Association between cardiovascular diseases and hypertensive disorders of pregnancy in a population of Cameroonian women at two hospitals of Yaounde: a case-control study

Cardiovascular diseases and hypertensive disorders of pregnancy

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Abstract

Background: Positive associations have been found between Hypertensive Disorders of Pregnancy gestational hypertension, preeclampsia and cardiovascular diseases within non-black African populations, but no data exist from sub-Saharan Africa. We aimed to assess this association in Cameroonian mothers.

Methods: We used a case-control study. Cases were women diagnosed with arteriosclerotic cardiovascular disease between 2012 and 2017 at the General and the Gyneco-obstetric hospital of Yaoundé. Controls were mothers of children who seeked pediatric care at the Gyneco-obstetric hospital of Yaoundé, with no diagnosis of cardiovascular disease. We abstracted data from patient files to assess cardiovascular disease, and used phone-based questionnaires to assess prior history of Hypertensive Disorders of Pregnancy. We used logistic regression and propensity scores for data analysis.

Results: Out of 1228 individuals selected, 173 cases and 339 controls participated in the study. We found no increased risk of cardiovascular diseases for women with a history of Hypertensive Disorders of Pregnancy (OR = 0.83, 95% CI, 0.51 to 1.34). Women with gestational hypertension had 2.33 (95% CI, 0.99 to 5.50) times the risk of women with no history of Hypertensive Disorders of Pregnancy, an inverse association was observed between preeclampsia and cardiovascular diseases (OR = 0.28, 95% CI, 0.10 to 0.72).

Conclusions: Cameroonian women with a history of gestational hypertension may have an increased risk of cardiovascular diseases. However, population-based studies with more accurate data on the exposure are needed.

Keywords: Hypertensive disorders of pregnancy, gestational hypertension, Preeclampsia, cardiovascular diseases, African women.

Introduction

Hypertensive Disorders of Pregnancy (i.e. preeclampsia, gestational hypertension and eclampsia) are recognized factors of maternal morbidity and mortality. The World Health Organization (WHO) multicounty survey on maternal and newborn health, estimated the global cumulative incidence of Hypertensive Disorders of Pregnancy between 2004 and 2008 at 2.7% overall; with a cumulative incidence of 2.2% for preeclampsia, 0.3% for gestational hypertension and 0.3 % for eclampsia [1]. In the African region, the cumulative incidence between 2002 and 2010 was much higher with 5.6% for preeclampsia, and 2.9% for eclampsia [2].

Previous studies have shown that these disorders during pregnancy negatively influence postpartum health outcomes. Williams (2003) [3] as well as Roberts and Hubel (2003) [4] highlighted Hypertensive Disorders of Pregnancy as essential determinants, that promote poor women's cardiovascular health postpartum. Many studies have found a positive association between Hypertensive Disorders of Pregnancy and a diagnosis of cardiovascular diseases later in life [5–8]. Most of these studies suggesting a round 1.5 to 2-fold elevated risk. However, to the best of our knowledge no such data exist for women from sub-Saharan Africa. We aimed to investigate whether a positive association between Hypertensive Disorders of Pregnancy, and cardiovascular diseases exists in a population of Cameroonian women at two reference hospitals of Yaoundé.

Methods

Study Setting

We recruited participants from the General hospital and the Gyneco-obstetric and Pediatric hospital of Yaoundé, Cameroon. Both hospitals are located on the same site and share the same catchment area. The General hospital of Yaoundé is the main cardiovascular disease treatment center in Yaoundé, while the Gyneco-obstetric and Pediatric hospital of Yaoundé is the main health facility of maternal and pediatric care. Patients who seek pediatric consultations at the General hospital are usually referred to the Gyneco-obstetric and Pediatric hospital for admission, likewise, patients who seek cardiovascular consultation at the Gyneco-obstetric and Pediatric hospital, are referred to the General hospital.

Participants

We used a case-control design and considered patients with complete administrative data (date of birth, name, phone number, name of the mother, name and phone number of a relative), residing in Yaoundé during the study period (from the 1st.01.2012 to the 5th.12.2017). Eligible cases consisted of all mothers aged 18 to 60 years old who were diagnosed with any form of arteriosclerotic cardiovascular diseases at the General hospital and the Gyneco-obstetric hospital during the study period. At the General hospital we only found the files of patients who continued to receive health care from the General hospital between 2015 to 2017; files of patients diagnosed with cardiovascular disease between 2012 and 2014, who did not continue their cardiology consultations at the General hospital were missing.

Controls consisted of mothers of children admitted at the Gyneco-obstetric hospital during the same period where the cases were diagnosed. In the absence of a patient roster for admitted children, we associated the first letters of the last name of each child to the end digit of their hospital registration

number. We randomly selected 10 letter-digit combinations from the patients letters-digit pool. We limited the selection to 10 arbitrary. We included all the patients who had the letter-digit combinations we selected.

We excluded: 1) participants with a diagnosis of any type of diabetes mellitus or any form of renal disease; 2) women with a diagnosis of cardiovascular diseases before their very first pregnancy; 3) women pregnant less than six months before the 5th October 2017; 4) participants who neither spoke English nor French.

Outcome Assessment

We abstracted the patients'diagnosis from the hospital files and included patients with any coronary heart diseases (ICD codes I20 to I25.9), cerebrovascular diseases (I60 to I69.8), and hypertensive diseases (I10 to I15.9). When the diagnosis was absent from a patients' files, we relied on the patients' drug prescription. We sought for the disease indicated for the treatment the physician prescribed, and classified the patient accordingly. When the diagnosis and the drug prescription were missing, we used the recorded blood pressure. If the patients had a systolic blood pressure $\geq$ 140 mmHg or a diastolic blood pressure $\geq$ 90 mmHg during three successive visits to the cardiologist, we included the patients as having any form of hypertensive disease. We aggregated the cardiovascular disease diagnosis in a single dichotomous variable.

Exposure Assessment

We assessed the history of Hypertensive Disorders of Pregnancy among participants using phone-based questionnaires. We used the standardized questionnaire from Diehl et al (2008) [9] which achieved a

80% sensitivity and a 90 % specificity in a group of women with a greater than 20-year history of preeclampsia. We translated the questionnaire to French and pretested it at the General hospital of Yaoundé. One of us (N.B.) trained the medical personnel to conduct the interviews with the participants. Prior to the interviews, we sent text messages to all the participants to inform them about the study. When participants were not answering, we called them back during two successive days three times per day. When the contact number on the file was a relative of the participant, we asked the participant's phone number to the relative. We also set appointments for phone interviews when the patient asked to be called later. We conducted all the interviews either in French or in English, from the 13th December 2017 to 23th April 2018.

We defined Hypertensive Disorders of Pregnancy to be present, if a participant answered positively to any of the questions a-c below:

a. During any of your pregnancies which lasted for more than 5 months or 20 weeks, which of the following did the physician diagnose? 1. Only high blood pressure or hypertension 2. Pre-eclampsia 3. Eclampsia 4. None of these diseases
b. During any of your pregnancies, which lasted for more than five months or 20 weeks, did a physician ever tell you that you had high blood pressure or hypertension?
c. During any of your pregnancies which lasted for more than five months or 20 weeks, were you prescribed any drug to lower your blood pressure or taking drugs such as Adalate, Aldomet, Loxen, or Tradate?

We classified as Preeclamptic/Eclamptic women who responded positively to any of the previous questions and positively to any of the d and e questions below. We considered individuals to have gestational hypertension, if they answered positively to at least one of a to c questions but responded

negatively to d and e of the following questions. Participants who responded negatively to both sets of questions were considered as not having a history of any type of hypertensive disorders of pregnancy.

d. Did your doctor tell you that, you had Protein in the urine or any positive urine test during any of the pregnancies where you had a diagnosis of high blood pressure, or given drug to lower your blood pressure?
e. During any of the pregnancies where you had a diagnosis of high blood pressure, or given drug to lower your blood pressure, did you have any seizure or loss of consciousness?

Sample size

We planned a study with one control per case. Prior data suggest that the odds ratio between a history of Hypertensive Disorders of Pregancy and coronary heart diseases was 2.28 [10], if the prevalence of Hypertensive Disorders of Pregnancy among African women is 5.6 % [2]. We needed 440 participants, i.e. 220 cases and 880 controls to achieve a 82% power to reject the null hypothesis at a 95% confidence level. However since we wanted to anticipate for unreachable phone calls, we included all the eligible case and twice the number of cases for controls.

Statistical Analyses

We compared the distribution of Hypertensive Disorders of Pregnancy (i.e. as an aggregate variable, Gestational hypertension, and Pre-eclampsia) among cases and controls .

We fitted four crude and adjusted logistic regression models to assess the association between Hypertensive Disorders of Pregnancy and cardiovascular diseases.

In the first model we evaluated the association between any Hypertensive Disorder (i.e. either gestational hypertension or preeclampsia) of Pregnancy and cardiovascular disease. We then analyzed

the association between each type of Hypertensive Disorders of Pregnancy and cardiovascular disease: Model 2: women with preeclampsia (E_1) vs women with no history of hypertensive disorder of pregnancy (E_0). Model 3: women with gestation hypertension (E_2 vs E_0). Model 4 treated Hypertensive Disorders of Pregnancy like a polytomous variable consisting of E_0, E_1, and E_2, the reference level was E_0.

For the adjusted analysis we considered the following covariates: smoking status (current, former smoker, never smoker), participant's age (age was included as a continuous variable since a test for linearity yielded non significant results), multiple gestation (yes/no), family history of cardiovascular diseases (yes/no), total number of pregnancies (<2, 2, >2; the cutoff was chosen since a previous study suggested a reduced risk of cardiovascular disease for 2 or more pregnancies [4]), marital status (single, married or unmarried couple, widowed, divorced) and level of education (less than secondary, secondary, higher than secondary). We computed propensity scores for each patient, which was the probability of each participant to have Hypertensive Disorders of Pregnancy given the covariates of the adjusted analysis. We categorized the propensity scores in six classes (default setting) and included these classes in a logistic regression model for models 1 to 3. For model four we used a classical multivariable logistic regression with the same covariates. We presented the resulting odds ratio (crude and adjusted), and 95% confidence intervals.

Sensitivity Analyses

We performed sensitivity analyses using Greenland (2006) [11] methods to assess the impact of exposure misclassification on the binary Hypertensive Disorder of Pregnancy variable. We considered that misclassification was either independent nondifferential or independent differential. We performed the analysis on the strata of propensity scores and used the Mantel-Haenzel formula to pool the

estimates. We obtained sensitivity and specificity estimates from Klemmensen et al. (2007) [12] and Diehl et al. (2008) [9]. We computed the E-value [13] to assess how strong unmeasured confounders would need to be to explain away the observed exposure-outcome relationship. We computed E-values on the adjusted estimates, under the assumption of low outcome incidence.

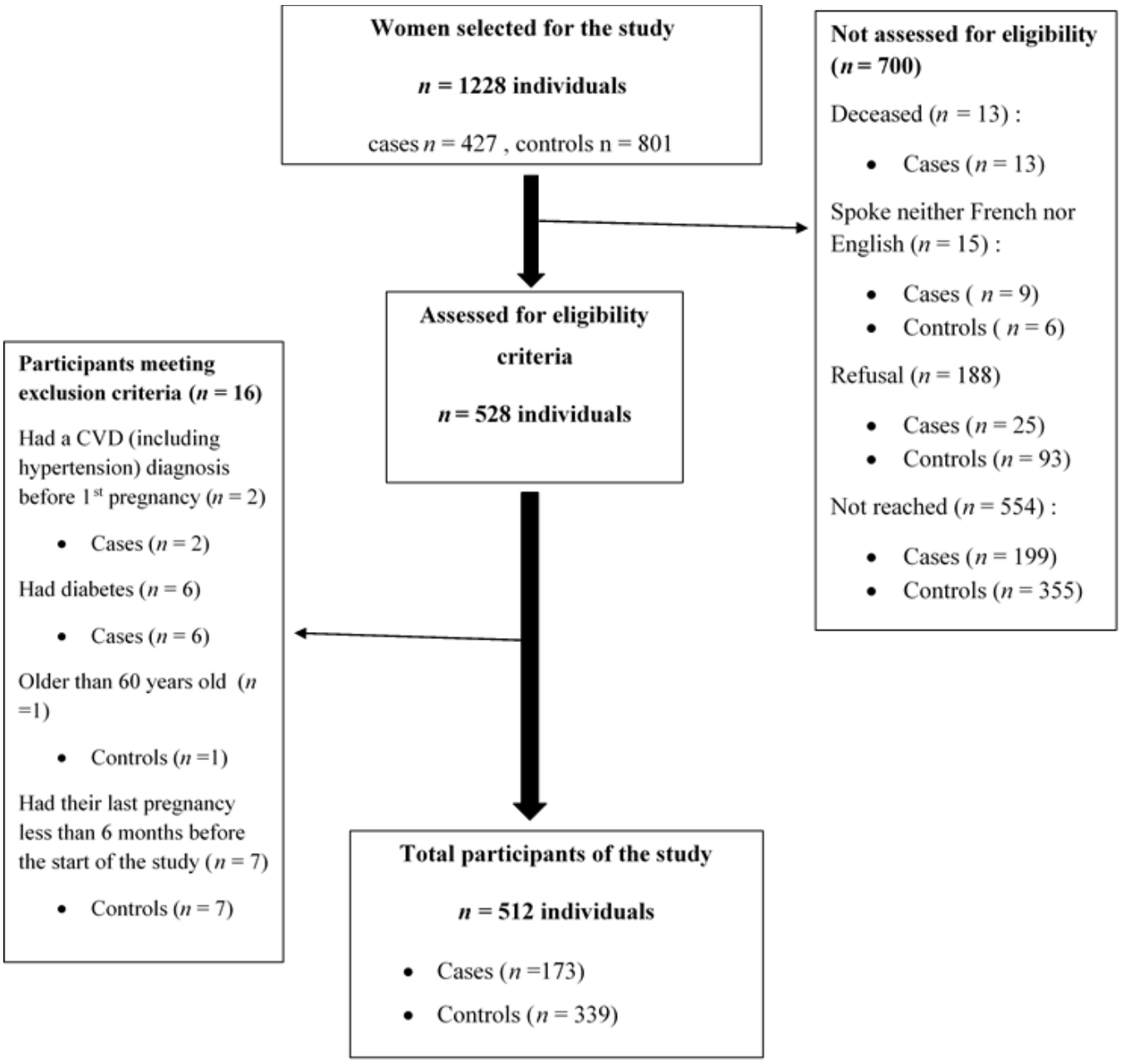
Ethical Considerations

We obtained informed consent from each participant before beginning the interviews. The Catholic University of Central Africa and the ethical review committee of the Gyneco-obstetric and Pediatric hospital of Yaoundé approved the study protocol.

Results

From the 1228 participants (427 cases and 801 controls) we selected, we reached 53% (n = 228) of cases, and 55.7% (n = 446) controls by phone. Overall 6% (n = 25) of cases and less than 1% (n = 93) of controls refused to participate; 2% (n = 9) of cases and <1% (n = 6) of controls neither spoke French nor English, 3% (n = 13) of cases have died, and 2% (n = 8) of the cases, 1% (n = 7) of the controls met exclusion criteria. Fig 1 presents the participation at each stage of the study.

Fig 1. Flow Diagram of Participants during the study



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181 Table 1 summarizes the participants characteristics. Cases were older and had more pregnancies than
182 controls (5 versus 3). Controls had higher education attainment, 37% of controls compared to 19.4% of
183 cases reported attending a higher education institution. About 17% of cases and around 2% of controls
184 reported being widow. Controls had a higher proportion of singles than cases (25.4 % vs 9.4%). We also

noted a lower proportion of divorced among controls than cases (<1% vs 6%). We did not find any difference among cases and controls in terms of family history of pregnancy, smoking status and multiple pregnancies..

Table 1. Characteristics of study participants

Variables	**Cases (*n* = 173)**	**Controls (*n* = 339)**	**Total (*n* = 512)**
Median age at diagnosis (IQR[b])	49 (11.75)	29 (9)	34 (20)
Missing observations	3	21	24
Median number of pregnancies (IQR)	5 (3)	3 (2)	3 (3)
Missing observations	3	2	5
Multiple pregnancy			
Yes	24 (14%)	63 (18.8%)	87 (17.2%)
No	148 (86%)	272 (81.2%)	420 (82.8%)
Missing observations	1	4	5
Smoking status			
Current smokers	3 (1.76%)	10 (3.02%)	13 (2.59%)
Former smokers	17 (10%)	23 (6.95%)	40 (7.98 %)
Never smokers	150 (88.2%)	298 (90%)	448 (89.4%)
Missing observations	3	8	11
Family history of CVDs			
Yes	82 (48.2%)	154 (45.6%)	236 (46.5 %)
No	88 (51.8%)	184 (54.4%)	272 (53.5%)
Missing observations	3	1	4

Education attainment			
Less than secondary	49 (28.8%)	36 (10.9%)	85 (17%)
Secondary	88 (51.8%)	172 (52.1%)	260 (52%)
Higher education	33 (19.4 %)	122 (37%)	155 (31 %)
Missing observations	3	9	12
Marital status			
Divorced	10 (5.88%)	3 (0.89%)	13 (2.57 %)
Couple (Married & Unmarried)	115 (67.6%)	242 (72.2%)	357 (70.7%)
Single	16 (9.41%)	85 (25.4%)	101 (20%)
Widow	29 (17.1%)	5 (1.49%)	34 (6.73%)
Missing observations	3	4	7

[b] Interquartile Range

We summarized the prevalence of a self-reported history of Hypertensive Disorders of Pregnancy in table 2. The reported prevalence of Hypertensive Disorders of Pregnancy was similar in cases (20.3 %) and controls (21.8 %). However, the proportion of women who reported having a history of gestational hypertension was higher in cases than in controls (11.6 % vs 8%).Cases had a slightly lower history of preeclampsia than controls (8.7% vs 12.8%).

Table 2. Distribution of the exposure among cases and controls

Variable	Cases	Controls	Total
Hypertensive disorders of pregnancy *			
No	137 (79.7%)	248 (78.2%)	385(78.7%)
Yes	35 (20.3%)	69 (21.8%)	104 (21.3%)
Missing observations	1	22	23
Hypertensive disorders of pregnancy **			
No	137 (79.7%)	248 (79.2%)	385 (79.4%)
Gestational hypertension	20 (11.6 %)	25 (7.99%)	45 (9.28%)
Preeclampsia	15 (8.72%)	40 (12.8%)	55 (11.3%)
Missing observations	1	26	27

* Hypertensive Disorders of pregnancy treated as a dichotomous variable

** Hypertensive Disorders of Pregnancy treated as a polytomous variable, including None, Gestational hypertension, Preeclampsia

We report the results of the crude and adjusted analysis in table 3. There was no evidence for an association of Hypertensive Disorders of Pregnancy and cardiovascular diseases (adjusted OR = 0.83, 95% CI: 0.51 to 1.45). Similarly, gestational hypertension was not associated with cardiovascular disease (adjusted OR = 1.47, 95% CI: 0.77 to 2.79). However, we found an inverse association between pre-eclampsia and cardiovascular diseases (adjusted OR = 0.47, 95% CI: 0.22 to 0.89).

When we treated Hypertensive Disorders of Pregnancy as polytomous variable (absent, gestational hypertension, preeclampsia, [model 4]), we found a positive association between gestational hypertension and cardiovascular diseases (Adjusted OR = 2.33, CI: 0.99 to 5.50). Similar to when treated as a dichotomous variable, we found an inverse association between preeclampsia and cardiovascular diseases (adjusted OR = 0.28, CI: 0.10 to 0.72). E-values were higher in the polytomous model as compared to the corresponding dichotomous models. Among the estimates in the different dichotomous adjusted models, the E-value was the highest for pre-eclampsia (3.87) and the lowest for the Hypertensive Disorders of Pregnancy (Yes/No) model (1.7).

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223 **Table 3. Results of the Crude and adjusted analyses**

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Exposure	Unadjusted results Odds ratio (95% CI)	Adjusted results Odds ratio (95% CI)	
Hypertensive disorder of pregnancies[a]	n = 489	n = 448	**E-value**
	0.92 (0.58 to 1.45)	0.83 (0.51 to 1.34)	1.70
Gestational hypertension[b]	n = 395	n = 395	
	1.37 (0.73 to 2.57)	1.47 (0.77 to 2.79)	2.3
Pre-eclampsia[c]	n = 403	n = 403	
	0.61 (0.32 to 1.18)	0.45 (0.22 to 0.89)	3.87
Hypertensive Disorders of Pregnancy[d]	n = 385	n = 321	
No HDP history (ref)	1	1	1
Gestational hypertension	1.45 (0.78 to 2.7)	2.33 (0.99 to 5.50)	4.09
Preeclampsia	0.68 (0.36 to 1.27)	0.28 (0.10 to 0.72)	6.60

[a,b,c] we computed propensity score and categorized them in six classes then added to a logistic regression model, each regression model treated the exposure as dichotomous

[d] we used a classical multiple regression model to adjust for confounding. The exposure was polytomous.

Variables included for adjustment : moking status, participant's age, multiple gestation, family history of cardiovascular diseases, total number of pregnancies, marital status and the level of education, we found a positive association between gestational hypertension and cardiovascular diseases

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Tables 4 displays the results of the sensitivity analysis for exposure misclassification by increasing specificity of the aggregate Hypertensive Disorders of Pregnancy variable. Under non-differential misclassification, all the corrected estimates are further away from the null than the uncorrected adjusted estimate (OR = 0.83), they increased as the specificity increased to come closer to the null. We did not observe a similar pattern for increasing or decreasing estimates of sensitivity.

Under differential misclassification, we observed an inverse association moving away from the null as the sensitivity estimates were higher among cases than in controls, whereas when the controls had a higher sensitivity estimates than cases we observed an increasing positive association pattern.

Table Estimates for the sensitivity analysis of the exposure (presented by increasing specificity)

Cases		**Controls**							
Sens.*	**Spe**.**	**Sens.***	**80**	**85.04**	**58.46**	**98**	**72.58**	**27.42**	**22.83**
		Spe.**	**90**	**92.22**	**92.64**	**95**	**98.62**	**99.69**	**99.68**
80	**90**		0.59[d]	0.51	0.32	0.50	0.29	0.1	0.09
85.04	**92.22**		0.78	0.68[d]	0.43	0.64	0.38	0.13	0.11
58.46	**92.64**		1.25	1.08	0.69[d]	1.03	0.62	0.22	0.18
98	**95**		0.90	0.78	0.49	0.74[d]	0.45	0.15	0.13
72.58	**98.62**		1.61	1.40	0.89	1.33	0.80[d]	0.28	0.23
27.42	**99.69**		4.61	4.00	2.54	3.80	2.28	0.81[d]	0.67
22.83	**99.68**		5.56	4.82	3.06	4.58	2.75	0.97	0.81[d]

[d] Non differential misclassification presented at the diagonal of each table

[*] Sensibility

[**]Specificity

Discussion

We hypothesized that Hypertensive Disorders of Pregnancy would be positively associated with cardiovascular diseases. After adjustment for smoking status, participant's age, multiple gestation, family history of cardiovascular diseases, total number of pregnancies, marital status and the level of education, we found a positive association between gestational hypertension and cardiovascular diseases, and an inverse association between preeclampsia and cardiovascular diseases.

The inverse association we found between preeclampsia and cardiovascular diseases, is counterintuitive; other studies found a positive association [5,7,14,15]. Our results may potentially be affected by recall bias and selection bias: Controls were much younger than cases (median age for controls was 29 vs 49 for cases), they were probably much better at recalling pregnancy outcomes than cases, since their pregnancies were more recent than cases' pregnancies. Additionally, We assumed that pediatric consultations were not linked to pregnancy and Hypertensive Disorders of Pregnancy. However, In our study sample, preeclampsia when treated as a dichotomous variable had a similar distribution with Hypertensive Disorders of Pregnancy when treated as a dichotomous variable (both had slightly higher prevalences among controls than cases). The results from the sensitivity analysis on Hypertensive Disorders of Pregnancy suggested that, even if cases were more likely classified as exposed, the corrected estimates will be inverse and away from the null. This result suggest that a higher prevalence of the preeclampsia among the controls, may have occurred if at the Gyneco-obstetric hospital of Yaoundé the files of neonate children were mixed with the files of children seeking for pediatric care. On the other hand, we cannot rule out the fact that children who were first admitted for neonatal care

could have been readmitted for pediatric care. For these reasons our initial assumption about independence between pediatric consultation and Hypertensive Disorders of Pregnancy may have not held, leading to a selection bias that increased the prevalence of preeclampsia among controls as Hypertensive Disorders of Pregnancy increase the likelihood of neonatal care .

The E-value for for the association of Hypertensive Disorders of Pregnancy and Cardiovascular disease was as low as 1.70. This indicates that residual confounding may explain that we failed to find an association between both variables. We found evidence for the positive association between gestational hypertension in the polytomous model and weaker evidence for the same association in the dichotomous model, this could be explained by increased power due to the polytomous variable and a better adjustment for confounding, the E-value estimates were higher in the polytomous model than in the dichotomous model.

It has been demonstrated that questionnaires measuring Hypertensive Disorders of Pregnancy have low sensitivity and result in low powered studies [12,16]. This low sensitivity could explain that our study did not find any effect for gestational hypertension, and Hypertensive Disorders of Pregnancy when analyzed as dichotomous variables. Also, of concern, is the potential bias caused by participants who we could not reach and those who refused to participate.

Our results suggest that gestational hypertension is positively associated with cardiovascular diseases. Similar results were found by Ray et al.(2005) [15], Lykke et al. (2009) [17], Kestenbaum et al. (2003) [14], and Black et al.(2016) [18]. There is an open debate about the biological mechanism linking Hypertensive Disorders of Pregnancy to cardiovascular diseases later in life. Roberts and Hubel (2010) [4], stated that Hypertensive Disorders of Pregnancy did not cause cardiovascular diseases , rather they

"Unravel" all the other risk factors of cardiovascular diseases. Hypertensive Disorders of Pregnancy and arteriosclerosis share endothelial dysfunction as a common characteristic. Some studies suggested that Hypertensive Disorders of Pregnancy are associated with unresolved endothelial dysfunction post-partum [19,20]. In fact higher levels of circulating anti-angiogenic factor sFlt1 and lower levels of circulating angiogenic factor, PIGF were found among women with previous Hypertensive Disorders of Pregnancy who had unresolved hypertension post-partum [21]. However, the exact period of endothelial dysfunction onset among women is uncertain. Noori et al.(2010) [22] observed that women who had lower flow mediated dilatation in early pregnancy, subsequently developed preeclampsia later. This suggest that endothelial disfunction may happen even before pregnancy.

Women with a history of Hypertensive Disorders of Pregnancy also exhibit both impaired carbohydrate and lipid metabolism [23]. Hypertensive Disorders of Pregnancy have been demonstrated to increase insulin resistance [24]. Further, higher levels of very low density lipoprotein cholesterol (VLDL) as well as low density lipoprotein (LDL) were found among women with a history of Hypertensive Disorders of Pregnancy [25,26]. Insulin resistance, as well as VLDL, and LDL may participate to endothelial dysfunction among women with Hypertensive Disorders of Pregnancy.

Because of the potential bias in our study, studies with a more accurate reporting of Hypertensive Disorders of Pregnancy and population-based samples are needed to provide unbiased and more precise estimates among black people. However, we recommend that clinicians should screen and gather information about women past pregnancies. Roberts and Hubel (2010) [4] proposed a sample guideline for screening women about past pregnancies. Women who have experienced a Hypertensive Disorder of Pregnancy are also encouraged to frequently check their blood pressure and should adopt healthy lifestyles behaviors.

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