes  | 37 (3.7)   |
| No   | 956 (96.3) |
| Pesticides for outdoor plants:                       |            |
| Yes  | 166 (17.0) |
| No   | 813 (83.0) |
| Missing data   | 14         |
| <b>Maternal environmental exposure to pesticides</b> |            |
| Proximity to a crop field (<1 km):                   |            |
| Yes  | 527 (58.2) |
| No   | 378 (41.8) |
| Missing data   | 88         |
| Proximity to a green area:                           |            |
| Yes  | 707 (72.7) |
| No   | 266 (27.3) |
| Missing data   | 20         |
| Proximity to a highway, railway or airport:          |            |
| Yes  | 366 (37.4) |
| No   | 612 (62.6) |
| Missing data   | 15         |

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### 3.2 Characteristics of in utero exposure to pesticides

The main characteristics of prenatal exposure to pesticides (as assessed by the mothers' questionnaire data) are summarized in Table 3 and 4.

**3.2.1 Occupational exposure to pesticides.** 43 mothers and 86 fathers (4.3% and 8.7% of the total sample, respectively) worked in an occupation in which there was potential for exposure to pesticides. Fifteen mothers and 42 fathers (1.5% and 4.2% of the total sample, respectively) had agricultural occupations.

**Table 4.** Characteristics of prenatal exposure to pesticides (n = 993) (continued).

| Variables  | n (%)      |
|--|------------|
| <b>Maternal dietary exposure to pesticides (total food intake)</b>   |            |
| Fruits and vegetables:   |            |
| Never or almost never  | 18 (1.8)   |
| Not every day  | 319 (32.3) |
| Every day  | 362 (36.6) |
| Several times a day  | 289 (29.3) |
| Missing data   | 5          |
| Cereals:   |            |
| Never or almost never  | 4 (0.4)    |
| Not every day  | 173 (17.6) |
| Every day  | 532 (54.1) |
| Several times a day  | 274 (27.9) |
| Missing data   | 10         |
| Dairy products:  |            |
| Never or almost never  | 8 (0.8)    |
| Not every day  | 111 (11.3) |
| Every day  | 430 (43.7) |
| Several times a day  | 436 (44.3) |
| Missing data   | 8          |
| Meat:  |            |
| Never or almost never  | 23 (2.4)   |
| Not every day  | 365 (37.5) |
| Every day  | 489 (50.2) |
| Several times a day  | 97 (10.0)  |
| Missing data   | 19         |
| <b>Maternal dietary exposure to pesticides (organic food intake)</b> |            |
| Fruits and vegetables:   |            |
| Never  | 518 (52.4) |
| Sometimes  | 375 (38.0) |
| Most of the time   | 95 (9.6)   |
| Missing data   | 5          |
| Dairy products:  |            |
| Never  | 654 (66.3) |
| Sometimes  | 265 (26.9) |
| Most of the time   | 68 (6.9)   |
| Missing data   | 6          |
| Meat:  |            |
| Never  | 827 (84.0) |
| Sometimes  | 137 (13.9) |
| Most of the time   | 20 (2.0)   |
| Missing data   | 9          |

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**3.2.2 Domestic exposure to pesticides.** 33% of the mothers were exposed to human antiparasitics, with 22% exposed to veterinary antiparasitics, 13% exposed to domestic insecticides, 4% exposed to pesticides for houseplants and 17% exposed to pesticides for garden plants.

**Table 5.** Multivariate associations between factors related to *in utero* exposure to pesticides and gestational age and prematurity.

| Variable                                    | Gestational age (weeks) |              | Prematurity    |                 |
|---|-------------------------|--------------|----------------|-----------------|
|   | n                       | Mean (SD)    | Cases/controls | OR [95% CI]     |
| <b>Total sample</b>                         | 924                     | -            | 24/900         | -               |
| <b>Occupational exposure</b>                |                         |              |                |                 |
| Mother:                                     |                         |              |                |                 |
| Yes   | 21                      | 39.2 (1.4)   | 1/20           | NA              |
| No  | 903                     | 39.5 (1.3)   | 23/880         | Reference       |
| Father:                                     |                         |              |                |                 |
| Yes   | 80                      | 38.8 (1.7)** | 6/74           | 3.7 [1.4, 9.7]* |
| No  | 844                     | 39.5 (1.3)   | 18/826         | Reference       |
| <b>Maternal domestic exposure</b>           |                         |              |                |                 |
| Human antiparasitics:                       |                         |              |                |                 |
| Yes   | 307                     | 39.6 (1.2)   | 7/300          | 0.8 [0.3, 2.0]  |
| No  | 617                     | 39.4 (1.4)   | 17/600         | Reference       |
| Veterinary antiparasitics:                  |                         |              |                |                 |
| Yes   | 201                     | 39.4 (1.4)   | 6/195          | 1.2 [0.5, 3.1]  |
| Non   | 721                     | 39.5 (1.3)   | 18/703         | Reference       |
| Missing data                                | 2                       | -            | 0/2            | -               |
| Pesticides against insects:                 |                         |              |                |                 |
| Yes   | 115                     | 39.6 (1.2)   | 3/112          | 1.0 [0.3, 3.4]  |
| No  | 794                     | 39.4 (1.3)   | 20/774         | Reference       |
| Missing data                                | 15                      | -            | 1/14           | -               |
| Pesticides for indoor plants:               |                         |              |                |                 |
| Yes   | 35                      | 39.4 (1.2)   | 1/34           | NA              |
| No  | 889                     | 39.5 (1.3)   | 23/866         | Reference       |
| Pesticides for outdoor plants:              |                         |              |                |                 |
| Yes   | 156                     | 39.5 (1.2)   | 2/154          | NA              |
| No  | 754                     | 39.5 (1.3)   | 21/733         | Reference       |
| Missing                                     | 14                      | -            | 1/13           | -               |
| <b>Maternal environmental exposure</b>      |                         |              |                |                 |
| Proximity to a crop field:                  |                         |              |                |                 |
| Yes   | 490                     | 39.4 (1.4)   | 17/473         | 2.1 [0.8, 5.4]  |
| No  | 356                     | 39.6 (1.3)   | 6/350          | Reference       |
| Missing data                                | 78                      | -            | 1/77           | -               |
| Proximity to a green area:                  |                         |              |                |                 |
| Yes   | 660                     | 39.5 (1.3)   | 19/641         | 1.8 [0.6, 5.3]  |
| No  | 244                     | 39.5 (1.3)   | 4/240          | Reference       |
| Missing data                                | 20                      | -            | 1/19           | -               |
| Proximity to a highway, railway or airport: |                         |              |                |                 |
| Yes   | 339                     | 39.5 (1.3)   | 8/331          | 0.9 [0.4, 2.2]  |
| No  | 571                     | 39.5 (1.3)   | 15/556         | Reference       |
| Missing data                                | 14                      | -            | 1/13           | -               |

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**3.2.3 Environmental exposure to pesticides.** 58% of the mothers lived near to a crop field crop, 73% lived near to a green area and 37% lived near to a highway, railroad line or airport.

**3.2.4 Dietary exposure to pesticides.** 29% of mothers consumed fruits and vegetables “several times” a day and 44% consumed milk products “several times a day”. Fifty percent consumed cereals “every day” and 50% consumed meat “every day”.

Only 10% of the mothers consumed organic fruits and vegetables “most of the time”, whereas the corresponding proportions organic milk products and organic meat were 7% and 2%, respectively.

**3.3 Multivariate associations between fetal growth and estimated in utero exposure to pesticides**

**3.3.1 Gestational age and prematurity (Table 5, 6).** Estimated paternal occupational exposure to pesticides was significantly associated with lower gestational age (−0.7 weeks, relative to infants whose parents were not occupationally exposed to pesticides;  $p = 0.006$ ) and a higher risk of prematurity (OR [95% CI]: 3.7 [1.4, 9.7];  $p = 0.02$ ). Maternal exposure (whether occupational, domestic, environmental or dietary) was not significantly associated with either gestational age or the risk of prematurity.

**3.3.2 Birth weight (as a continuous variable) and low birth (Table 7, 8).** Estimated maternal occupational exposure was associated with higher risk of low birth weight (OR [95% CI]: 4.2 [1.2, 15.4];  $p = 0.01$ ). Exposure to human and veterinary antiparasitics were both significantly associated with a lower birth weight (−70 g;  $p = 0.02$  and −85 g;  $p = 0.04$ , respectively). Exposure to pesticides for houseplants was also associated with lower birth weight (−160 g;  $p = 0.03$ ). No association with dietary exposure was observed.

**3.3.3 Birth length (as a continuous variable) and low birth length (Table 9, 10).** The risk of low of low birth length was significantly associated with the mother’s residence in an urban area (OR [95% CI]: 2.9 [1.5, 5.5];  $p = 0.01$ ). No associations with parental occupational exposure or dietary exposure were observed.

**3.3.4 Birth head circumference at birth (as a continuous variable) and small head circumference (Table 11, 12).** In multivariate statistical models, no significant association was found between head circumference at birth or small head circumference on one hand and the variables describing the *in utero* exposure to pesticides on the other.

**Discussion**

To the best of our knowledge, this study is the first one to simultaneously examine the association between all sources of *in utero* exposure to pesticides (i.e. occupational, domestic, environmental and dietary sources) and four common descriptors of fetal development (gestational age, birth weight, birth length and head circumference at birth). The prevalence of fetal growth restriction with respect to these parameters (i.e. prematurity, low birth weight, low birth length and small head circumference) was also considered.

Fetal growth is conditioned by many different environmental, genetic, metabolic, nutritional and placental factors. It is well known that adverse fetal growth is a good predictor of neonatal mortality and morbidity [17–19]. Fetal growth restriction may therefore be a determining factor for some diseases of childhood (since infants with poor head growth appear to run an increased risk of cerebral palsy, cognitive impairment and behavioral disorders) [20,21] (ii) diseases of adolescence (since extremely low birth weight may be associated with a higher prevalence of developmental delay, neurosensory impairments (seizures, visual

**Table 6.** Multivariate associations between factors related to *in utero* exposure to pesticides and gestational age and prematurity (continued).

|  |     |            |        |                 |
|--|-----|------------|--------|-----------------|
| Place of residence during pregnancy:                   |     |            |        |                 |
| Rural locality   | 714 | 39.4 (1.4) | 21/693 | Reference       |
| Urban locality   | 123 | 39.6 (1.3) | 1/122  | NA              |
| Missing data   | 87  | -          | 2/85   | -               |
| <b>Maternal dietary exposure (total food intake)</b>   |     |            |        |                 |
| Fruits and vegetables:                                 |     |            |        |                 |
| Never or almost never                                  | 16  | 39.3(1.4)  | 0/16   | NA              |
| Not every day  | 298 | 39.5(1.3)  | 8/290  | Reference       |
| Every day  | 333 | 39.4(1.3)  | 10/323 | 1.1 [0.4, 2.9]  |
| Several times a day                                    | 272 | 39.6(1.3)  | 6/266  | 0.8 [0.3, 2.4]  |
| Missing data   | 5   | -          | 0/5    | -               |
| Cereals:   |     |            |        |                 |
| Never or almost never                                  | 4   | 39.7 (0.5) | 0/3    | NA              |
| Not every day  | 162 | 39.4 (1.2) | 3/159  | Reference       |
| Every day  | 488 | 39.5 (1.4) | 15/473 | 1.7 [0.5, 5.9]  |
| Several times a day                                    | 260 | 39.5(1.3)  | 6/254  | 1.3 [0.3, 5.1]  |
| Missing data   | 79  | -          | 0/79   | -               |
| Dairy products:  |     |            |        |                 |
| Never or almost never                                  | 7   | 39.6 (0.7) | 0/7    | NA              |
| Not every day  | 105 | 39.4 (1.1) | 2/103  | Reference       |
| Every day  | 399 | 39.4 (1.3) | 10/389 | 1.3 [0.3, 6.1]  |
| Several times a day                                    | 405 | 39.5 (1.4) | 12/393 | 1.6 [0.4, 7.1]  |
| Missing data   | 8   | -          | 0/8    | -               |
| Meat:  |     |            |        |                 |
| Never or almost never                                  | 22  | 39.5 (2.0) | 1/21   | NA              |
| Not every day  | 338 | 39.5 (1.2) | 4/334  | Reference       |
| Every day  | 458 | 39.4 (1.4) | 16/442 | 3.0 [1.0, 9.1]  |
| Several times a day                                    | 88  | 39.5 (1.6) | 3/85   | 3.0 [0.7, 13.4] |
| Missing  | 87  | -          | 0/87   | -               |
| <b>Maternal dietary exposure (organic food intake)</b> |     |            |        |                 |
| Fruits and vegetables:                                 |     |            |        |                 |
| Never  | 481 | 39.4 (1.4) | 13/468 | 0.6 [0.2, 1.9]  |
| Sometimes  | 347 | 39.6 (1.2) | 7/340  | 0.5 [0.1, 1.6]  |
| Most of the time                                       | 91  | 39.3 (1.5) | 4/87   | Reference       |
| Missing data   | 5   | -          | 0/5    | -               |
| Dairy products:  |     |            |        |                 |
| Never  | 607 | 39.5 (1.3) | 17/590 | 1.8 [0.2, 13.9] |
| Sometimes  | 247 | 39.5 (1.3) | 6/241  | 1.6 [0.2, 13.3] |
| Most of the time                                       | 64  | 39.5 (1.3) | 1/63   | Reference       |
| Missing data   | 6   | -          | 0/6    | -               |
| Meat:  |     |            |        |                 |
| Never  | 773 | 39.5 (1.3) | 21/752 | Reference       |
| Sometimes  | 124 | 39.5 (1.3) | 2/122  | NA              |
| Most of the time                                       | 18  | 39.2 (1.4) | 1/17   | NA              |
| Missing data   | 78  | -          | 0/78   | -               |

\*p = 0.05;

\*\*p = 0.01;

\*\*\*p = 0.001.

NA: an odds ratio was not available because too few cases were observed (n<3).

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**Table 7.** Multivariate associations between (i) variables related to *in utero* exposure to pesticides, (ii) birth weight (BW, in g) and low birth weight (LBW).

| Variables                                   | BW (g) |              | LBW            |                   |
|---|--------|--------------|----------------|-------------------|
|   | n      | Mean (SD)    | Cases/controls | OR [95% CI]       |
| <b>Total sample</b>                         | 932    |              | 42/786         |                   |
| <b>Occupational exposure</b>                |        |              |                |                   |
| Mother:                                     |        |              |                |                   |
| Yes   | 19     | 3177 (521)   | 3/14           | 4.2 [1.2, 15.4]** |
| No  | 913    | 3343 (491)   | 39/772         | Reference         |
| Father:                                     |        |              |                |                   |
| Yes   | 83     | 3213 (517)   | 1/96           | NA                |
| No  | 849    | 3353 (488)   | 41/690         | Reference         |
| <b>Domestic exposure</b>                    |        |              |                |                   |
| Humans antiparasitic:                       |        |              |                |                   |
| Yes   | 309    | 3397 (477)*  | 11/241         | 0.8 [0.4, 1.6]    |
| No  | 623    | 3312 (497)   | 31/545         | Reference         |
| Veterinary antiparasitic:                   |        |              |                |                   |
| Yes   | 206    | 3286 (520)*  | 10/177         | 1.1 [0.5, 2.3]    |
| No  | 724    | 3358 (482)   | 31/608         | Reference         |
| Missing data                                | 2      | -            | 1/1            | -                 |
| Pesticides against insects:                 |        |              |                |                   |
| Yes   | 120    | 3373 (472)   | 4/95           | 0.8 [0.3, 2.2]    |
| No  | 796    | 3338 (493)   | 37/680         | Reference         |
| Missing data                                | 16     | -            | 1/11           | -                 |
| Pesticides for indoor plants:               |        |              |                |                   |
| Yes   | 33     | 3186 (464)** | 2/26           | NA                |
| No  | 899    | 3346 (492)   | 40/760         | Reference         |
| Pesticides for outdoor plants:              |        |              |                |                   |
| Yes   | 156    | 3369 (479)   | 2/136          | NA                |
| No  | 762    | 3337 (492)   | 40/638         | Reference         |
| Missing data                                | 14     | -            | 0/12           | -                 |
| <b>Environmental exposure</b>               |        |              |                |                   |
| Proximity to a crop field:                  |        |              |                |                   |
| Yes   | 490    | 3328 (491)   | 25/411         | 1.2 [0.6, 2.4]    |
| No  | 359    | 3352 (486)   | 15/304         | Reference         |
| Missing data                                | 83     | -            | 2/71           | -                 |
| Proximity to a green area:                  |        |              |                |                   |
| Yes   | 663    | 3365 (498)   | 26/564         | 0.6 [0.3, 1.1]    |
| No  | 250    | 3275 (470)   | 16/204         | Reference         |
| Missing data                                | 19     | -            | 0/18           | -                 |
| Proximity to a highway, railway or airport: |        |              |                |                   |
| Yes   | 344    | 3380 (523)   | 15/259         | 0.9 [0.5, 1.8]    |
| No  | 573    | 3317 (470)   | 27/484         | Reference         |
| Missing data                                | 15     | -            | 0/13           | -                 |

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problems), learning disabilities and hyperactivity) and diseases of adulthood (hypertension, diabetes and hyperlipidemia) [20,21]. Unfortunately, these factors are only seldom analyzed in the literature.

The inconsistency of the literature results may be explained (at least in part) by the fact that studies evaluating the association between pesticide exposure and fetal growth have used several

different definitions of low birth weight. In fact, studies considering the proportion of small-for-gestational-age infants generally consider the 10<sup>th</sup> percentile and include only the gestational age (plus, in some cases, the baby's gender) as an adjustment parameter. In contrast, our study low birth weight or length as being below the 5<sup>th</sup> percentile after adjustment for various maternal and neonatal characteristics (the mother's age, weight,



**Table 8.** Multivariate associations between (i) variables related to *in utero* exposure to pesticides, (ii) birth weight (BW, in g) and low birth weight (LBW) (continued).

| <b>Dietary exposure (Total food intake)</b>   |     |            |        |                |
|---|-----|------------|--------|----------------|
| Fruits and vegetables:                        |     |            |        |                |
| Never or almost never                         | 17  | 3152 (501) | 2/13   | Reference      |
| Not every day                                 | 298 | 3316 (481) | 16/250 | 0.4 [0.1, 2.0] |
| Every day                                     | 342 | 3329 (483) | 11/289 | 0.3 [0.1, 1.3] |
| Several times a day                           | 270 | 3388 (511) | 13/230 | 0.4 [0.1, 1.8] |
| Missing data                                  | 5   | -          | 0/4    | -              |
| Cereals:                                      |     |            |        |                |
| Never or almost never                         | 4   | 3525 (527) | 0/4    | NA             |
| Not every day                                 | 164 | 3360 (466) | 7/141  | Reference      |
| Every day                                     | 495 | 3321 (489) | 22/409 | 0.6 [0.3, 1.5] |
| Several times a day                           | 259 | 3360 (508) | 12/227 | 1.1 [0.4, 2.8] |
| Missing data                                  | 71  | -          | 1/5    | -              |
| Dairy products:                               |     |            |        |                |
| Never or almost never                         | 8   | 3098 (431) | 1/5    | NA             |
| Not every day                                 | 103 | 3251 (473) | 8/86   | Reference      |
| Every day                                     | 408 | 3345 (475) | 17/341 | 0.5 [0.1, 4.5] |
| Several times a day                           | 405 | 3357 (510) | 16/348 | 0.3 [0.0, 2.3] |
| Missing data                                  | 8   | -          | 0/6    | -              |
| Meat:   |     |            |        |                |
| Never or almost never                         | 22  | 3275 (520) | 1/20   | NA             |
| Not every day                                 | 340 | 3329 (465) | 19/288 | Reference      |
| Every day                                     | 458 | 3332 (494) | 19/388 | 0.7 [0.4, 1.4] |
| Several times a day                           | 93  | 3393 (557) | 3/78   | 0.6 [0.2, 2.0] |
| Missing data                                  | 80  | -          | 0/12   | -              |
| <b>Dietary exposure (organic food intake)</b> |     |            |        |                |
| Fruits and vegetables:                        |     |            |        |                |
| Never   | 483 | 3304 (509) | 23/399 | 1.6 [0.5, 5.4] |
| Sometimes                                     | 354 | 3399 (472) | 16/300 | 1.5 [0.4, 5.2] |
| Most of the time                              | 90  | 3283 (453) | 3/83   | Reference      |
| Missing data                                  | 5   | -          | 0/5    | -              |
| Dairy products:                               |     |            |        |                |
| Never   | 617 | 3327 (505) | 32/508 | 1.4 [0.7, 2.8] |
| Sometimes                                     | 245 | 3367 (469) | 10/216 | Reference      |
| Most of the time                              | 64  | 3346 (439) | 0/4    | NA             |
| Missing data                                  | 6   | -          | 0/6    | -              |
| Meat:   |     |            |        |                |
| Never   | 777 | 3329 (490) | 39/657 | Reference      |
| Sometimes                                     | 126 | 3422 (492) | 2/108  | NA             |
| Most of the time                              | 20  | 3238 (518) | 1/16   | NA             |
| Missing data                                  | 70  | -          | 0/5    | -              |

\*P<0.05;

\*\*P<0.01.

BW: birth weight; LBW: Low birth weight; NA: an odds ratio was not available because too few cases were observed (n<3).

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and height, the rank of birth, the gestational age and the baby's gender), as recommended by the AUDIPOG study [15–16].

In the present study, we considered almost all the confounding factors known or suspected in the literature to have an effect on fetal development. However, some of these factors (such as the consumption of alcohol and/or illicit drugs during pregnancy)

could not be analyzed further because of the low number of affirmative replies. For ethical reasons, we chose not to probe a number of other factors (such as the parent's financial situation and ethnic origin); this might constitute a source of study bias. Moreover, the fact that pesticide levels were not measured in this study might constitute another source of bias; however, data

**Table 9.** Multivariate associations between (i) variables related to *in utero* exposure to pesticides, (ii) birth length (BL, in cm) and low birth length).

| Variable                                    | BL (cm) |            | LBL            |                 |
|---|---------|------------|----------------|-----------------|
|   | n       | Mean (SD)  | Cases/controls | OR [95% CI]     |
| Total sample                                | 922     |            | 56/764         |                 |
| <b>Occupational exposure</b>                |         |            |                |                 |
| Mother:                                     |         |            |                |                 |
| Yes   | 19      | 49.5 (1.9) | 2/15           | NA              |
| No  | 903     | 49.5 (2.1) | 54/749         | Reference       |
| Father:                                     |         |            |                |                 |
| Yes   | 79      | 49.3 (2.0) | 1/67           | NA              |
| No  | 843     | 49.5 (2.1) | 55/697         | Reference       |
| <b>Domestic exposure</b>                    |         |            |                |                 |
| Humans antiparasitics:                      |         |            |                |                 |
| Yes   | 309     | 49.8 (2.0) | 19/252         | 1.0 [0.6, 1.9]  |
| No  | 613     | 49.3 (2.1) | 37/512         | Reference       |
| Veterinary antiparasitics:                  |         |            |                |                 |
| Yes   | 201     | 49.3 (2.1) | 9/173          | 0.7 [0.3, 1.4]  |
| No  | 719     | 49.5 (2.1) | 46/590         | Reference       |
| Missing data                                | 2       | -          | 1/1            | -               |
| Pesticides against insects:                 |         |            |                |                 |
| Yes   | 115     | 49.5 (1.9) | 8/88           | 1.3 [0.6, 2.9]  |
| No  | 793     | 49.5 (2.1) | 46/666         | Reference       |
| Missing data                                | 14      | -          | 2/10           | -               |
| Pesticides for indoor plants:               |         |            |                |                 |
| Yes   | 35      | 49.2 (2.0) | 4/26           | 2.2 [0.7, 6.5]  |
| No  | 887     | 49.5 (2.1) | 52/738         | Reference       |
| Pesticides for outdoor plants:              |         |            |                |                 |
| Yes   | 157     | 49.7 (2.2) | 9/130          | 0.9 [0.4, 1.9]  |
| No  | 752     | 49.4 (2.1) | 47/623         | Reference       |
| Missing data                                | 13      | -          | 0/11           | -               |
| <b>Environmental exposure to pesticides</b> |         |            |                |                 |
| Proximity to a crop field (<1 km):          |         |            |                |                 |
| Yes   | 491     | 49.6 (2.1) | 32/404         | 1.0 [0.6, 1.8]  |
| No  | 350     | 49.3 (2.0) | 22/289         | Reference       |
| Missing data                                | 81      | -          | 2/71           | -               |
| Proximity to a green area:                  |         |            |                |                 |
| Yes   | 655     | 49.6 (2.2) | 42/541         | 1.1 [0.6, 2.1]  |
| No  | 249     | 49.2 (1.9) | 14/206         | Reference       |
| Missing data                                | 18      | -          | 0/17           | -               |
| Proximity to a highway, railway or airport: |         |            |                |                 |
| Yes   | 339     | 49.6 (2.1) | 23/276         | 1.2 [0.7, 2.9]  |
| No  | 570     | 49.4 (2.1) | 33/477         | Reference       |
| Missing data                                | 13      | -          | 0/11           | -               |
| Level of urbanization:                      |         |            |                |                 |
| Rural                                       | 726     | 49.5 (2.1) | 34/606         | Reference       |
| Urban                                       | 119     | 49.1 (2.0) | 15/93          | 2.9 [1.5, 5.5]* |
| Missing data                                | 77      | -          | 7/65           | -               |

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**Table 10.** Multivariate associations between (i) variables related to *in utero* exposure to pesticides, (ii) birth length (BL, in cm) and low birth length) (continued).

| <b>Dietary exposure (total food intake)</b>   |     |            |        |                |
|---|-----|------------|--------|----------------|
| Fruits and vegetables:                        |     |            |        |                |
| Never or almost never                         | 18  | 49.3 (2.2) | 1/15   | Reference      |
| Not every day                                 | 301 | 49.4 (2.0) | 19/253 | 1.1 [0.1, 9.0] |
| Every day                                     | 329 | 49.4 (2.2) | 19/268 | 1.1 [0.1, 8.5] |
| Several times a day                           | 269 | 49.7 (2.1) | 17/224 | 1.1 [0.1, 9.2] |
| Missing data                                  | 5   | -          | 0/4    | -              |
| Cereals:                                      |     |            |        |                |
| Never or almost never                         | 4   | 50.2 (1.7) | 0/4    | NA             |
| Not every day                                 | 159 | 49.4 (2.1) | 11/132 | Reference      |
| Every day                                     | 493 | 49.4 (2.1) | 27/402 | 0.8 [0.4, 1.7] |
| Several times a day                           | 256 | 49.6 (2.2) | 18/218 | 1.0 [0.5, 2.2] |
| Missing data                                  | 81  | -          | 0/8    | -              |
| Dairy products:                               |     |            |        |                |
| Never or almost never                         | 7   | 48.1 (1.2) | 0/5    | NA             |
| Not every day                                 | 105 | 49.3 (2.1) | 8/87   | Reference      |
| Every day                                     | 396 | 49.4 (2.0) | 21/328 | 0.7 [0.3, 1.6] |
| Several times a day                           | 407 | 49.6 (2.2) | 27/339 | 0.9 [0.4, 2.0] |
| Missing data                                  | 7   | -          | 0/5    | -              |
| Meat:   |     |            |        |                |
| Never or almost never                         | 22  | 49.3 (2.2) | 0/20   | NA             |
| Not every day                                 | 338 | 49.4 (2.1) | 25/279 | Reference      |
| Every day                                     | 457 | 49.5 (2.1) | 24/382 | 0.7 [0.4, 1.3] |
| Several times a day                           | 87  | 49.6 (2.3) | 6/71   | 0.9 [0.4, 2.4] |
| Missing data                                  | 89  | -          | 1/12   | -              |
| <b>Dietary exposure (organic food intake)</b> |     |            |        |                |
| Fruits and vegetables:                        |     |            |        |                |
| Never   | 484 | 49.3 (2.2) | 36/388 | 1.5 [0.6, 4.0] |
| Sometimes                                     | 345 | 49.7 (1.9) | 15/330 | 0.6 [0.3, 2.1] |
| Most of the time                              | 88  | 49.4 (2.1) | 5/83   | Reference      |
| Missing data                                  | 5   | -          | 0/4    | -              |
| Dairy products:                               |     |            |        |                |
| Never   | 611 | 49.4 (2.1) | 39/498 | 1.1 [0.6, 2.0] |
| Sometimes                                     | 242 | 49.6 (2.0) | 15/207 | 2.0 [0.4, 9.0] |
| Most of the time                              | 62  | 49.8 (2.0) | 2/55   | Reference      |
| Missing data                                  | 3   | -          | 0/4    | -              |
| Meat:   |     |            |        |                |
| Never   | 769 | 49.4 (2.1) | 47/642 | Reference      |
| Sometimes                                     | 126 | 49.6 (1.9) | 7/102  | 0.9 [0.4, 2.1] |
| Most of the time                              | 18  | 49.0 (2.1) | 1/14   | NA             |
| Missing data                                  | 80  | -          | 1/6    | -              |

\*P<0.05;

\*\*P<0.01.

BL: birth length, LBL: low birth length. NA: an odds ratio was not available because too few cases were observed (n<3).

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obtained from maternal questionnaires were used as a proxy for pesticide exposure.

#### 4.1 Occupational exposure to pesticides

Our results revealed that 4.3% of the mothers and 8.7% of the fathers had an occupation that potentially involved pesticide

exposure. We found that 1.5% of the mothers and 4.2% of the fathers worked in agriculture (i.e. 2.9% of all parents). The literature studies differ in terms of their locations, study populations, exposure assessment methods and fetal parameters - making it difficult to compare the respective results. Our results highlighted an association between self-reported maternal occu-

**Table 11.** Multivariate associations between (i) variables related to *in utero* exposure to pesticides, (ii) head circumference at birth (HCB, in cm) and (iii) small head circumference at birth.

| Variable                                    | HCB (cm) |            | SHCB           |                |
|---|----------|------------|----------------|----------------|
|   | N        | Mean (SD)  | Cases/controls | OR [95% CI]    |
| Total sample                                | 911      |            | 34/822         |                |
| <b>Occupational exposure</b>                |          |            |                |                |
| Mother:                                     |          |            |                |                |
| Yes   | 21       | 34.5 (1.7) | 2/36           | NA             |
| No  | 890      | 34.4 (1.4) | 32/786         | Reference      |
| Father:                                     |          |            |                |                |
| Yes   | 79       | 34.2 (1.6) | 4/70           | 1.3 [0.5, 4.2] |
| No  | 832      | 34.4 (1.4) | 30/752         | Reference      |
| <b>Domestic exposure</b>                    |          |            |                |                |
| Human antiparasitics:                       |          |            |                |                |
| Yes   | 305      | 34.5 (1.4) | 9/276          | 0.7 [0.3, 1.5] |
| No  | 606      | 34.3 (1.4) | 25/546         | Reference      |
| Veterinary antiparasitics:                  |          |            |                |                |
| Yes   | 193      | 34.3 (1.5) | 8/175          | 1.1 [0.5, 2.6] |
| No  | 717      | 34.4 (1.4) | 26/646         | Reference      |
| Missing data                                | 1        | -          | 0/1            | -              |
| Pesticides against insects:                 |          |            |                |                |
| Yes   | 115      | 34.4 (1.3) | 7/99           | 1.9 [0.8, 4.4] |
| Non   | 781      | 34.4 (1.4) | 27/709         | Reference      |
| Missing data                                | 15       | -          | 0/14           | -              |
| Pesticides for indoor plants:               |          |            |                |                |
| Yes   | 33       | 34.2 (1.4) | 2/29           | NA             |
| No  | 878      | 34.4 (1.4) | 32/793         | Reference      |
| Pesticides for outdoor plants:              |          |            |                |                |
| Yes   | 149      | 34.6 (1.4) | 8/135          | 1.5 [0.7, 3.5] |
| No  | 748      | 34.4 (1.4) | 26/674         | Reference      |
| Missing data                                | 14       | -          | 0/13           | -              |
| <b>Environmental exposure</b>               |          |            |                |                |
| Proximity to a crop field:                  |          |            |                |                |
| Yes   | 487      | 34.4 (1.4) | 20/437         | 1.3 [0.6, 2.8] |
| No  | 345      | 34.4 (1.4) | 11/314         | Reference      |
| Missing data                                | 79       | -          | 3/71           | -              |
| Proximity to a green area:                  |          |            |                |                |
| Yes   | 644      | 34.5 (1.4) | 21/586         | 0.7 [0.3, 1.3] |
| No  | 249      | 34.2 (1.4) | 12/219         | Reference      |
| Missing data                                | 18       | -          | 1/17           | -              |
| Proximity to a highway, railway or airport: |          |            |                |                |
| Yes   | 332      | 34.4 (1.4) | 12/301         | 0.9 [0.5, 1.9] |
| No  | 565      | 34.5 (1.4) | 22/508         | Reference      |
| Missing data                                | 14       | -          | 0/13           | -              |

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paternal exposure to pesticides during pregnancy and the risk of low birth weight. We also found an association between estimated paternal occupational exposure to pesticides on one hand and low gestational age and the risk of the prematurity on the other. However, it is important to note that our cohort was recruited from the general population, in which only some of the parents were occupationally exposed to pesticides. This situation contrasts

with literature studies of specifically exposed cohorts of farmers or other agricultural workers. The retrospective study of the general population performed in the USA by Savitz et al. [3] found an association between small-for-gestational-age status and self-reported occupational parental exposure to pesticides. In Colombia, the study by Restrepo et al. [5] revealed a moderately strong relationship between an increased risk of prematurity and reported

**Table 12.** Multivariate associations between (i) variables related to *in utero* exposure to pesticides, (ii) head circumference at birth (HCB, in cm) and (iii) small head circumference at birth (continued).

|   |     |            |        |                |
|---|-----|------------|--------|----------------|
| Place of residence during pregnancy:          |     |            |        |                |
| Rural locality                                | 722 | 34.4 (1.4) | 24/649 | Reference      |
| Urban locality                                | 114 | 34.4 (1.5) | 9/102  | 2.4 [1.1, 5.3] |
| Missing data                                  | 75  | -          | 1/71   | -              |
| <b>Dietary exposure (total food intake)</b>   |     |            |        |                |
| Fruits and vegetables:                        |     |            |        |                |
| Never or almost never                         | 18  | 34.0 (1.3) | 0/16   | NA             |
| Not every day                                 | 292 | 34.4 (1.4) | 16/263 | Reference      |
| Every day                                     | 334 | 34.4 (1.4) | 11/297 | 0.6 [0.3, 1.3] |
| Several times a day                           | 262 | 34.5 (1.5) | 7/241  | 0.5 [0.2, 1.2] |
| Missing data                                  | 5   | -          | 0/5    | -              |
| Cereals:                                      |     |            |        |                |
| Never or almost never                         | 4   | 34.7 (2.2) | 0/4    | NA             |
| Not every day                                 | 162 | 34.4 (1.4) | 5/148  | Reference      |
| Every day                                     | 488 | 34.4 (1.4) | 24/428 | 2.6 [1.0, 6.9] |
| Several times a day                           | 247 | 34.5 (1.4) | 5/232  | 0.6 [0.2, 2.3] |
| Missing data                                  | 92  | -          | 0/10   | -              |
| Dairy products:                               |     |            |        |                |
| Never or almost never                         | 7   | 33.1 (1.1) | 2/4    | Reference      |
| Not every day                                 | 104 | 34.3 (1.3) | 5/94   | 0.1 [0.0, 0.8] |
| Every day                                     | 395 | 34.4 (1.4) | 14/356 | 0.1 [0.0, 0.5] |
| Several times a day                           | 397 | 34.4 (1.5) | 13/360 | 0.1 [0.0, 0.4] |
| Missing data                                  | 8   | -          | 0/8    | -              |
| Meat:   |     |            |        |                |
| Never or almost never                         | 22  | 34.0 (1.4) | 1/20   | NA             |
| Not every day                                 | 336 | 34.5 (1.4) | 11/302 | Reference      |
| Every day                                     | 449 | 34.4 (1.4) | 16/409 | 1.1 [0.5, 2.3] |
| Several times a day                           | 85  | 34.4 (1.6) | 6/73   | 2.3 [0.8, 6.3] |
| Missing                                       | 101 | -          | 0/18   | -              |
| <b>Dietary exposure (organic food intake)</b> |     |            |        |                |
| Fruits and vegetables:                        |     |            |        |                |
| Never   | 481 | 34.2 (1.4) | 25/425 | 2.6 [1.1, 6.1] |
| Sometimes                                     | 340 | 34.6 (1.4) | 7/312  | Reference      |
| Most of the time                              | 85  | 34.4 (1.3) | 2/80   | NA             |
| Missing data                                  | 5   | -          | 0/5    | -              |
| Dairy products:                               |     |            |        |                |
| Never   | 612 | 34.3 (1.4) | 25/549 | 1.3 [0.3, 5.6] |
| Sometimes                                     | 231 | 34.6 (1.5) | 7/210  | 1.0 [0.2, 4.7] |
| Most of the time                              | 62  | 34.5 (1.3) | 2/57   | Reference      |
| Missing data                                  | 2   | -          | 0/6    | -              |
| Meat:   |     |            |        |                |
| Never   | 762 | 34.4 (1.4) | 31/688 | Reference      |
| Sometimes                                     | 123 | 34.7 (1.5) | 3/110  | 0.6 [0.2, 2.0] |
| Most of the time                              | 17  | 34.1 (1.2) | 0/15   | NA             |
| Missing data                                  | 91  | -          | 0/9    | -              |

HCB: head circumference at birth. SHCB: small head circumference at birth. NA: an odds ratio was not available because too few cases were observed (n<3). doi:10.1371/journal.pone.0099090.t012

occupational exposure to pesticides among female workers and the wives of male workers in floriculture. In contrast, the study in agricultural areas in Norway by Kristensen et al. [4] found that the

rates of prematurity and small-for-gestational-age status were lower for farmers than for non-farmers. In the latter study, pesticide exposure was assessed by means of national census data

on indicators such as farm size, the number and types of livestock, and so on.

Despite some small discrepancies between the above-mentioned results, there appears to be a general consensus in which maternal and/or paternal occupational exposure to pesticides is associated with adverse effects on fetal development and adverse birth outcomes.

#### 4.2 Domestic exposure to pesticides

Our study also considered domestic pesticides but did not focus on any one substance or group of substances in particular (in contrast to several literature studies). We found that self-reported maternal exposure to pesticides for houseplants was correlated with lower birth weight. In contrast, we did not find any association between maternal exposure to pesticides for outdoor plants and poor fetal growth. Our findings are consistent with Petit et al.'s [14] results on insecticide use on indoor plants in the Brittany region of western France but not with their data on use on garden plants. In fact, Petit et al.'s retrospective study found that higher self-reported *in utero* exposure to household insecticides for use on plants (and especially outdoor plants) was related to lower birth weight and head circumference [14].

We did not find any association between fetal growth and maternal exposure to domestic insecticides. Our findings are consistent with those of Petit et al. [14] regarding the association between residential use of insect control on one hand and birth weight and head circumference at birth on the other hand. Similarly, our results are in line with the reports by Berkowitz et al. [8] and Whyatt et al. [9] in the USA, which did not find any association between self-reported use of domestic pesticides, prenatal personal ambient air or umbilical cord blood levels of some domestic insecticides on one hand and birth weight, birth length or head circumference at birth on the other. The questionnaire used in these two studies of the same cohort probed domestic use of pesticides against three groups of pests only (cockroaches, rodents and others). In the retrospective study performed by Savitz et al. [3] in the USA, self-reported exposure to household pesticides was associated with the risk of small-for-gestational-age status but not with prematurity. The questionnaire used in Savitz et al.'s study [1] probed exposure very generally via a single question on whether or not the mother and/or the father had been exposed to household pesticides.

In the present study, we found that maternal exposure to veterinary antiparasitics was associated with a lower birth weight. To the best of our knowledge, our study is the first to have assessed the relationship between maternal exposure to veterinary antiparasitics and fetal growth. In contrast, we did not find any association between fetal growth and maternal exposure to human antiparasitics.

#### 4.3 Environmental exposure to pesticides

In our questionnaire, environmental exposure was assessed as self-reported proximity (within 1 km) of the mother's home during

pregnancy to areas in which pesticides are usually widely applied (crop fields, green areas and transportation networks (highways, railroads and airports)). We did not observe any association between fetal growth and this proximity, in agreement with the results of the study by Petit et al. [14] in France; the latter researchers did not find any association between agricultural activities in the mother's place of residence during early pregnancy (based on data on agricultural activities from the national census) and birth weight (as a continuous variable) or the risk of low birth weight. In contrast, Xiang et al.'s [6] study in the USA (based on remote sensing and a geographic information system (GIS)) found an association between low birth weight and total crop production area within a 300 m buffer zone around the mother's residence. However, Xiang et al. [6] did not examine fetal growth parameters other than low birth weight. However, it is possible that the mothers in the present MecoExpo study (especially those living on the outskirts of cities) may have over-estimated the distance between their residence and crop fields.

#### 4.4 Dietary exposure to pesticides

We did not find a significant association between fetal growth on one hand and overall or organic food intake on the other. Our questionnaire asked the mother about her eating behavior during a period (pregnancy) in which the diet is very likely to change. We cannot rule out the presence of recall bias, since the questionnaire was completed after delivery.

In conclusion, our present results demonstrate that both maternal and paternal occupational exposure to pesticides during pregnancy is associated with low gestational age and a greater risk of prematurity and low birth weight. Maternal domestic exposure to pesticides for houseplants and to veterinary antiparasitics was associated with low birth weight. Our questionnaire served as a wide-ranging tool for characterizing all the possible sources of prenatal exposure to pesticides. In the future, we could better characterize the exposure pathways and the nature of the compounds involved by complementing our questionnaire-based data with data generated by tools such as GISs and environmental or biological assays of pesticide residues.

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#### Author Contributions

Conceived and designed the experiments: FM VB KT AFB SD ESB KC. Performed the experiments: FM TB CD KC. Contributed reagents/materials/analysis tools: TB KT AFB. Wrote the paper: FM VB ESB KC.

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