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Title

Maternal age at first childbirth and geographical variation in HBV prevalence in Cameroon: Important role of mother-to-child transmission

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Keywords

Hepatitis B; mother-to-child transmission; demographic health survey (DHS); spatial analysis; Africa

Running title

Spatial variation of HBV in Cameroon

Summary

A nationwide population-based survey observed marked spatial variation in HBV prevalence in Cameroon. Maternal age at first childbirth, a proxy for HBV mother-to-child transmission, was significantly associated with HBsAg-positivity, suggesting a crucial role of MTCT in maintaining high HBV endemicity.

Abstract

Background

The prevalence of hepatitis B virus (HBV) infection varies geographically around the world. However, the underlying reasons for this variation are unknown. Using a nationally representative population-based sample from all 58 administrative divisions in Cameroon, we examined the association between median maternal age at first childbirth in a preceding generation, a proxy for the frequency of mother-to-child transmission (MTCT) of HBV in a region, and the risk of chronic HBV infection, defined as positive surface antigen (HBsAg), in the index generation.

Methods

We estimated a division-specific median maternal age at first childbirth using historical data from Demographic Health Surveys (DHS) in 1991/1998/2004/2011. We tested HBsAg in 2011 DHS participants. We used maps to display spatial variation and spatial models for the analysis.

Results

In 14,150 participants (median 27 years old, 51% females), the overall weighted prevalence of HBsAg was 11.9% (95%CI: 11.0–12.8), with a wide geographical variation across the divisions (range: 6.3-23.7%). After adjusting for confounding factors and spatial dependency, lower maternal age at first childbirth was significantly associated with positive HBsAg at the division level (β: 1.89 [95%CI: 1.26-2.52], p<0.001), and at the individual level (OR: 1.20 [95%CI: 1.04-1.39], p=0.016). A similar ecological correlation was observed across other African countries.

Conclusions

The significant association between the maternal age at first childbirth and HBsAg-positivity suggests a crucial role of MTCT in maintaining high HBV endemicity in some areas in Cameroon. This underlines an urgent need to effectively prevent MTCT in order to achieve WHO's global hepatitis elimination goals.

Introduction

Hepatitis B virus (HBV) infection imposes a major health burden worldwide. Approximately 257 million persons live with chronic HBV infection, and 887,000 HBV-related deaths occur annually [1]. In 2016, WHO launched an ambitious plan to eliminate HBV as a major public health threat globally by 2030.

HBV burden is not ubiquitously distributed across continents, and disproportionally affects sub-Saharan Africa and East Asia, where the adult prevalence of hepatitis B surface antigen (HBsAg), a marker of current infection, exceeds 8% and 5%, respectively [2, 3]. A wide variation in HBsAg prevalence is also recognized across countries within the same region, and even between villages within the same division [4, 5]. A classical mathematical model of HBV transmission dynamics, before the wide implementation of infant hepatitis B vaccination, explained that such a variation in HBsAg prevalence might be attributed to a feedback mechanism that relates to the rate of transmission, average age at infection, and age-dependent probability of developing chronic infection [6]. The risk of chronic HBV infection is inversely correlated with age at HBV infection: 80-90% in neonates perinatally infected by infectious mothers, 20-30% in children infected through horizontal transmission, and <5% in those infected during adulthood. Also, the average age at which individuals become infected with HBV is largely dependent on the prevalence of chronic HBV infection in the population: the higher the prevalence, the younger the age of infection [6]. In this loop of positive feedback, mother-to-child transmission (MTCT) could play a central role; compared to women who acquired chronic HBV infection through horizontal transmission, women who acquired chronic infection through MTCT are more likely to maintain persistent viral replication with positive hepatitis B e antigen (HBeAg) well into their childbearing years, thus are more prone to replicate MTCT [7-11].

However, the question of whether a high frequency of HBV MTCT could lead to a high HBsAg prevalence in a population has not been proven epidemiologically due to the difficulty in measuring the rate of MTCT in a given adult population. For example, at the time of sero-survey of an adult population (index generation), it is extremely difficult to ascertain whether their mothers (previous generation) carried HBsAg and HBeAg during their pregnancies. Alternatively, maternal age at first childbirth could be an indirect marker of HBV MTCT [12, 13]. HBeAg loss occurs spontaneously with age in people with chronic HBV infection; therefore, younger mothers, if chronically infected with HBV, have a higher likelihood of having HBeAg and a high viral load, which increases their baby's risk of perinatal infection [9, 14, 15]. Moreover, if the first child is infected through MTCT, this child is more likely to develop chronic HBV infection and is at greater risk of infecting subsequent siblings in the household through horizontal transmission, even when the mother has lost HBeAg and becomes less infectious during subsequent pregnancies [5, 16].

We therefore assessed a population-level association between the median age at first childbirth, a proxy for the frequency of HBV MTCT, and the prevalence of HBsAg using a nationally representative population-based sample in Cameroon. This country in Central Africa has a high HBsAg prevalence and a majority (>50-80%) of adults have been exposed to the virus, as indicated by a positive HBV core antibody (anti-HBc) [17, 18]. Hepatitis B vaccination starting at 6 weeks of age was integrated into the national infant immunization program in 2005. To further examine the above hypothesis, we also conducted an ecological analysis for a country-level association between the median age at first childbirth and the prevalence of HBsAg within the African continent.

Methods

Historical demographic data

We used publicly available data from a series of cross-sectional nationally representative household surveys (Demographic Health Surveys (DHSs)) conducted in 1991/1998/2001/2011 [19]. Secondary use of these data was approved by the University of Sheffield Research Ethics Committee (Ref: 033994).

HBV sero-survey in 2011

We also used data from a HBV sero-survey of the 2011 DHS participants. Cameroon is divided administratively into ten regions and 58 divisions. The 2011 DHS was conducted in all 58 divisions from January to August 2011 using a two-stage stratified probability sampling [20]. From each of 578 census clusters, a fixed number (25-30) of households were selected; a total of 14,214 households participated in the DHS interview (Supplementary Figure 1). All women aged 15-49 years and all men aged 15-59 years living in half of these households were further invited to participate in the sero-survey. Following an informed consent, capillary blood was collected as dried blood spots (DBS). DBS eluate was tested for HBsAg at the Centre Pasteur du Cameroun using a chemiluminescent microparticle immunoassay (ArchitectPlus, Abbott). The use of DBS was 99% sensitive and 100% specific to detect HBsAg compared to plasma sample [21]. The study was approved by the National Ethics Committee of Cameroon.

Study variables and data sources

The median age at first childbirth was computed at a cluster level (division), whilst HBsAg-positivity was considered both at an individual level (binary variable: positive/negative) and a division level (continuous variable: HBsAg prevalence). Since the age of the index participants in 2011 ranged from 15 to 59 years, and thus their birth years ranged from 1952 to 1996, we

computed the median age at first childbirth in women who were at their reproductive age (15-49 years) during this particular period (1952–1996) (Supplementary Figures 2-3). We first computed the division-level estimates from each of the historical DHS data (1991/1998/2004/2011) and then pooled these using random-effects inverse-variance models. As the maternal age at first birth may change over time, we stratified this period into two: 1952-1981 (corresponding to the years of birth of the older index cohort aged 30–59 years in 2011) and 1982-1996 (younger index cohort aged 15–29 years in 2011).

We identified the following as *a priori* confounders for the association between the median maternal age at first childbirth and the risk of chronic HBV infection: sibship size, wealth index, and age (Supplementary Figure 4). Sibship size was defined as the number of children born to the same biological mother as the respondent, irrespective of whether a sibling was alive or not at the time of the 2011 survey. Sibship size for each household in a division was aggregated to estimate the division-level mean sibship size. We used household wealth quintiles developed by the DHS program based on household characteristics in the 2011 survey. We categorized the age of participants in the 2011 DHS into three categories (15–29, 30–44, and 45–59 years) and also aggregated the ages to estimate the mean age of individuals in the division.

Statistical analyses

Descriptive analyses

HBsAg prevalence was weighted to take into account the stratified sampling and sampling probabilities. Due to a clustering of HBsAg-positivity within households (intraclass correlation coefficient (ICC): 0.39) and within divisions (ICC: 0.05), we used multilevel logistic regression to assess differences in weighted HBsAg prevalence across various participant groups.

Spatial variation

We used maps to display the spatial variation of HBsAg prevalence and relevant covariates. To avoid spatial variation fixed by the administrative boundaries, we generated smoothed interpolated maps using empirical Bayesian kriging. The division-level variables were assumed to follow a Gaussian distribution. We used Local Moran's I index to identify and map clusters of high/low HBsAg prevalence and local spatial outliers. Global spatial autocorrelation was assessed using the Global Moran's I index.

Division-level association between median maternal age at first childbirth and HBsAg prevalence

Using Pearson's correlation coefficient and bivariate linear regression analyses we assessed the division-level association between the median maternal age at first childbirth and the HBsAg prevalence. *A priori* confounders were included in a multiple linear regression model. Since there was evidence of global spatial autocorrelation (Moran's I=0.34), we adopted spatial models and selected the Eigenvector Spatial Filtered (ESF) model [22] as the best model based on the Moran's I value of the residuals, the AIC, and the R^2. Since the association between the median maternal age at first childbirth and spatial variation of HBsAg-positivity might be modified by age of the index generation, we stratified regression analyses into two age groups (older versus younger index cohort as described above).

Individual-level association between median maternal age at first childbirth and HBsAg positivity.

We also assessed the association between the division-level median age at first childbirth and individual risks of HBsAg-positivity using multilevel logistic regression models accounting for spatial dependency [23]. We used ESF to account for spatial dependency and computed marginal odds ratios using generalized estimation equations with robust standard errors.

Country-level correlation between median maternal age at first childbirth and HBsAg prevalence in Africa.

Median age at first childbirth in each African country was obtained from the earliest available DHS. Country-level prevalence of HBsAg was obtained from two published global estimates [2, 3]. Pearson's correlation coefficient was used to assess the country-level correlation between the median maternal age at first childbirth and the prevalence of HBsAg in Africa.

The analyses were done using STATA, R and ArcGIS.

Results

HBsAg prevalence

Of 14,202 DBS collected in the 2011 DHS, 14,150 (99.6%) were tested for HBsAg. The median number of sero-survey participants was 2 (IQR: 1–3) per household and 185.5 (104–288) per division. The median age of sero-survey participants was 27 (IQR: 20–37) years, and there were 7,224 (51%) females (Table 1). The overall weighted prevalence of HBsAg in Cameroon was 11.9% (95%CI: 11.0–12.8). The prevalence was significantly higher in persons aged 15–29 years (12.3% [p = 0.011]), males (14.1% [p <0.001]), and persons in the poorest wealth quintile (17.5% [p = 0.023]). There was also a marked geographical variation with the lowest prevalence observed in the North-West region (7.0%) and the highest in the Far-North region (17.7%). The mean (±SD) prevalence of HBsAg per division was 11.1 ± 3.8%, with a remarkably wide range (6.3%-23.7%). The mean age at first childbirth per division from 1952 to 1996 was 19.0 ± 0.8 years (range: 17.4-21.1). The mean sibship size per division was 7.0 ± 0.5 (range: 5.8-8.8, Table 2).

Spatial variation of HBsAg prevalence and covariates

There was a cluster of divisions with the highest HBsAg prevalence in the northern part of Cameroon and clusters of divisions with the lowest HBsAg prevalence in the Adamawa plateau and western part of the country (Figure 1, Supplementary Figure 5). Median age at first childbirth followed a similar pattern; divisions with the lowest maternal age at first childbirth were clustered in the north and those with the highest maternal age were clustered in the west. Divisions in the northern and central parts had the highest mean sibship size while those in the west and east had the lowest. The highest mean wealth index was observed in the central and south-western parts.

Division-level association

A significant correlation was observed at the division level between the prevalence of HBsAg and the following covariates: median age at first childbirth (r=0.56, p<0.001), sibship size (r=0.37, p=0.004), mean wealth index (r=0.44, p<0.001), and mean age of the index cohort (r=0.28, p=0.030) (Supplementary Figure 6). There was also a significant correlation between the median age at first childbirth and the other covariates (Supplementary Figure 7).

On bivariate linear regression, the following division-level variables were all significantly associated with the division-level HBsAg prevalence (Table 3): median maternal age at first childbirth (β: -2.60 [95%CI: -3.72, -1.48]), mean sibship size (β: 2.64 [0.88, 4.40]), mean wealth index (β: -2.11 [-3.33, -0.91]), and mean age (β: -0.55 [-1.06, -0.03]). After adjusting for the mean sibship size, mean wealth index, mean age, and spatial dependency, on average, a unit increase in the division-level median age at first childbirth was significantly associated with a two-percent decrease in the division-level HBsAg prevalence (β: -1.89 [95%CI: -2.52, -1.26]). The division-level associations between the median age at first childbirth and the HBsAg prevalence remained

significant for the younger index cohort aged 15-29 years (β: -2.56 [-4.25, -0.87]) but not for the older cohort aged 30-59 years (β: -0.76 [-2.23, 0.72]) (Supplementary Figure 9).

Individual-level association

After adjusting for individual age, household wealth, division-level mean sibship size, and spatial dependency, a unit increase in the division-level median maternal age at first childbirth was associated with a 17% lower risk of HBsAg-positivity at the individual level (OR: 0.83 [95%CI: 0.72–0.96]). The significant associations were also observed in the index cohort aged 15-29 years (adjusted OR: 0.81 [0.68–0.96]) and in those aged 30-44 years (0.82 [0.70–0.96]); however, no association was observed in the oldest age group (45–59 years) (Table 4).

Country-level correlation in Africa

There was a significant negative correlation between country-level median maternal age at first childbirth and country-level HBsAg prevalence estimated by Schweitzer *et al* [2]. (r=-0.45, p=0.003), and country-level HBsAg prevalence estimated by the Polaris Observatory Collaborators [3] (r=-0.40, p=0.032) (Fig 2).

Discussion

Using nationally representative DHS data of adults in Cameroon born before the infant hepatitis B vaccination program, we found a high overall HBsAg prevalence (11.9%), an important spatial variation of HBsAg-positivity, and a statistically significant association between the median maternal age at first childbirth and HBsAg-positivity both at the division and individual level. These findings suggest an important role of MTCT in maintaining the high HBV endemicity in some areas in Cameroon. We also confirmed a significant country-level correlation between the maternal age at first childbirth and the HBsAg prevalence across Africa.

We assumed that a division with younger median age at first childbirth would have a higher frequency of MTCT compared to a division with an older median age. This is because HBeAg-positivity and/or high viral load, the major determinants of HBV MTCT, are lost over time in persons chronically infected with HBV [9, 14, 15]. In the natural history of chronic HBV infection, HBeAg is almost invariably present in children newly infected with HBV and is spontaneously lost over time at an annual rate of 6-7% [9, 10]. The prevalence of HBeAg in HBsAg-positive women is therefore estimated to decrease with age: 40.2%, 30.0%, and 22.7% in women in Central Africa aged 10-19, 20-29, and 30-39 years, respectively [14]. Indeed, lower maternal age has been identified as a risk factor for HBV MTCT [24].

The prevalence of HBeAg in HBsAg-positive pregnant women would have been a more direct marker of the frequency of MTCT. Although such nationwide data does not exist in Cameroon, previous cross-sectional studies in some regions in Cameroon supported our findings. In Yaoundé, capital city with a lower HBV prevalence (10.2% in our study), none of HBsAg-positive pregnant women were found to carry HBeAg [25]. In contrast, in the Far-North region, a zone with high HBV prevalence (17.7% in our study), 22.0% of HBsAg-positive pregnant women had HBeAg [26]. Moreover, in these HBsAg-positive pregnant women, the HBeAg prevalence was significantly higher in those aged <20 years (31.1%) than in those aged >28 years (14.3%, p=0.01) [26].

We adequately addressed potential confounders for the association between maternal age at first childbirth and HBsAg positivity. However, there is still a risk of residual confounding with unmeasured variables. Worldwide, there is a wide geographical variation in the distribution of predominant HBV genotypes, and this may have a role in defining local HBV epidemiology [27]. For example, in East Asia where genotypes B and C predominate, genotype C was found to be

associated with more frequent MTCT [28], and this might have contributed to a relatively high HBV prevalence in this region [29]. In Cameroon, there is a predominance of genotypes A and E, similar to other Central and West African countries [26, 30]. Whilst a relatively higher prevalence of genotype A has been documented in Central, West, South and East of Cameroon [30], a predominance of genotype E was reported in North where the prevalence of HBsAg is very high [26]. More studies are needed to elucidate the role of African genotypes, particularly its association with a specific mode of HBV transmission. Variation in host genetics such as the human leukocyte antigen (HLA) genes may also influence the natural history of HBV infection [31, 32], and this may need to be accounted in a future study. The risk of HBV MTCT in women co-infected with HIV may be different, especially when they receive antiretroviral therapy that is also active against HBV [33]. Nevertheless, the 2011 DHS participants were born in 1952-1996, before the wide availability of such an antiretroviral regimen.

Our findings provide two important implications for the control of hepatitis B. First, even in the absence of any preventive measure, delaying the age of marriage and childbearing may spontaneously result in a reduction in HBsAg prevalence. This confirms historical findings reported in South Africa in the pre-vaccination era [34]. Second, our study provides an important rationale for preventing HBV MTCT in Cameroon. The current hepatitis B vaccination schedule using pentavalent vaccine (6-10-14 weeks) effectively prevents horizontal transmission but not MTCT [33]. In 2020, the Government launched a national strategic plan for HBV and identified the introduction of birth dose hepatitis B vaccine as a priority. Moreover, to further eliminate the risk of MTCT, an additional strategy such as peripartum antiviral prophylaxis in HBV-infected women with a high viral load (≥200,000 IU/mL) or a positive HBeAg test should be considered as recently recommended by WHO [35-37].

The study has limitations. Since our exposure of interest (maternal age at first childbirth) was estimated at a cluster level, there is a possibility of ecological fallacy. This is particularly relevant for the country-level assessments across Africa. For the estimates within Cameroon, we tried to limit the bias by assessing the division-level effect on the individual-level outcome (HBsAg positivity). Evaluating the association between an individual's birth order and HBsAg positivity could also be informative to support our hypothesis; unfortunately, birth order was not systematically collected for the DHS respondents.

In conclusion, we found that maternal age at first childbirth, a proxy for the frequency of MTCT, is significantly associated with HBsAg-positivity. This suggests the crucial role of HBV MTCT in maintaining high HBV endemicity in some areas in Cameroon. We also found this correlation across the African countries. These findings underline an urgent need to scale up interventions to effectively prevent MTCT in Cameroon and other African countries.

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Potential conflict of Interests

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Tables

Table 1. Characteristics of participants in the 2011 HBsAg sero-survey (N=14,150)

Variables	Total, n (%)	HBsAg positive, n (weighted %)	*p value
Individuals (N= 14,150)			
Age group			0.010
15-29 years	8,051 (56.9)	972 (12.3)	
30-44 years	4,386 (31.0)	504 (12.2)	
45-59 years	1,713 (12.1)	145 (9.1)	
Gender			<0.001
Female	7,224 (51.1)	664 (9.7)	
Male	6,926 (49.0)	957 (14.1)	
Education			0.021**
No education	598 (8.6)	246 (13.4)	
Primary	2,355 (34.0)	586 (12.4)	
Secondary	3,441 (49.7)	704 (11.2)	
Higher	532 (7.7)	85 (10.8)	
Occupation *(missing = 2447)*			0.301
Not working/Student/Retired	911 (7.8)	121 (13.2)	
Farmers/Hunters/Fishers	4,599 (39.3)	580 (13.3)	
Military/Drivers	507 (4.3)	57 (12.1)	
Craftsmen	2,097 (17.9)	236 (10.8)	
Higher functions	525 (4.5)	60 (12.1)	
Intermediate professions	3,064 (26.2)	335 (11.5)	
DHS Wealth Index Quintiles			0.043**
Poorest	2,092 (14.8)	363 (17.5)	
Poorer	2,827 (20.0)	345 (12.8)	
Middle	2,979 (21.1)	293 (11.3)	
Richer	3,054 (21.6)	301 (9.5)	
Richest	3,198 (22.6)	319 (10.3)	
Marital status			0.123
Never in union	5,136 (36.3)	627 (12.2)	
Married/living with partner	8,014 (56.6)	889 (11.8)	
Divorced/separated/widowed	1,000 (7.1)	105 (11.1)	
Type of residence			0.595
Rural	7,136 (50.4)	907 (13.3)	
Urban	7,014 (49.6)	714 (10.7)	
Region			<0.001
Adamawa	1,117 (7.9)	89 (8.3)	
Centre	2,376 (16.8)	158 (11.1)	
East	936 (6.6)	102 (10.9)	
Far-North	1,379 (9.8)	267 (17.7)	
Littoral	2,176 (15.4)	91 (9.5)	
North	1,537 (10.9)	265 (17.5)	
North-West	1,377 (9.7)	100 (7.0)	
West	1,196 (8.5)	110 (9.2)	
South	922 (6.5)	97 (10.7)	
South-West	1,134 (8.0)	122 (11.1)	
Ethnicity			<0.001
Arab-choa/peulh/haoussa/kanuri	1,293 (9.2)	121 (10.7)	

Biu-mandara	1,478 (10.5)	278 (18.3)	
Adamaoua-oubangui	1,522 (10.8)	255 (18.1)	
Bantoede-southwest	212 (1.5)	13 (5.9)	
Grassfields	1,990 (14.1)	179 (8.7)	
Bamilike/Bamoun	3,032 (21.5)	278 (9.4)	
Cetier/ngoe/oroko	673 (4.8)	55 (8.6)	
Beti/bassa/mbam	2,996 (21.3)	344 (11.6)	
Kako/meka/pygmie	563 (4.0)	56 (9.8)	
Stranger/other	328 (2.3)	33 (10.9)	
Injections in past 12 months *(missing = 11)*			0.867
0	8,367 (59.2)	989 (12.3)	
1-2	2,772 (19.6)	310 (11.5)	
3-9	2,356 (16.7)	250 (11.1)	
>9	644 (4.6)	72 (11.0)	
Number of sexual partners in lifetime			0.020
0	2,070 (14.9)	243 (11.3)	
1-2	4,568 (32.9)	513 (11.9)	
3-9	4,922 (35.5)	585 (12.4)	
>9	2,313 (16.7)	259 (11.8)	
Place of circumcision (Male only = *6,926)*			0.908
Health facility/Home of Health worker	3,244 (51.5)	425 (13.1)	
Ritual site	487 (7.7)	81 (17.8)	
Home/other home	2,572 (40.8)	335 (13.7)	
Anti-HCV antibody			0.012
Negative	13,991 (98.9)	1,616 (12.0)	
Positive	159 (1.1)	5 (4.4)	
HIV			0.841
Negative	13,501 (95.4)	1,553 (11.9)	
Positive	649 (4.6)	68 (11.6)	

*p value for association between the variable and HBsAg positivity using weighted univariate multilevel logistic regression to account for clustering of HBV within households and within divisions.

**p value for linear trend

Table 2. Description of covariates at division level

Variable	N = 58 divisions	
	Mean (SD)	**Range**
Prevalence of HBsAg per division in 2011 (%)		
Persons aged 15 – 59 years (all index cases)	11.1 (3.8)	6.3-23.7
Persons aged 15 – 29 years (younger index cohort)	11.8 (5.6)	2.5-28.5
Persons aged 30 – 59 years (older index cohort)	10.7 (5.3)	3.2-30.3
Median age at first childbirth per division (years)		
Time period 1952 to 1996	19.0 (0.8)	17.4-21.1
Time period 1952 to 1981	18.9 (0.9)	17.1-21.1
Time period 1982 to 1996	19.0 (0.7)	17.5-20.7
Mean sibship size per division	7.0 (0.5)	5.8-8.8
Mean wealth index per division*	2.8 (0.8)	1.3-4.6
Mean age per division (years)	27.2 (2.0)	23.1-31.5

* Wealth index ranges from 1 to 5; 1 is the poorest and 5 is the richest wealth quintile.

Table 3. Spatial association between the division-level median maternal age at first childbirth and the division-level HBsAg prevalence, stratified by the age group (N=58 divisions of Cameroon)

	Univariate OLS		Multiple OLS		Multiple *ESF	
Variable	β (95% CI)	*p* value	aβ (95% CI)	*p* value	aβ (95% CI)	*p* value
Median age at first childbirth	-2.60 (-3.72 – -1.48)	<0.001	-1.89 (-3.38 – -0.40)	0.013	-1.89 (-2.52 – -1.26)	<0.001
Mean sibship size	2.64 (0.88 – 4.40)	0.004	0.83 (-1.06 – 2.73)	0.381	0.83 (0.03 – 1.64)	0.042
Mean wealth index	-2.11 (-3.33 – -0.91)	<0.001	-0.90 (-2.33 – 0.53)	0.211	-0.91 (-1.51 – -0.30)	0.004
Mean age	-0.55 (-1.06 – -0.03)	0.039	0.03 (-0.52 – 0.58)	0.913	0.02 (-0.20 – 0.26)	0.796
Model parameters						
Eigenvector selection	-	-	-	-	9 vectors selected	-
Moran's I of residuals	-	-	0.597	<0.001	-0.17	0.527
AIC	-	-	309.56	-	216.58	-
R^2	-	-	0.319	-	0.899	-
Stratified analysis: Persons aged 15 – 29 years (younger index cohort with birth period 1982 to 1996)						
Median age at first childbirth	-3.32 (-5.17 – -1.47)	0.001	-2.56 (-4.81 – -0.31)	0.026	-2.56 (-4.25 – -0.87)	0.004
Mean sibship size	3.26 (0.65 – 5.87)	0.015	1.42 (-1.44 – 4.29)	0.325	1.42 (-0.73 – 3.57)	0.190
Mean wealth index	-2.13 (-3.99 – -0.28)	0.025	-0.55 (-2.62 – 1.53)	0.600	-0.54 (-2.10 – 1.01)	0.484
Model parameters						
Eigenvector selection	-	-	-	-	6 vectors selected	-
Moran's I of residuals	-	-	0.300	<0.001	-0.12	0.509
AIC	-	-	352.99	-	325.04	-
R^2	-	-	0.213	-	0.609	-
Stratified analysis: Persons aged 30 – 59 years (older index cohort with birth period 1952 to 1981)						
Median age at first childbirth	-1.35 (-2.96 – 0.27)	0.099	-0.76 (-2.41 – 0.89)	0.360	-0.76 (-2.23 – 0.72)	0.308
Mean sibship size	1.85 (-0.71 – 4.41)	0.152	0.34 (-2.39 – 3.07)	0.802	0.34 (-2.11 – 2.79)	0.779
Mean wealth index	-2.40 (-4.12 - -0.68)	0.007	-2.06 (-4.00 - -0.12)	0.038	-0.54 (-3.81 – -0.31)	0.015
Model parameters						
Eigenvector selection	-	-	-	-	4 vectors selected	-
Moran's I of residuals	-	-	0.131	0.022	-0.11	0.521
AIC	-	-	345.18	-	336.38	-

R^2	-	-	0.144	-	0.366	-

OLS: Ordinary least squares regression

ESF: Eigenvector spatial filtering regression *ESF chosen as best spatial model (see Supplementary Figure 8 for performance of the ESF model)

β: Linear regression coefficient for a unit increase in the covariate (median age at first childbirth in years, mean sibship size, mean wealth index, and mean age in years)

aβ: adjusted linear regression coefficient, adjusted for the other variables on the table

Table 4. Association between the division-level median maternal age at first childbirth and the individual-level HBsAg positivity, stratified by the age group (N=14,150)*

	Univariate multilevel logistic regression		Multiple multilevel logistic regression		Multiple multilevel logistic regression with ESF	
Variable	OR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
Individual level						
Age group		0.001		0.001		0.001
15-29 years	Ref.		Ref.		Ref.	
30-44 years	0.95 (0.83 – 1.07)		0.93 (0.82 – 1.06)		0.93 (0.82 – 1.05)	
45-59 years	0.67 (0.54 – 84)		0.65 (0.52 – 0.81)		0.64 (0.52 – 0.80)	
Household level						
DHS Wealth Index Quintiles		<0.001		0.008		0.004
Poorest	Ref.		Ref.		Ref.	
Poorer	0.66 (0.51 – 0.86)		0.76 (0.58 – 0.99)		0.81 (0.63 – 1.03)	
Middle	0.52 (0.39 – 0.70)		0.61 (0.45 – 0.84)		0.64 (0.50 – 0.83)	
Richer	0.52 (0.40 – 0.68)		0.65 (0.49 – 0.86)		0.67 (0.52 – 0.85)	
Richest	0.53 (0.40 – 0.69)		0.71 (0.52 – 0.97)		0.69 (0.52 – 0.91)	
Division level						
Mean sibship size	1.55 (1.23 – 1.96)	<0.001	1.17 (0.93 – 1.47)	0.180	1.12 (0.88 – 1.44)	0.346
Median age at first childbirth	0.76 (0.67 – 0.86)	<0.001	0.86 (0.76 – 0.97)	0.013	0.83 (0.72 – 0.96)	0.016
Model parameters						
Eigenvector selection	-	-	-	-	4 vectors selected	-
Deviance	-	-	9922.51		9871.42	-
Stratified analysis: Persons aged 15–29 years (N=8,051)						
Median age at first childbirth	0.70 (0.61 – 0.81)	<0.001	0.82 (0.71 – 0.94)	0.006	0.81 (0.68 – 0.96)**	0.013
Stratified analysis: Persons aged 30–44 years (N=4,386)						
Median age at first childbirth	0.84 (0.73 – 0.96)	0.013	0.88 (0.77 – 1.00)	0.061	0.82 (0.70 – 0.96)**	0.014
Stratified analysis: Persons aged 45–59 years (N=1,713)						
Median age at first childbirth	0.83 (0.68 – 1.03)	0.088	1.05 (0.84 – 1.32)	0.643	1.01 (0.79 – 1.28)**	0.944

* Marginal (population average) odds ratios reported

**Adjusted for age group, DHS Wealth Index, Mean sibship size

Figure legends

Figure 1. Spatial distribution of HBsAg positivity and covariates in Cameroon

Figure 2. Ecological correlation between country-level median maternal age at first childbirth and country-level HBsAg prevalence in Africa. A: HBsAg prevalence estimated by Schweitzer *et al.* **B:** HBsAg prevalence estimated by The Polaris Observatory Collaborators.

Figure 1. Spatial distribution of HBsAg positivity and covariates in Cameroon

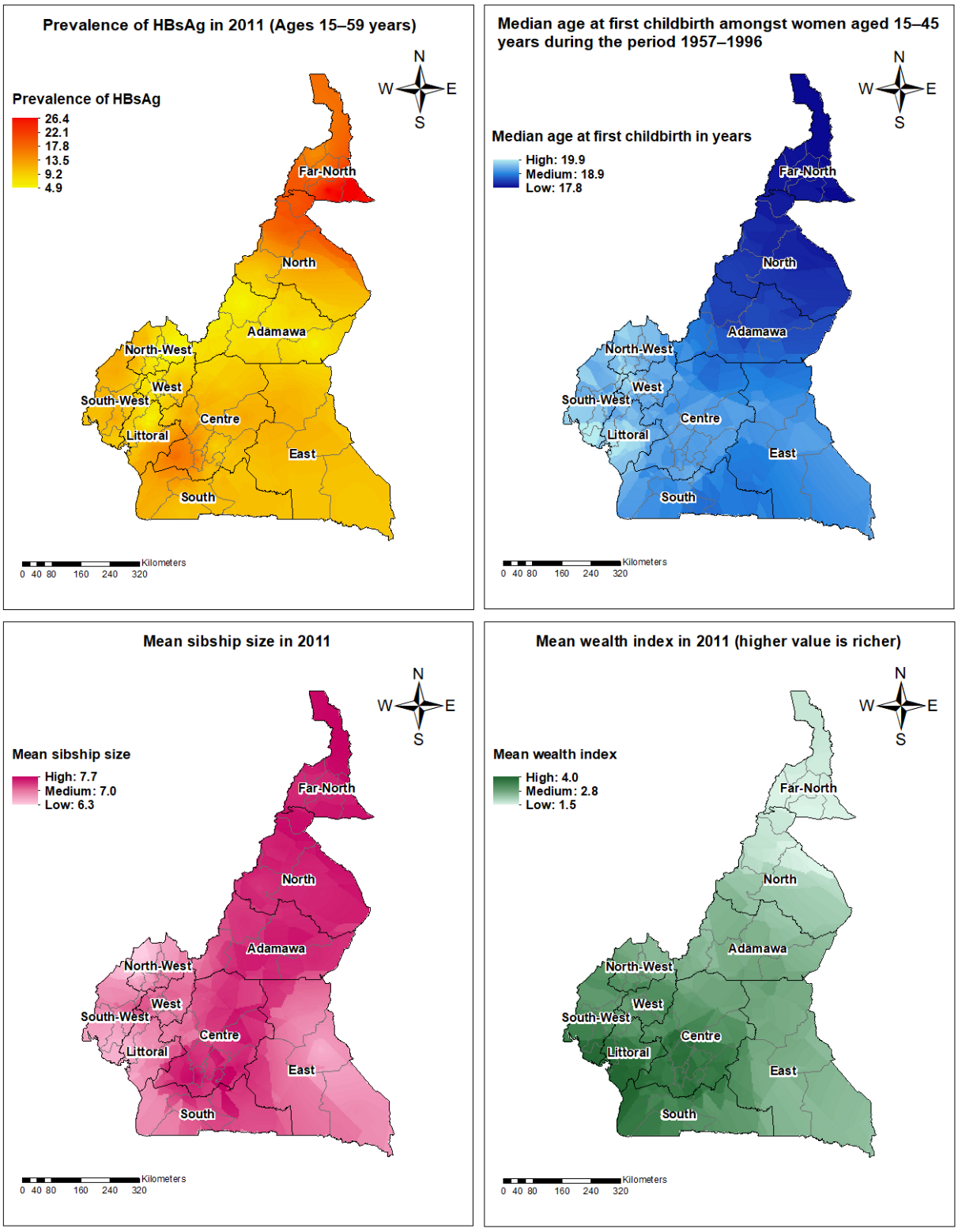
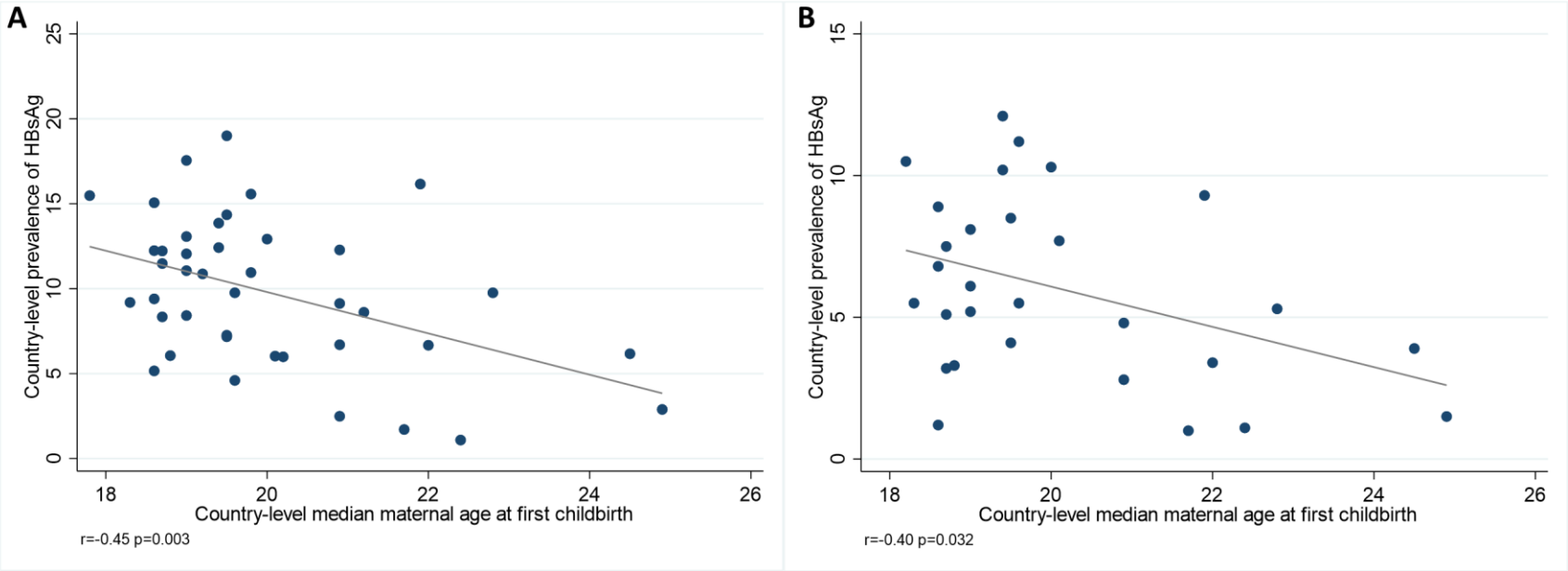


Figure 2. Ecological correlation between country-level median maternal age at first childbirth and country-level HBsAg prevalence in Africa.

A: HBsAg prevalence estimated by Schweitzer *et al.*

B: HBsAg prevalence estimated by The Polaris Observatory Collaborators.



Supplementary material

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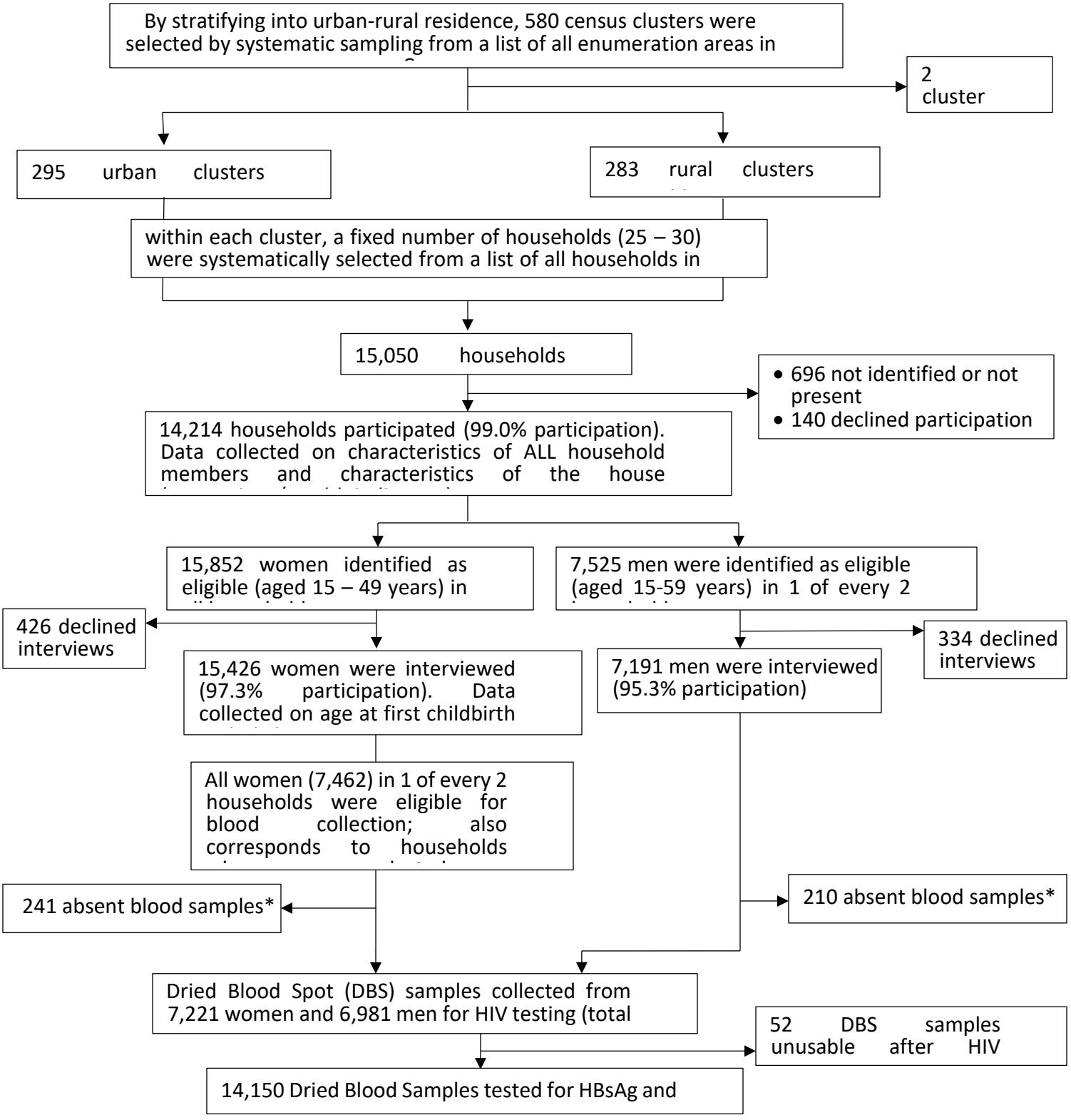
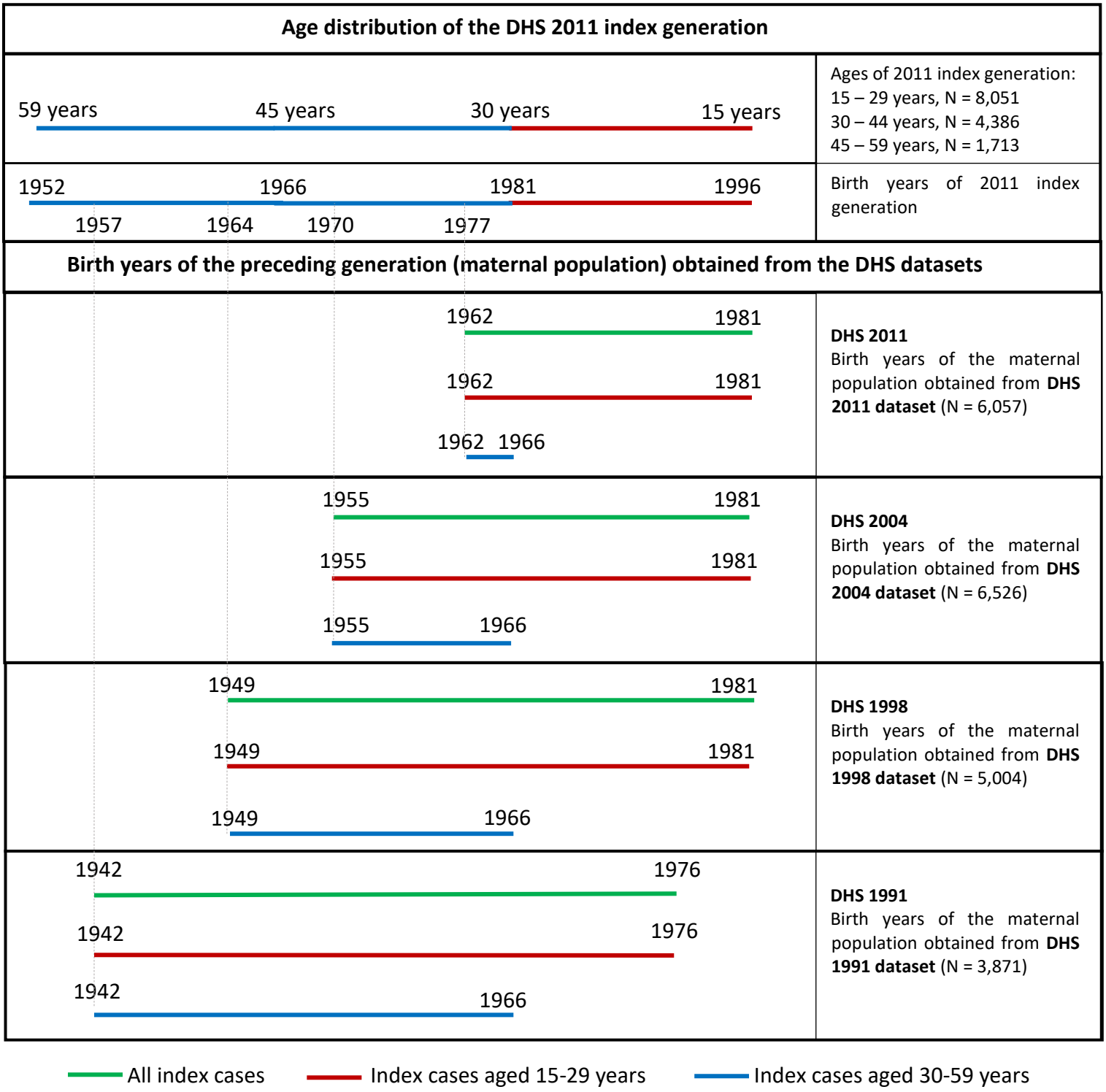
Supplementary Figure 1: Flowchart of participants in Cameroon DHS 2011



*includes persons who denied giving blood, absent at time of blood collection, missing samples, and other reasons such as labelling inconsistencies and insufficient samples

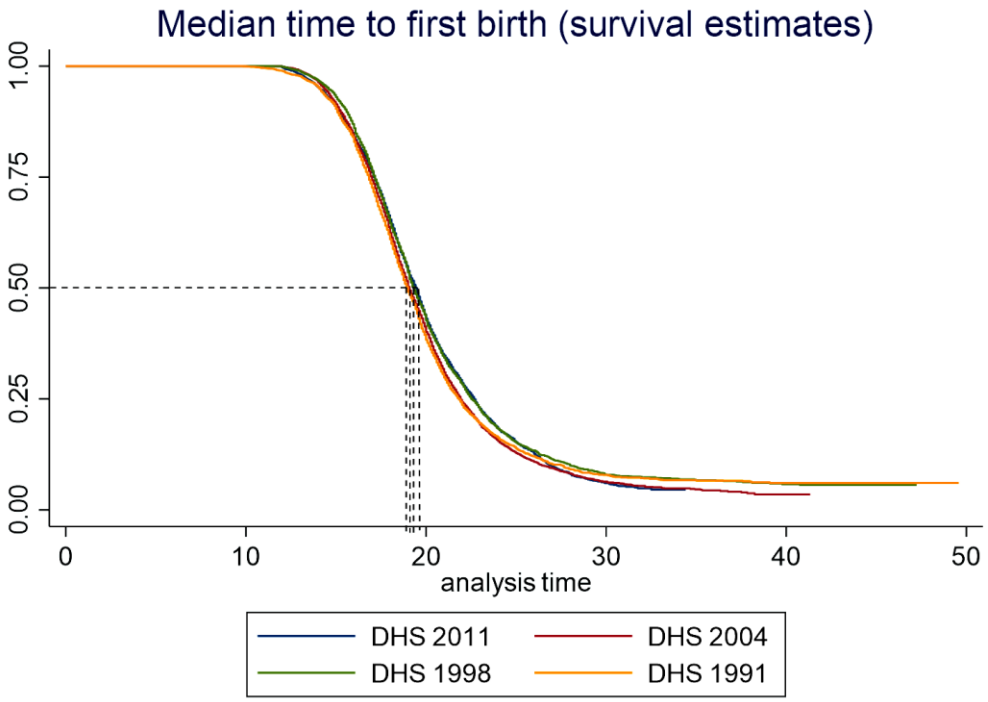
Supplementary Figure 2: Computation of median maternal age at first childbirth from the DHS datasets



Years of birth of the index cohort and the maternal cohort by the DHS datasets

Type	All index cohort	Old index cohort (blue)	Young index cohort (red)
Ages of the index cohort in 2011	15-59 years	30-59 years	15-29 years
Years of birth of the index cohort	1952 - 1996	1952 - 1981	1982 - 1996
Years of birth of the maternal cohort, assuming the reproductive age of 15-49 years	1903 - 1981	1903 - 1966	1933 - 1981
Years of birth of the maternal cohort covered by the DHS 2011 dataset (providing maternal cohort for index cases born between 1977 – 1996)	1962 - 1981	1962 - 1966	1962 - 1981
Maternal dates of birth from DHS 2004 (providing maternal cohort for index cases born between 1970 – 1996)	1955 - 1981	1955 - 1966	1955 - 1981
Maternal dates of birth from DHS 1998 (providing maternal cohort for index cases born between 1964 – 1996)	1949 - 1981	1949 - 1966	1949 - 1981
Maternal dates of birth from DHS 1991 (providing maternal cohort for index cases born between 1957 – 1991)	1942 - 1976	1942 - 1966	1942 - 1976

Supplementary Figure 3: Computation of median maternal age at first childbirth for Fako division (as an example)



Median time to first delivery from the various datasets	Effect Size with 95% CI	Weight (%)
DHS 2011	19.67 [19.08, 20.26]	42.67
DHS 2004	19.75 [18.93, 20.57]	22.01
DHS 1998	19.08 [18.31, 19.86]	24.68
DHS 1992	19.67 [18.48, 20.85]	10.64
Overall	19.54 [19.16, 19.93]	

Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00

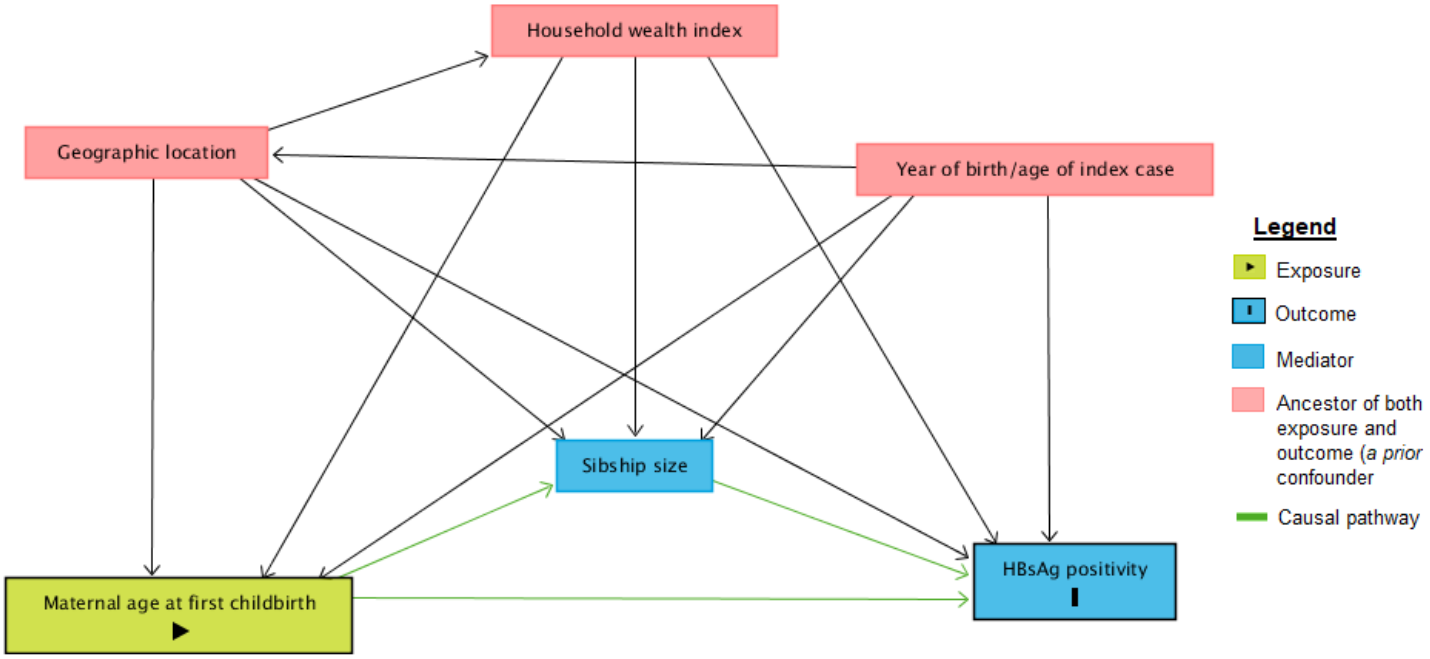
Test of $\theta_i = \theta_j$: Q(3) = 1.80, p = 0.62

Test of θ = 0: z = 99.26, p = 0.00

18 19 20 21

Random-effects ML model for Division of Fako

Supplementary Figure 4: Directed Acyclic Graph



[1] **Minimal set of adjustment for estimating the total effect (MTCT & early childhood transmission due to a large sibship size):** Geographic location, Household wealth index, Year of birth/age of index case

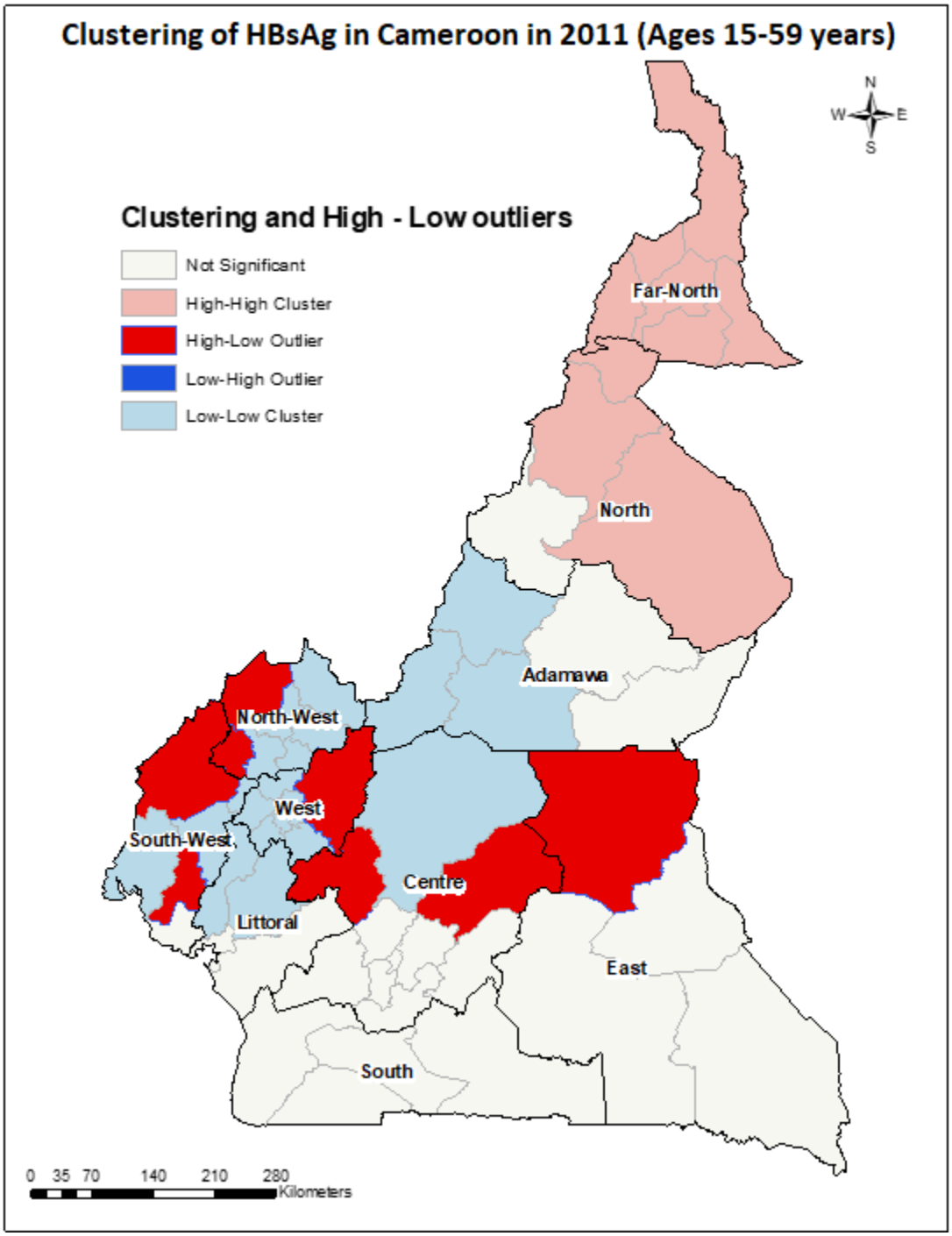
Minimal set of adjustment for estimating the direct effect (MTCT only): Geographic location, Household wealth index, Sibship size, Year of birth/age of index case**.** This blocks the pathway through sibship size (early childhood transmission due to a large sibship size).

In the analysis (scatter plots), all *a priori* confounders were shown to be associated with both the exposure and the outcome.

Effect modification: Possible effect modification of the association between maternal age at birth of the first child and chronic HBV infection by age/period of birth based on *a priori* knowledge.

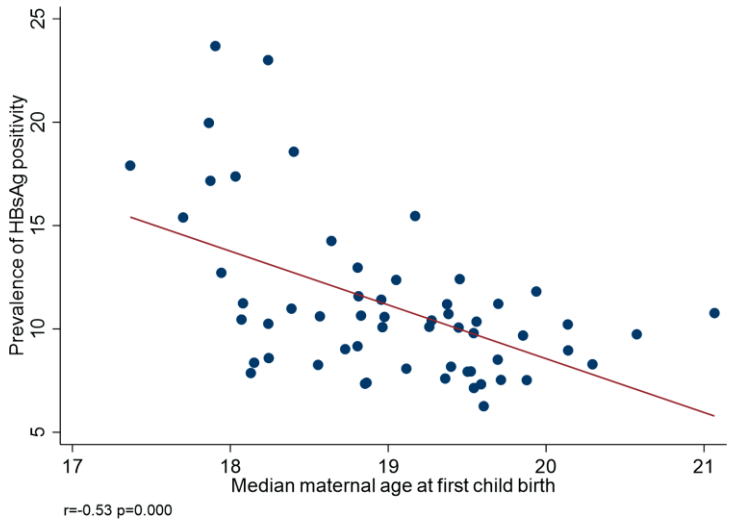
[1] Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology (Cambridge, Mass) 1999; 10(1): 37-48.

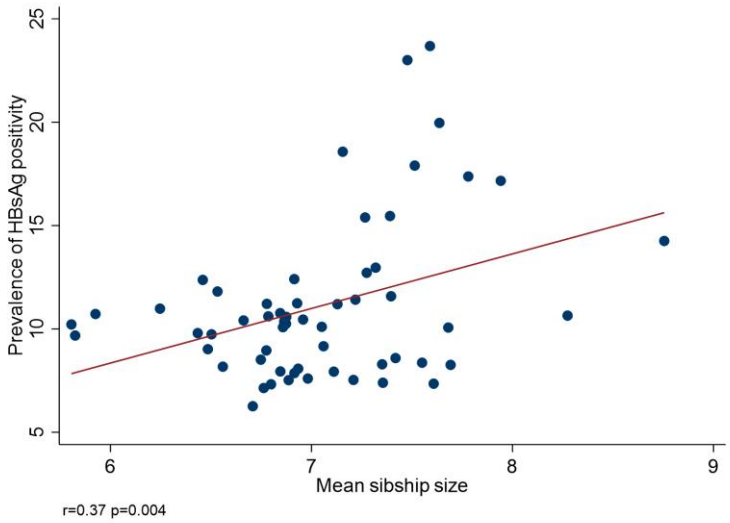
Supplementary Figure 5: Clusters and Spatial Outliers of HBsAg in Cameroon based on Local Moran's I values.

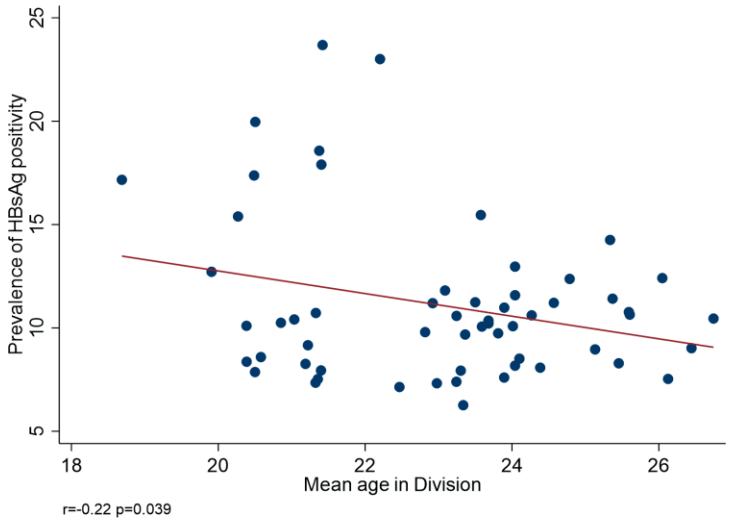


Global Moran's Index: 0.338, p-value: <0.001

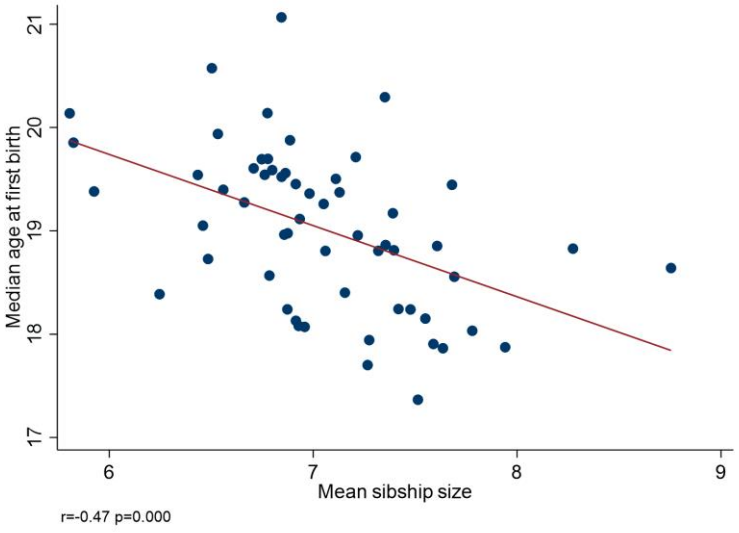
Supplementary Figure 6: Ecological correlations between the prevalence of HBsAg and the covariates at division level (N=58 divisions of Cameroon)

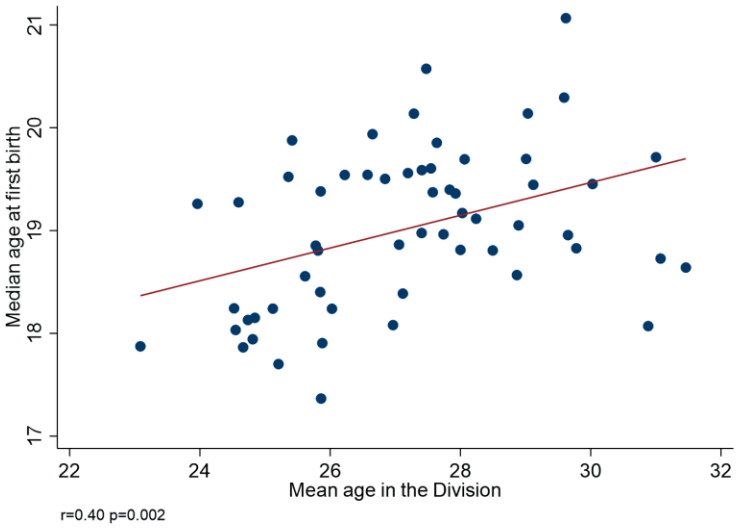




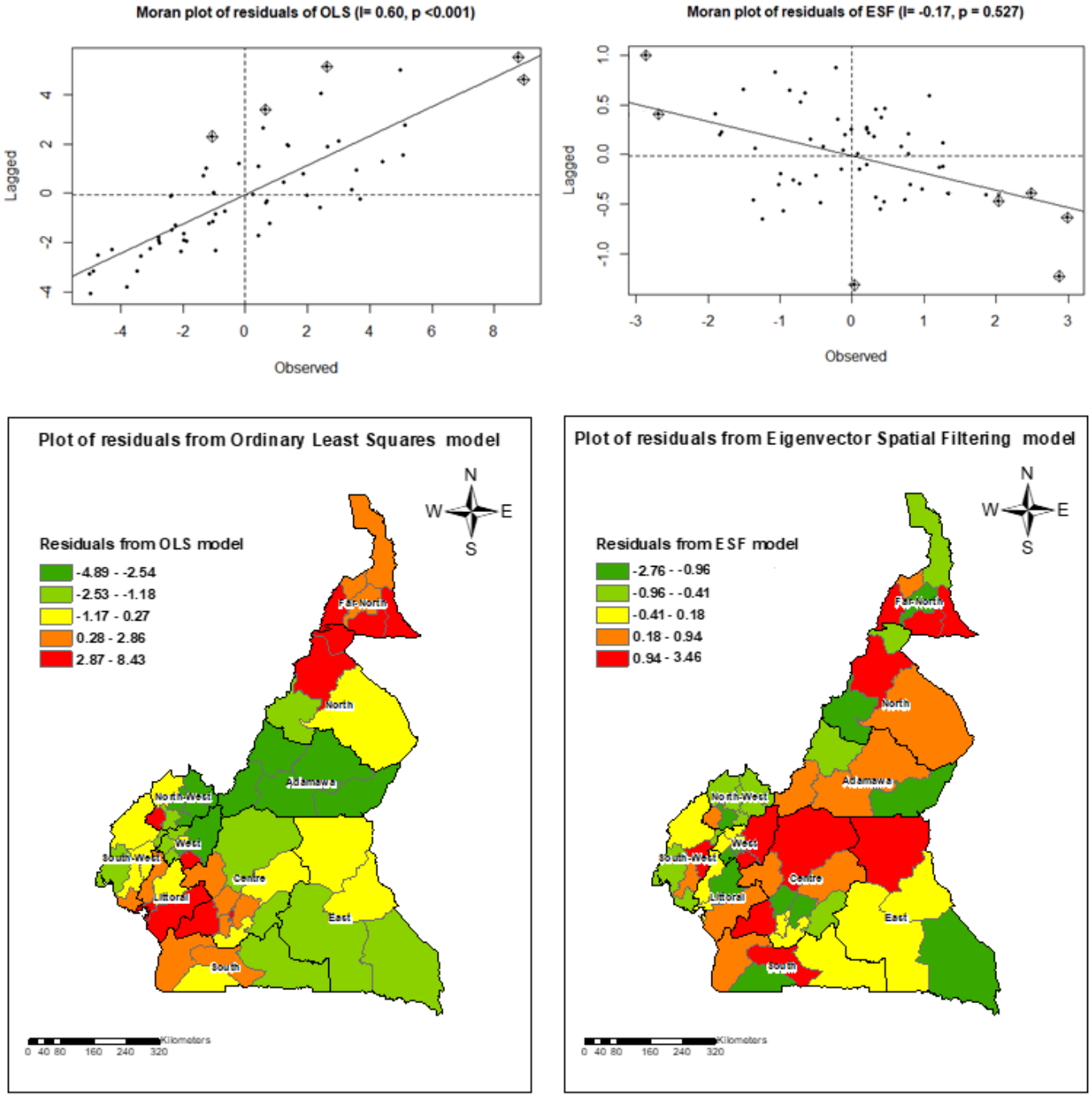


Supplementary Figure 7: Ecological correlations between the median maternal age at first childbirth and the other covariates at division level (N=58 divisions of Cameroon)





Supplementary Figure 8: Performance of the ESF model in adjusting for spatial autocorrelation



* Choropleths of the residuals from the models. There are aggregations of the residuals from the OLS model indicating spatial autocorrelation, while the residuals from the ESF model are randomly distributed implying minimal spatial autocorrelation in the ESF model.

OLS: Ordinary least squares; ESF: Eigenvector spatial filtering

Supplementary Figure 9: Scatter plot with linear model fitted showing interaction between the current age and the association between the division-level median maternal age at first childbirth and the division-level prevalence of HBsAg