RESEARCH ARTICLE

Risk factors for major external structural birth defects among children in Kiambu County, Kenya: a case-control study

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Abstract

Background: Although major external structural birth defects continue to occur globally, the greatest burden is shouldered by resource-constrained countries largely with no surveillance systems. To the best of our knowledge, few studies have been published on the risk factors for these defects in developing countries. The objective of this study was to identify the risk factors for major external structural birth defects among children in Kiambu County, Kenya.

Methods: A hospital-based case-control study was used to identify the risk factors for major external structural birth defects in Kiambu County. A structured questionnaire was used to gather information retrospectively on exposure to environmental teratogens, multifactorial inheritance, and sociodemographic-environmental factors during the study participants' last pregnancies. Descriptive analyses (means, standard deviations, medians, and ranges) were used to summarize continuous variables, whereas, categorical variables were summarized as proportions and percentages in frequency tables. Afterward, logistic regression analyses were conducted to estimate the effects of the predictors on major external structural birth defects in the county.

Results: From the multivariable analyses, maternal age ≤ 34 years old, (aOR: 0.41; 95% CI: 0.18-0.91; $P=0.03$), and preceding siblings with history of birth defects (aOR: 5.21; 95% CI: 1.35-20.12; $P=0.02$) were identified as the significant predictors of major external structural birth defects.

Conclusions: Maternal age ≥ 35 years old, and siblings with a history of birth defects were identified as the risk factors for major external structural birth defects in Kiambu County, Kenya. This pointed to a need to create awareness among couples against delaying childbearing beyond 35 years of age and the need for clinical genetic services for women of reproductive age with history of births affected

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Any reports and responses or comments on the article can be found at the end of the article.

by congenital anomalies.

Keywords

Major external structural birth defects, risk factors, case-control study, Kenya

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Introduction

Worldwide, an estimated 7.9 million children are born every year with a birth defect, of which approximately 3.3 million die before age five and around 3.2 million could be physically disabled for life^{1,2}. More than 94% of such defects occur in the developing countries where about 95% of these children do not survive beyond childhood¹. Birth defects are defined as abnormalities of body structures or functions that develop during the organogenesis period (first-trimester of gestation) and are detectable during pregnancy, at birth, or soon after^{2,3}. These defects may be classified as major when associated with significant adverse health effects requiring medical/surgical care; otherwise, they are described as minor^{1,2}. Alternatively, they can be classified as external when visible at birth or soon after; or internal when advanced medical imaging techniques are required for their detection⁴⁻⁶. Consequently, the phrase 'major external structural birth defects' (MESBDs) denotes congenital physical abnormalities that are clinically obvious at birth or soon after which call for medical and/or surgical interventions^{1,2}. The causes of these defects can be classified into three categories: (i) identifiable environmental factors (teratogens/micronutrient deficiencies); (ii) identifiable genetic factors; and (iii) complex genetic and idiopathic environmental factors, described as multifactorial inheritance^{1,4,7-10}. One-third of these causes are attributed to identifiable environmental and genetic factors, whereas the rest are believed to be multifactorial inheritance-related^{1,4,7-10}. Additionally, environmental endowment of women of reproductive age is thought to operate through their socioeconomic and sociodemographic characteristics leading to causes of MESBDs, described as sociodemographic-environmental factors^{1,4,8-10}. Completing more years of education could improve maternal health because educated women are more likely to make informed reproductive health choices than those with low levels of education with a view to improving birth outcomes¹¹⁻¹⁴. Some of the notable maternal decisions include planned pregnancy, preconception folic acid intake in anticipation of conception, and prompt prenatal care^{11,13,15-20}. Maternal occupation could be dependent on educational levels nonetheless occupations such as farming could expose women of reproductive age to teratogenic pesticides²¹. Organogenesis occurs in the first eight weeks of gestation; however, approximately half of pregnancies are usually unplanned/unintended, thus not recognized until the end of the first trimester^{1,4,22-24}.

To our knowledge, many studies on the risk factors have been published in developed countries, however, such publications are scanty in developing countries owing to the rarity of the defects, unplanned/unintended pregnancies, and difficulties in identifying these women until the end of the first trimester when the defects have already formed⁴. To address this gap, this study investigated maternal periconceptional exposure to environmental, sociodemographic-environmental, and multifactorial inheritance-related risks factors for MESBDs in Kiambu County, Kenya. The study assessed: maternal periconceptional exposure to pesticides and teratogenic therapeutic medicines proxied by maternal chronic illnesses (epilepsy and depression); multifactorial inheritance proxied by the history of siblings with birth defects, sex of the last born child, nature of pregnancy, and parity; and sociodemographic-environmental factors consisting of

maternal age, level of education, occupation, and adequate prenatal care proxied by gestational age and preconception folic acid intake. The findings of this study could provide great public health opportunities for the formulation of specific treatment strategies, preventive measures, risk-based surveillance systems, and clinical genetic services for the most prevalent MESBDs, regionally and nationally. Consequently, the objective of this study was to identify the risk factors for MESBDs among children in Kiambu County, Kenya.

Methods

Study design and settings

A hospital-based case-control study was conducted to identify the risk factors for MESBDs. The study participants were recruited as they presented to the child welfare clinics, neonatal/paediatric units and occupational clinics for care during data collection period from May 31st 2018 to and July 31st 2019. A case-control design was the optimal design for this study considering its suitability for the investigation of rare outcomes, as is the case with MESBDs. Even though a population-based design would have been more preferable, the ease of recruiting case and control subjects within the hospital settings disproportionately favoured the hospital-based design. This was an observational study, therefore was reported as per the STROBE guidelines²⁵.

The study was conducted in 13 hospitals comprising three county referral hospitals (Kiambu, Gatundu, and Thika), eight sub-county hospitals (Karuri, Kihara, Wangige, Nyathuna, Lari, Tigoni, Lussigetti, and Kigumo), and two faith-based hospitals (Presbyterian Church of East Africa Kikuyu Orthopedic and African Inland Church Cure International) situated within Kiambu County, Kenya. Notably, neither population-based or hospital-based surveillance systems for MESBDs existed in the county nor the study hospitals. Nonetheless, cases detected by primary health providers during childbirth and in neonatal care were recorded for the compilation of monthly hospital reports and subsequent entry into the District Health Information System (DHIS). The cases were drawn from Kiambu, Thika, Gatundu, Tigoni, Kikuyu, and Cure hospitals, which provided occupational and rehabilitative health services to children with MESBDs. The controls, on the other hand, were drawn from Kiambu, Gatundu, Thika, Karuri, Kihara, Wangige, Nyathuna, Lari-Rukuma, Tigoni, Lussigetti, and Kigumo hospitals, which provided child welfare services to the under-fives. Kiambu is the second-most densely inhabited county with an estimated population of 2.4 million people out of an estimated national population of 47.5 million²⁶. Its economic mainstay is largely agriculture, comprising tea, coffee, and dairy farming²⁶. Of the county's total estimated population, approximately 2.2% aged ≥5 years are living with lifelong disabilities²⁶. A study carried out in the county between 2014 and 2018 observed defects of the musculoskeletal system as the most prevalent single system defects followed by central nervous, orofacial clefts genital, ocular, and anal organ defects²⁷.

Study population and eligibility of participants

The study population consisted of children aged ≤5 years old seeking health services at the study hospitals during the study

period spanning from May to July 2019. All children whose mothers consented to participate in the study were recruited.

Case definition and recruitment

Cases were defined as children aged ≤ 5 years born with at least one MESBD to resident women of Kiambu County and seeking health care services at the neonatal units, paediatric wards, child welfare clinics and/or occupational therapist clinics of the study hospitals during the three-month study period. The Research Assistants (RAs) liaised with team leads of the departments listed above to identify cases of MESBDs. The team leads had been working in these departments, thus were conversant with the cases seeking services. The team lead invited the mothers of the children who met the case definition to comfortable private rooms within the departments where informed consent was sought and interviews conducted by the RAs. All cases that met this definition and whose carers consented to participate were prospectively recruited into the study until the required sample was attained (see *Sample size determination*).

Control definition and recruitment

Controls were children aged ≤ 5 years born without any forms of birth defects to resident women of Kiambu County and attending routine child-welfare clinics at the study hospitals during the same three-month study period. The Research Assistants liaised with team leads of the child welfare clinics to identify the children without any form of birth defects and were seeking routine immunization, and growth monitoring services. The team leads had been working in these clinics, hence were familiar with most of the under-fives seeking the services. These services are provided between 8.00 am and 5.00 pm from Monday to Friday; the team leads introduced the RAs who then briefed the potential participants on the study objectives. Because of the relatively large number of controls available, they were selected by simple randomization using sealed envelopes upon definition of the sample population and frequency-matched to the cases by the day of presentation.

Sample size determination

The sample size was estimated as per the Kelsey JL *et al.*²⁸ formula specified for case-control studies as follows: -

$$n_1 = \frac{(Z_{\alpha} + Z_{\beta})^2 \bar{p}q (r+1)}{r(p_1 - p_2)^2}$$

$$\bar{q} = 1 - \bar{p}$$

$$n_2 = rn_1$$

$$p_1 = \frac{p_2 OR}{1 + p_2 (OR - 1)}$$

$$\bar{p} = \frac{p_1 + rp_2}{r+1}$$

Where: n_1 is the number of cases and n_2 is the number of controls; p_1 is the proportion of cases whose caregivers did not

begin prenatal care in the first trimester (primary exposure), p_2 is the proportion of controls whose care-givers did not begin prenatal care in the first-trimester set at 57%^{22,23}. Remarkably, $Z_{\alpha/2}$ (1.96) and Z_{β} (-0.84) are the values specifying the desired two-tailed confidence level (95%) and statistical power (80%), respectively. The odds ratio (OR) for the effect of the primary exposure (cases whose caregivers did not begin prenatal care in the first trimester) was hypothesized to be 3.0^{22,23}. The ratio (r) of unexposed to exposed individuals was set at 3, and given the estimates, a total sample size of 408 participants was derived (102 cases, and 306 controls).

Data collection process and study variables

Before data collection, four nursing graduate interns were recruited and trained as RAs on sound interviewing techniques, and information derivation/validation from antenatal care (ANC) booklets. This was to ensure the data collection process spanning three months (May 31st to July 31st, 2019) was conducted in a standardized manner. The ANC booklet contains maternal profile, medical/surgical history, previous pregnancy history, clinical notes, and physical examination findings on ANC visits among others. Maternal profile includes name, age, parity gravidity, height, weight, last menstrual period (LMP), expected date of delivery (EDD) and date of first ANC. Face-to-face structured questionnaires (see *Extended data*) were administered to the mothers of the study participants by RAs in comfortable secluded rooms within neonatal units and occupational therapy clinics for cases and child welfare clinics for the controls. Data were gathered retrospectively on exposures to environment-teratogens (pesticides and teratogenic medicines proxied by chronic illnesses), multifactorial inheritance (parity, nature of pregnancy, history of siblings with MESBDs and sex of the lastborn child) and sociodemographic-environmental factors (maternal age, education level, occupation, and adequate prenatal care proxied by gestational age and preconception folic acid intake). The predictors were assessed as shown in [Table 1](#).

A conceptual framework depicting the predictor-outcome relationship is displayed in [Figure 1](#). The flow chart of the simple-random systematic sampling strategy is shown in [Figure 2](#).

Ethical considerations

Ethical approval for this study was obtained from the Kenyatta National Hospital [KNH]-University of Nairobi [UoN] Ethics Review Committee [Ref. No: KNH-ERC/A/44]. The purpose of the study was explained to participants and written informed consent was obtained from the mothers of the study subjects before engaging in the study.

Minimizing bias

Considering potential biases inherent in case-control studies that were likely to invalidate the study results, deliberate attempts were made to minimize their occurrence. First and foremost, the research assistants were trained on sound interviewing techniques and information derivation/validation from ANC booklets to minimize interviewer and minimize information biases, respectively. In a bid to minimize recall bias, gestational age (weeks) at the first ANC were estimated from the dates

Table 1. Study variables and their assessments.

Variable (type)	Method of assessment
Pesticide exposure (nominal)	Captured as yes/no
Chronic illness (nominal)	Captured as a nominal variable, categorized and labelled; 1= 'hypertension', 2= 'no chronic illnesses' and 3= 'other chronic illnesses'
ANC began 8 weeks post-conception began (nominal)	Captured as yes/no
Gestational age (weeks) at first ANC (continuous)	Captured in weeks, categorized and labelled; 1≤ eight weeks, and 2≥ nine weeks to first ANC visit.
Preconception folic acid intake (nominal)	Captured as yes/no
Sex of the lastborn child (nominal)	Entered as male or female
History of siblings with birth defect (nominal)	This was captured as yes/no
Parity (continuous)	Abstracted from the antenatal booklet as a continuous variable, categorized as and labelled; =1= 'primiparous'. And >1= 'multiparous'
Nature of pregnancy (nominal)	Entered as single or multiple
Maternal age (continuous)	Captured in years
Level of education (ordinal)	Captured as no schooling, primary, secondary, college certificate, college diploma, and university degree, categorized and labelled; 1≤ primary, 2=secondary, and 3=tertiary
Maternal occupation (nominal)	Captured as a nominal variable, categorized into three groups: employed, farming, and unemployed.

ANC, antenatal care; MESBDs major external structural birth defects.

Figure 1. Causal diagram of factors thought to influence major external structural birth defects (MESBDs) among children in Kiambu County, Kenya.

of the last menstrual period and dates of the first ANC obtained from the ANC booklets.

Data processing and statistical analysis

Following data collection, filled questionnaires were manually checked daily for accuracy and completeness and subsequently entered into a Microsoft Excel spreadsheet (Microsoft Office Professional Plus 2019) by two independent data managers to reduce potential errors. The excel dataset was validated and exported to Stata software version 14.0 (Stata Corporation, Texas, USA) for further cleaning, coding, and analyses. Descriptive analyses (means, medians, standard deviations, and ranges)

were used to summarize continuous variables, whereas proportions and percentages for categorical variables were generated and presented in frequency tables. Afterward, the effect of each predictor on the odds of MESBDs was assessed using univariable logistic regression models at a liberal P-value ($P \leq 0.20$)²⁹. Gestational age (weeks) at first ANC as a continuous variable was categorized into groups (≤ 8 weeks and ≥ 9 weeks) for evaluation in the univariable analyses^{1,4,22–24}. Additionally, parity as a continuous variable was grouped into two groups; primiparous or multiparous categories for assessment in the univariable analyses^{30,31}. However, maternal age as a continuous variable was insignificant in the univariable analyses, thus,

Figure 2. Flow chart of the systematic sampling strategy used in this study.

recategorized into two groups; ≤ 34 years, and ≥ 35 and reassessed for statistical significance; women aged at least 35 years have previously been reported to have an increased likelihood of giving birth to children with MESBDs³². Variables found statistically significant in the univariable analyses were fitted to a multivariable model where a backward stepwise approach was used to eliminate variables from the model at P-value >0.05 . To minimize the confounding effects, elimination of non-significant predictors was only considered when their exclusion from the model did not yield more than a 30% change in the effects of the remaining variable²⁹. Two-way interactions were fitted between the remaining variables of the final model and assessed for significance. A Hosmer-Lemeshow test was used to assess the goodness of fit of the logistic model, with a P-value of >0.05 being suggestive of a good fit.

Results

A total of 408 study respondents (102 cases and 306 controls) were enrolled in this study. The cases consisted of cleft lip with palate 1 (0.98%), cleft palate 3 (9.94%), clubbed hand 1 (0.98%), club foot 91 (89.22%), hydrocephalus 1 (0.98%), limb defects 4 (3.92%), and persistent cloacal 1 (0.98%)³³.

Descriptive statistics

Sociodemographic-environment: The median age of the study respondents was 26 years with a mean of 27.31 years (SD=5.73, R; 17-47) (Table 2). The median age of mothers in the case group was 28 years with a mean of 28.73 (SD=5.95, R; 19-47), whereas the median age of mothers in the control group was 26 years with a mean of 26.84 (SD=5.58, R; 17-42) (Table 2). Of the 408 study participants, 184 (45.10%) had attained a

secondary level of education; 38 (37.25%) and 146 (47.71%) in the case and control groups, respectively (Table 2). Environmental-teratogens: Of the 408 study respondents, 15 (3.68%) were exposed to farm-sprayed pesticides, of which four (3.92%) were in the case group and 11 (3.59%) were in the control group (Table 2).

Multifactorial inheritance: Of the 408 study respondents, 404 (98.77%) had single gestations for the current child, of which 99 (97.06%) and 304 (99.35%) were in the case and control groups, respectively (Table 2). Of the study participants, 15 (3.68%) had given birth to children with birth defect in previous gestations, with 9 (8.82%) in the case group and 6 (1.96%) in the control group (Table 2).

Logistic regression analyses

Notably, all the factors assessed for statistical significance in the univariable analyses were associated with MESBDs at $P \leq 0.20$; age, education, occupation, sex of the lastborn child, history of siblings with birth defects, preconception folic acid intake, nature of pregnancy, pesticide exposure, chronic illnesses, parity, gestational (age) weeks at first ANC, and ANC beginning eight weeks post-conception (Table 3). Subsequently, these variables were fitted to the multivariable model for the final analysis, except gestational age at first ANC, education, occupation, and prenatal care beginning eight weeks post-conception being distal relative to pesticide exposure and preconception folic acid intake (Figure 1).

In the multivariable analysis, only maternal age, and history of siblings with MESBDs were shown to be significant predictors at a 5% significance level (Table 4). Compared to women aged

Table 2. Descriptive statistics of the study respondents (N=408).

Variables	Measurements	Observations (N=408), n (%)	Cases (N=102), n (%)	Controls (N=306), n (%)
Maternal age	≤34	356 (87.25)	82 (80.39)	274 (89.54)
	≥35	52 (12.75)	20 (19.61)	32 (10.46)
Mean		27.31	28.73	26.84
Median		26	28	26
Standard deviation (SD)		5.73	5.95	5.58
Range (R)		17-47	19-47	17-42
Maternal education	≤Primary	94 (23.04)	27 (26.47)	67 (21.90)
	Secondary	184 (45.10)	38 (37.25)	146 (47.71)
	Tertiary	130 (31.86)	37 (36.27)	93 (30.39)
Maternal occupation	Farming	24 (5.88)	7 (6.86)	17 (5.56)
	Unemployed	206 (50.49)	40 (39.22)	166 (54.25)
	Employed	178 (43.63)	55 (53.92)	123 (40.20)
Parity	Primiparous	127 (37.35)	28 (35.00)	99 (38.08)
	Multiparous	213 (62.65)	52 (65.00)	161 (61.92)
Mean		2.12	2.14	2.12
Median		2	2	2
Standard deviation (SD)		1.21	1.41	1.22
Range (R)		1-8	1-6	1-8
Nature of pregnancy	Multiple	5 (1.23)	3 (2.94)	2 (0.65)
	Single	403 (98.77)	99 (97.06)	304 (99.35)
Sex of lastborn child	Female	199 (48.77)	45 (44.12)	154 (50.33)
	Male	209 (51.23)	57 (55.88)	152 (49.67)
Sibling with a birth defect	No	393 (96.32)	93 (91.18)	300 (98.04)
	Yes	15 (3.68)	9 (8.82)	6 (1.96)
Gestational age (weeks) at to first antenatal visit		23 (9.09)	9 (18.75)	14 (6.83)
		230 (90.91)	39 (81.25)	191 (93.17)
Mean		20.1	18.35	20.40
Median		20	18	21
Standard deviation (SD)		7.54	8.13	7.36
Range		4-40	4-35	4-40
Pesticide exposure	No	393 (96.32)	98 (96.08)	295 (96.41)
	Yes	15 (3.68)	4 (3.92)	11 (3.59)
Chronic illnesses	Hypertension	17 (4.17)	4 (3.92)	13 (4.25)
	No chronic illness	382 (93.63)	96 (94.12)	286 (93.46)
	Others chronic illnesses	9 (2.21)	2 (1.96)	7 (2.29)
Preconception folic acid intake	No	230 (56.65)	59 (57.84)	171 (56.25)
	Yes	176 (43.35)	43 (42.16)	133 (43.75)
ANC began eight weeks post-conception	No	330 (80.88)	77 (75.49)	253 (82.68)
	Yes	78 (19.12)	25 (24.51)	53 (17.32)

SD, standard deviation; R, range.

Table 3. Univariable analysis of factors associated with MESBDs among children in Kiambu County, Kenya.

Variable	Value	Odds ratio	95% CI	P-value
Maternal age*	≥35	Reference		0.10
	≤34	0.48	0.26-0.88	0.02
Maternal education*	Tertiary	Reference		<0.01
	Secondary	0.65	0.39-1.10	0.11
	≤Primary	1.01	0.56-1.82	0.97
Maternal occupation*	Farming	Reference		0.05
	Employed	1.09	0.43-2.77	0.86
	Unemployed	0.59	0.23-1.51	0.27
Preconception folic acid intake*	No	Reference		<0.01
	Yes	0.94	0.60-1.47	0.78
Prenatal care began eight weeks post gestation*	No	Reference		<0.01
	Yes	1.55	0.90-2.66	0.11
Gestational age (weeks) at first prenatal clinic*	≤8 weeks	Reference		0.30
	≥9 weeks	0.32	0.13-0.79	0.02
Parity*	Primiparous	Reference		<0.01
	Multiparous	1.14	0.68-1.93	0.62
Nature of pregnancy*	Multiple	Reference		0.66
	Single	0.22	0.04-1.32	0.10
Sex of the lastborn child*	Female	Reference		<0.01
	Male	1.28	0.82-2.01	0.28
Siblings with MESBDs*	No	Reference		<0.01
	Yes	4.84	1.68-13.95	<0.01
Chronic illnesses*	No	Reference		<0.01
	Hypertension	0.92	0.29-2.88	0.88
	Other chronic illnesses	0.85	0.17-4.17	0.84
Pesticide-sprayed farms*	No	Reference		<0.01
	Yes	1.09	0.34-3.52	0.88

*Variables eligible for inclusion in the multivariable model ($P \leq 0.20$). CI, confidence interval; MESBD, major external structural birth defect.

Table 4. Multivariable analysis of factors associated with MESBDs among children in Kiambu County, Kenya.

Variable	Value	aOR	95% CI	P-value
Maternal age	≥35	Reference		
	≤34	0.41	0.18-0.91	0.03
Siblings with MESBDs	No	Reference		
	Yes	5.21	1.35-20.12	0.02

aOR, adjusted odds ratio; CI, confidence interval; MESBD, major external structural birth defect.

≥35 years old, holding all factors constant, women aged ≤34 years old were 59% less likely to give birth to children with MESBDs (adjusted odds ratio (aOR): 0.41; 95% CI: 0.18-0.91; $P=0.03$) (Table 4). Additionally, compared to the history of siblings without MESBDs holding all factors constant, siblings with history of MESBDs were 5.21 times likely to have MESBDs (aOR: 5.21; 95%CI: 1.35-20.12; $P=0.02$) (Table 4).

Discussion

To our knowledge, this was the first case-control study conducted to identify the risk factors for MESBDs in the entire country. The study findings corroborated other studies that maternal age

greater than 34 years had a strong association with the occurrence of MESBDs³⁴. The study observed that women aged ≤34 years old were 59% less likely to give birth to children with MESBDs compared to those aged over 35-years-old. Older maternal age has been strongly associated with MESBDs such as neural tube defects and orofacial clefts³⁴. Maternal age is a multifaceted risk factor whose mechanisms of action in the occurrence of MESBDs are underpinned by human biology and socio-economic endowment among women of reproductive age. From the biologic standpoint, genetic mutations and accumulation of chromosomal aberrations during the maturation of male germ cells have been attributed to the occurrence of MESBDs^{1,35,36}. The amount of deoxyribonucleic acid damage in sperm of men aged 36–57 is three times that of men <35 years, increasing the likelihood of MESBDs in aging couples^{35,37}. This observation could have been due to environment-physiological interactions as a result of the couples' socioeconomic endowments¹. Similarly, the study results mimicked other research findings across the world and revealed that women whose preceding offspring had MESBDs were at most risk of giving birth to children with MESBDs in the succeeding births. This phenomenon points to the genetic epidemiology implicating multifactorial inheritance in the occurrence of these defects, thus contributing to the global debate on the burden of MESBDs in developing countries^{8,38–40}. Of the 102 cases observed; 1 had cleft lip with palate (0.98%), 3 had cleft palate (9.94%), 1 had clubbed hand (0.98%), 91 had club foot (89.22%), 1 had hydrocephalus (0.98%), 4 had limb defects (3.92%), and 1 had persistent cloacal (0.98%). Defects of a single organ system such as orofacial clefts, talipes, neural tube defects and limb defects have been associated with multifactorial inheritance^{1,7}. Nevertheless, some limitations were inherent in this study; there was a likelihood of differential recall bias among the study respondents; cases were more likely to remember their pre-conception period owing to the experience of MESBDs in the last birth than the controls, thus could affect their estimates.

Conclusions

This study showed that maternal age and history of siblings with MESBDs were the predictors of MESBDs in Kiambu County in Kenya. This pointed to a need to create awareness among couples not to delay childbearing beyond 34 years of age and provision of clinical genetic services such as genetic counseling and screening for families with a history of birth defects. To address this burden, the county should begin by designing and

formulating a hospital-based surveillance framework for the most MESBDs to inform specific public health interventions aimed at controlling and preventing specific MESBDs. Additionally, creating public awareness of the risk factors and prevention strategies for these defects through short message during media broadcasts, mobile phone digital platforms, community dialogues, and roadshows. Further, we recommend that similar studies be conducted nationally to inform surveillance, prevention, and control strategies for the most common MESBDs.

Data availability

Underlying data

Figshare: Risk factors for major external structural birth defects among children in Kiambu County, Kenya: a case-control study. <https://doi.org/10.6084/m9.figshare.13614548.v1>³³.

Extended data

Harvard Dataverse: Risk factors for major external structural birth defects among children in Kiambu County, Kenya: a case-control study. <https://doi.org/10.7910/DVN/ZDEOZ5>

This project contains the following extended data:

- 2_mesbds_kmbu_ke_questionnaire.pdf (copy of questionnaire)
- 2_mesbds_kmbu_ke.do (syntax used for analysis)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Rogath Kishimba

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This is a good and important research area for newborn health particularly now when a lot has been done on infectious unlike non infectious diseases. We have observed a great decrease of infant mortality given the available maternal and newborn interventions on infectious diseases. A higher contribution of non infectious disease particularly birth defects may be observed on neonatal and infant mortality with time. Below are my inputs and comments regarding this study;

- The title, abstract and introduction are well written.
- Current citations were used.
- The study design is appropriate however selection of cases was not appropriate given the study title and objectives. It can be admitted as one of study limitation.
- Cases were sampled from child welfare clinics, neonatal/pediatric units, occupational and rehabilitation clinics. All these data sources represent survivors of MESBDs and most probably non fatal MESBDs. It is difficult to get fatal MESBDs like neural tube defects (NTDs) cases from this subpopulation as majority will not survive to meet them in rehabilitation clinics.
- The ascertainment period from the case definition is too high (5years and below). This may lead to potential recall bias as it will be very difficult for a mother to remember what happened in her pregnancy in the 3-4 years ago. Again may lead to recruitment of survivors and non fatal MESBDs cases. This could be mitigated for at least to consider/restrict enrolment into the study for children below 1 or 2 years only.
- I understand well that the data sources were the above mentioned clinics which are complimented by the ANC booklets. However the methodology section again mentioned about DHIS and I was wondering whether it was also another data source which was used. It needs clarity for the reader to well understand sources of data for this study.

- The methodology section need more clarity on maternal age. Is it the age of the mother during conception of the referred case? or the age of the mother during the data collection? It is also very important to define "residence" as it has implication on maternal exposures. The residence is important during conception and antenatal period. This is the period when environmental exposures can have impact on the unborn child. There is no any significance of considering residence post delivery.
- Sample size calculation is Ok. However you can not estimate proportion of controls (p_2) using a study with a different objectives from your intended study.
- The hypothesized odds ratio for the effect of the primary exposure is too high. This is the risk which you allow to be detected in your study. At least you can allow a minimal risk of odds ratio between 1.5 and 2.
- Results were well written however there is a need to your interpretation and conclusion to reflect your exact results. If the maternal age ≤ 34 years was found to be protective does not mean the maternal age ≥ 35 years is a risk. Remember this age category was your reference. If you want to refer the age category ≥ 35 years then make the other category " ≤ 34 years" a reference in your logistic regression analysis. Otherwise I advise to interpret and make conclusion exactly as what you found in your result section.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Maternal and Child Health Epidemiologist

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Apr 2021

George Agot, University of Nairobi, Nairobi, Kenya

Sampling of cases: Survivor bias has since been included as a limitation of this study because some of these defects for example neural tube defects are potentially fatal, yet such data could not be gathered because we adopted a retrospective approach to gather the information.

The ascertain period for cases: It is true this period could potentially attract recall bias. This period was preferred considering the defects are extremely rare coupled with unavailability of surveillance systems in the county. Even though we preferred <5 years, we encountered children aged <4 years and approximately 78% were aged <2 years, thus, this limitation was somehow reduced by default.

DHIS: This was not used as a source of data in this study, however was intended to inform the readers on how data on birth defects are routinely gathered in the county in the absence of surveillance systems.

Maternal age: Maternal age was defined as maternal age at conception.

Residence: Residence was defined as maternal place of residence at conception, thus introduced in the model and controlled for in multivariable logistic analysis.

Sample size calculation: The choice of literature for p2 was informed by maternal periconceptional period, especially 8 weeks of gestation when defects are expected to have formed yet most women do not plan their pregnancies, thus making it difficult for health care workers to identify these women in good time to effectively implement public health preventive measures before the defects form. Majority of such women attend first ANC at the end of second trimester of gestation when the defects have already formed.

Hypothesized odds ratio: Hypothesized odds ratio for the effects of the primary exposure is actually 2.0 (universally accepted) and not 3.0 as presented in the manuscript. This was a typing error and has been corrected.

Results: The reference category for maternal age was changed to <35 years, but showed no association in the univariable analysis.

Conclusions: The conclusions have been aligned to the study findings and interpretations.

Competing Interests: None

Reviewer Report 07 April 2021

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Marcia L. Feldkamp

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The investigators present a hospital-based case-control study conducted in Kiambu County, Kenya.

The paper is well-written and the methodology easy to follow that was used to investigate risk factors for major external structural malformations. The investigators are to be commended for evaluating risk factors for structural malformations in a developing country. This is an important step toward understanding potential risk factors for the ultimate goal of primary prevention. I have a few suggestions for the investigators to consider that may strengthen the paper.

Methods:

1. There are inconsistencies with the specified time period of data collection/enrollment of subjects: "May 31, 2018 to and July 31, 2019"; "May to July 2019"; "three-month study period".
2. Exposure time period should be clarified for pesticides and how the exposure determined. The investigators should also consider investigating maternal tobacco use, pre-gestational diabetes (specifically), and periconception infections.
3. The investigators conducted a sample size calculation based on all cases. The challenge with this idea is that birth defects are a very heterogeneous group and lumping them altogether suggests that their risk factors are similar. Unfortunately, this is not the case.

Results:

1. Table 3: no need to have a p value listed for the reference group.
2. Since the investigators report an increased risk for maternal age >35 years, did any of the cases have a chromosomal etiology?
3. Did affected siblings have the same type of birth defect?

Discussion - Limitations: small sample size, based on combining several different types of birth defects.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, birth defects

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Apr 2021

George Agot, University of Nairobi, Nairobi, Kenya

Methods

1. Data collection period: This has been corrected to imply a three-month data collection period from May 31, 2019 to July 31, 2019. It was a typing error, but has since been corrected.

2. Exposure time period for pesticides: This variable has been defined as maternal exposure to farm-sprayed pesticides at conception. Increased likelihood of maternal exposure to pesticides was considered because agriculture is the economic mainstay in the county. **Maternal tobacco use:** -This variable was assessed as a variable of interest, however was dropped because only 2 out of 408 respondents reported its use. **Pre-gestational diabetes:** - This was not assessed as a variable of interest, however it was alluded to and assessed among other chronic illnesses as a proxy for measuring maternal use of teratogenic therapeutic agents for conditions such as epilepsy, depression, hypertension and diabetes mellitus. **Infections:** - Infection is indeed an important predictor for birth defects, however, it was beyond the scope of this study since data were gathered retrospectively.

3. Sample size calculation: Birth defects are largely heterogeneous in their etiology, however the defects were lumped together for sample size calculation because of the extreme rarity of these defects coupled with unavailability of hospital-based/population-based surveillance programs in the county. Nevertheless, this has been cited as a limitation of the study.

Results

1. Table 3: P-values for binomial variables were deleted, whereas likelihood ratio test (LRT) was performed for nominal variables/variables with more than two categories to estimate the associated P-values for each variable.

2. Maternal age: The reference category for maternal age was changed to <35 years, but showed no association in the univariable analysis. Nonetheless, the study results were suggestive of chromosomal etiology because some cases were reported to occur with down syndrome, whereas autism was also reported by control subjects as a defect in the previous births.

3. Siblings with same types of birth defects: Yes this was observed in the study. A recurrence of clubfoot was reported by some case subjects, whereas other types of birth defects were reported by case subjects to have occurred with clubfoot

Discussion: Small sample sample based on combined several different types of birth defects has been cited as a limitation of this study.

Competing Interests: None

Reviewer Report 16 March 2021

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Yoseph Worku

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It is interesting, technically sound and intelligibly written manuscript.
There are minor points to be improved.

In the abstract, the results and the conclusions part should show consistent interpretation and conclusion. The conclusion should base on age < 35 years. The reference is Age $\geq$ 35 years (would have been better to take the <35 years as a reference). While presenting the classes, since it is dichotomized, it is better to show a common number as a margin of the classes . E.g. <35 and $\geq$ 35 OR $\leq$ 9 and $\geq$ 9.

The Conceptual Framework should reflect the classifications of the risk factors presented in the Introduction. Some of the variables need to be regrouped in themes and the Framework should be redesigned accordingly.

Some of the variables need to be defined. E.g. Pesticide exposure, chronic illness,...
Check the Sample Size Determination part - the Epi Info calculation does not show the same number.

In the univariable analyses, why p-values for the reference categories are included?
The discussion is a bit shallow. Comparison with more literatures, more in-depth look in to the implications and significances of the findings, and addressing also key relevant factors without significant association in the current study can improve the Discussion part. The paternal age was also mentioned as key factor in previous studies but not assessed in the current study. Why?
There are also other possible limitations not mentioned. E.g. survivor bias and not controlling for some relevant variables in the multivariable analysis like the paternal age.

The conclusion is a bit beyond the scope of the study. E.g. awareness level of couples or the community is not assessed. Detailed and in-depth discussion by citing other relevant literatures can help readers to better understand the situation and to deduce more appropriate conclusions.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health and Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 11 Apr 2021

George Agot, University of Nairobi, Nairobi, Kenya

Abstract: Conclusions have been aligned to the study results and interpretations. Maternal age <35 years has been used as the reference category, and presented as <35 years, and ≥35 years, however it was not included in the inclusion because it was no longer associated with dependent variable in the univariable analyses.

Gestational age: Gestational age has also been presented as <9 weeks, and ≥9 weeks.

Pesticides exposure: Exposure redefined as maternal exposure to farm-sprayed pesticides before conception.

Chronic illnesses: Chronic illnesses were used as a proxy for measuring maternal use of teratogenic therapeutic agents for chronic conditions such as epilepsy, depression, hypertension and diabetes mellitus. In this respect, it was not used as a measure for particular chronic illnesses.

Conceptual framework: Redesigned to reflect the three classes of major external structural birth defects described in the study introduction.

Univariable analyses: P-values for binomial variables were deleted, whereas likelihood ratio test (LRT) was performed for nominal variables/variables with more than two categories to estimate the associated P-values for each variable.

Discussion: Discussion of the significant variables was improved to include their implications, and significance. Variables that showed no associations were also explained with reference to other studies.

Paternal age: Paternal age was introduced in the model, however it showed no association with the defects in the univariable analyses. Nevertheless, it was controlled for in the multivariable, but still showed no association. Further, because of potential collinearity with maternal age, paternal age was controlled for without maternal age in the multivariable analyses, however, still showed no association with birth defects.

Limitations of the study: Survivor bias was included as a limitation of this study because some of these defects for example neural tube defects are potentially fatal.

Conclusions: Conclusions were aligned to the study findings and interpretations.

Competing Interests: None

Author Response 11 Apr 2021

George Agot, University of Nairobi, Nairobi, Kenya

Sample size determination: The sample computation was reconfirmed and found consistent with formula provided, however the hypothesized odds ratio is 2.0 (universally accepted, and not 3.0 as presented. This typing error has since been corrected.

Competing Interests: None

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