Research article

Maternal hepatitis B status and Sex at birth: A cross-sectional study in a Ghanaian population

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A B S T R A C T

Maternal carrier status of hepatitis B has been associated with excess sons while maternal immunity to it has been associated with excess daughters at birth. However, the proportion of males at birth (sex ratio) is relatively low in Sub-Saharan Africa despite the relatively high prevalence of hepatitis B. However, no known study has tested this hypothesis in the Ghanaian population; hence the aim of the study. The study was cross-sectional between January and September 2023 at the Tamale Central Maternal and Child Health unit. The study involved 380 mothers of whom mothers with daughters (MD) were 145 (38.2 %) while the rest were mothers with sons (MS). The mothers were aged between 18 and 43 years and were sampled within one week of delivery to singleton births. Maternal venous blood samples were collected and tested for hepatitis B surface antigen (HBsAg), surface antibody (HBsAb), envelop antigen (HBeAg) envelope antibody (HBeAb) and core antibody (HBcAb) using immunochromatographic technique and total testosterone (TT), using ELISA. There was no significant difference in the serum total testosterone level between MD and MS (0.32 ± 0.13 vs 0.32 ± 0.27, P = 0.991). Moreover, while the mothers were seropositive for HBsAg (10.5 %), HBsAb (35.5 %), HBeAg (0.0 %), HBeAb (5.3 %) and HBcAb (11.8 %), there was no significant association between sex at birth and maternal hepatitis B status for HBsAg (χ^2: 0.531, P = 0.472), HBsAb (χ^2: 2.655, P = 0.140), HBeAb (χ^2: 0.251, P = 0.633) and HBcAb (χ^2: 0.101, P = 1.000). Maternal hepatitis B status may not be associated with the offspring sex at birth in the studied population from Ghana.

1. Introduction

The sex ratio can be defined as either the proportion of males (male/male + female) or the ratio of males to females (male/female)

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in a given population [1]. The primary sex ratio in mammals, per the Mendelian theory of random assortment, is 0.5 or 50 % since the Y- and X-bearing spermatozoa are produced in equal numbers and have equal chances of fertilizing the ovum. However, the secondary sex ratio is generally skewed towards males (>0.50) in many populations [2]. The sex ratio may be < 1.00 in Sub-Saharan Africa to as high as 1.24 in some Asian countries such as China and India [3,4]. The cause of the male-bias sex ratio is not well understood, however, socio-cultural, economic status, and exposure to toxicants and hormones among other factors have been suggested as possible determinants. Many theories, including the widely cited Trivers and Willard hypothesis (TWH), have attempted to proffer the proximate cause of the male-bias sex ratio. The TWH posits that mammalian females produce sons when in good condition as a guarantee for offspring in the following generation, especially in polygamous settings where a male offspring in good condition has a higher chance of mating with many females to produce many offspring [5]. However, previous attempts to validate the TWH in many mammalian and human populations failed. As a consequence, several other theories have been advanced including maternal stress, maternal blood glucose, maternal rank, cryptic female choice and the hormonal hypothesis [6,7].

Infectious diseases have also been associated with the offspring sex at birth. It has been suggested that maternal seropositivity for hepatitis B surface antigen can increase the sex ratio from 105 (1.05) to 150 (1.50) in some populations [8]. A previous study reported that parental seropositivity for hepatitis B surface antigen and negative for the surface antibody increased the sex ratio to about 250 (2.50) in Greece [8]. In an attempt to explain the pronounced male-bias sex ratio in China, Oster [9] conducted a cross-country analysis of data on the sex ratio and maternal hepatitis B status. The authors concluded that maternal hepatitis B status could account for about 75 % of the deficit in China's female population and about 20 % in South Asia. Similar previous micro-studies, in some European populations, have sought to confirm this conclusion [10,11]. It has been suggested that parental carriers of hepatitis B tend to produce excess sons while immune parents tend to produce excess daughters [10]. These observations have been attributed to the relatively high circulating testosterone levels in carriers of hepatitis B and low testosterone levels in persons immune to hepatitis B [12]. The mechanism may be explained by the hormonal hypothesis which suggests that high parental testosterone level at the time of conception is associated with excess sons at birth [13]. Recent studies have challenged the prevalent notion that the mammalian female reproductive tract merely serves as a passive conduit for fertilization [14,15]. Instead, it has been revealed that females can actively store, transport, and sort spermatozoa through various physical, biochemical, and genetic mechanisms facilitated by adaptations in the reproductive tract. This active involvement of females in sperm selection has been termed 'cryptic female choice' [15]. Moreover, the presence of spermatozoa in the oviduct triggers the upregulation of oviductal epithelia, leading to the expression of proteins that influence sperm motility, storage, and viability. Notably, testosterone levels in the intratubular environment play a significant role in sperm selection [16]. Studies in bovine and mice have demonstrated that elevated oviductal testosterone before ovulation can modify the zona pellucida of the developing oocyte, making it more selective for Y-bearing spermatozoa during fertilization, potentially biasing the sex ratio [16–18]. This observation lends support to the follicular testosterone hypothesis, which suggests that females can adjust their strategy of sex determination based on androgen levels during each menstrual cycle or estrus [16]. Another proposed mechanism is that maternal tolerance to the hepatitis B surface antigen may translate into tolerance for male embryos or male tissue and vice versa. It could also be that the hepatitis B virus tends to replicate faster in female conceptions than male leading to the selective loss of female foetuses [8,19].

However, a subsequent and larger demographic study found no significant association between maternal hepatitis B status and the sex ratio [8]. Another opinion was that paternal rather than maternal hepatitis B status, was the determinant of the offspring's sex at birth [11]. This too, was challenged by a similarly larger demographic study where maternal and/or paternal hepatitis B status were found not to be associated with the offspring sex at birth [20]. These disparities in findings could, however, stem from disparities in research methodology such as differences in sample size, data quality, errors in statistical analysis and the presence of confounding factors [8,21].

Previous studies have examined the sex ratio in Sub-Saharan Africa (SSA). A study involving 17 countries in Eastern and Southern Africa found that there were variabilities in the sex ratio between ethnicities with the Bantu population having a sex ratio as low as 0.989 [3]. A larger data from 56 surveys comprising over a million births from 29 SSA countries reported a sex ratio of 1.033 (95%CI: 1.029–1.037), which was lower than the world's average of 1.055 [22]. A similar demographic survey, covering 33 countries in SSA with over 2 million births, reported an average sex ratio of 1.034 [23]. Surprisingly, the sex ratio in SSA is relatively low despite the relatively high hepatitis B prevalence in the region [4]. The association between maternal hepatitis B status and the offspring sex at birth is still controversial since it is affected by many factors [24]. The true value of the study is to contribute data on the subject from Ghana which, hitherto, is lacking. Since previous findings indicate that solely mothers carrying HBsAg(+) exhibited a higher sex ratio compared to noncarriers, this implies that the mother's carrier status holds greater significance than the father's status in influencing the sex ratio of offspring [8]. In this study, maternal hepatitis B status was examined to determine its association with the offspring sex at birth.

2. Materials and methods

2.1. Study design and population

The study was cross-sectional between January and September 2023 at the Tamale Central Maternal and Child Health (MCH) unit. The MCH is a Ghana Health Service unit that offers antenatal and postnatal services to the public in the Tamale metropolitan area. The study involved 380 mothers of whom those with daughters were 145 (38.2 %) while the rest were mothers with sons. The mothers were aged between 18 and 43 years. All the women were conveniently recruited, within one week of delivery. Mothers who were registered at the clinic and were receiving postnatal services at the time of the study were included. The obstetric and clinical records of the

women were consulted to ensure that those who were enrolled were women who gave birth to only singleton babies and were devoid of any form of chronic diseases or conditions affecting the levels of circulating testosterone. The initial number of mothers who were enrolled was 391, however, seven (7) were found to have twins while 1 had triplets at birth. The other three (3) declined to consent to participate in the study. The study was conducted in a single city to avoid location-dependent variabilities. The mothers.

2.2. Sample size determination

A previous study has found the prevalence of hepatitis B virus surface antigen seropositivity (HBsAg+) among parturient women in peri-urban Ghana to be 10.2 % (20/196; 0.102) [25]. Using the Cochrane formula for cross-sectional studies, the minimum sample size was estimated to be 139.

$$n = \frac{Z2pq}{d}$$

Where:

n = minimun sample size.
Z = z-score at 95 % confidence interval (1.96)
p = prevalence (0.102)
q = 1-p
d = margin of error (0.05)

3. Data collection

3.1. Sociodemographic, obstetric and medical history

The sociodemographic and clinical data were collected using an interviewer-administered questionnaire. The maternal age, marital status, educational status, cultural and religious affiliations were documented. In addition, the offspring's birth order and sex were also collected. The medical history of chronic conditions and the hepatitis B vaccination status were documented.

3.2. Blood collection and analysis

A single venous blood sample was collected from the mothers between 8 a.m. and 12 p.m. each day as this period coincides with the highest circulating testosterone. The blood samples were dispensed into a gel-separator tube and then stored at 4°C to clot. The clotted samples were centrifuged at 3500×g for 10 min to obtain serum. The serum samples were aliquoted into Eppendorf tubes and then frozen at −20°C before analysis. Maternal serum level of testosterone was analyzed in duplicate using the AccuBind® Microplate ELISA test system (Monobind Inc., Lake Forest, CA 92630, USA). Testosterone levels were measured using a competitive enzyme immuno-assay (product code: 3725-300). The within-assay and between-assay coefficients of variation (CV) for testosterone were ≤5.6 % and ≤7.9 %, respectively, with a sensitivity of 0.0576 ng/mL (accuracy range: 0.29–21.9 ng/mL). The serum hepatitis B surface antigen (HBsAg), surface antibody (HBsAb), envelop antigen (HBeAg), envelop antibody (HBeAb) and core antibody (HBcAb) were determined using an immunochromatographic test kit (Wondfo Biotech, Guangzhou, China). All measurements were done following the manufacturers' instructions and using the recommended reagents. The serum samples were never thawed and refrozen before or during the analysis.

3.3. Data analysis

The data were first collected on a Microsoft Excel sheet before analysis in SPSS (v27) software (IBM Corp, Armonk, NY). The categorical variables were dummy-coded before analysis. Categorical variables were presented as frequency (per cent). Chi-square or Fisher's Exact tests were then used to determine the differences in the distribution of data between groups. Continuous variables were checked for normality using the Kolmogorov-Smirnov test since the sample size was above 50. The continuous variables were then summarized as mean ± standard deviation. The differences between groups were determined using the unpaired student *t*-test (2-tailed). All statistical analyses were considered significant at a *P*-value less than 0.050.

3.4. Ethical approval

The study complied with all guidelines regarding human subject studies as contained in the Declaration of Helsinki (1964) or its later amendments. The study was approved by the institutional review board of the University for Development Studies (UDS/RB/013/23). A written consent was obtained from all the women before they were enrolled into the study. The study was not compulsory and a participant could opt out at any stage of the study. The data were de-identified to ensure anonymity and treated with most confidentiality. The study was not limited by one's political, religious, cultural or other affiliations.

4. Results

4.1. Sociodemographic characteristics

Table 1 summarizes the sociodemographic characteristics of the study population. The vast majority of mothers were married, comprising 97.4 % of the total participants, while single or cohabiting mothers accounted for 1.5 % each. However, there was no significant difference in marital status between mothers with sons and those with daughters ($\chi2 = 2.241$, P = 0.326). In terms of cultural identity, the majority identified as Mole-Dagomba (90.8 %), with the Akan representing the minority at 1.5 %. This distribution was primarily due to the Mole-Dagomba being indigenous to the study area, but it did not substantially affect the distribution of mothers by cultural affiliation ($\chi2 = 2.823$, P = 0.244). Similarly, the majority of mothers identified as Muslim (96.1 %), reflecting Islam's dominance in the region. Nonetheless, both mothers with sons and daughters were proportionately represented across religious affiliations ($\chi2 = 1.076$, P = 0.556). Regarding education, most mothers had attained secondary-level education (28.9 %), and a majority were self-employed (61.8 %). However, there were no significant differences in the distribution of mothers by educational status ($\chi2 = 3.176$, P = 0.365) or occupation ($\chi2 = 2.700$, P = 0.259). Additionally, only 21.1 % of mothers had received prior hepatitis B vaccination, with the majority being unvaccinated (78.9 %). Nonetheless, there were no significant disparities in vaccination status ($\chi2 = 0.004$, P = 1.000).

4.2. Maternal age, circulating total testosterone and birth order

Table 2 compares the mean and standard deviation of maternal age (in years), total testosterone levels, and offspring birth order between mothers with daughters and those with sons. The maternal age mean ± standard deviation was similar among mothers with daughters and those with sons (29.1 ± 6.0 vs. 29.2 ± 5.3; P = 0.913). Additionally, there was no significant difference in serum testosterone levels between mothers with daughters and those with sons (0.32 ± 0.13 vs. 0.32 ± 0.27; P = 0.991). Furthermore, the birth order of offspring was comparable between mothers of female and male offspring (2.5 ± 1.2 vs. 2.7 ± 1.5; P = 0.420). These comparisons all exhibited negligible effect sizes (Hedge's g < 0.20).

4.3. Maternal hepatitis B status, testosterone level and offspring's sex at birth

Table 3 presents the relationship between maternal seropositivity for hepatitis B antigens and antibodies and the sex of the offspring at birth. The majority of mothers tested seronegative for the hepatitis B surface antigen (340 out of 380; 89.5 %), with 125 of them having daughters and 215 having sons. Seropositivity for the hepatitis B surface antigen was observed in only 40 mothers, comprising 10.5 % of the total, with an equal distribution of 20 among mothers with daughters and those with sons. However, no significant association was found between hepatitis B surface antigen status and the sex of the offspring at birth ($\chi2 = 0.531$; P =

Table 1
Maternal sociodemographic characteristics stratified by the offspring sex at birth.

Characteristic	Mothers	Live-births Daughters	Sons	χ2, df	P-value
Marital status				2.241, 2	0.326
Married	370(97.4)	140(96.6)	230(97.9)		
Co-habitation	5(1.3)	0(0.0)	5(2.1)		
Single	5(1.3)	5(3.4)	0(0.0)		
Cultural affiliation				2.823, 2	0.244
Mole-Dagomba	345(90.8)	135(93.1)	210(89.4)		
Akan	5(1.3)	5(3.4)	0(0.0)		
Others	30(7.9)	5(3.4)	25(10.6)		
Religious affiliation				1.076, 1	0.556
Islam	365(96.1)	135(93.1)	230(97.9)		
Christianity	15(3.9)	10(6.9)	5(2.1)		
Educational status				3.176, 3	0.365
None	85(22.4)	30(20.7)	55(23.4)		
Basic	95(25.0)	45(31.0)	50(21.3)		
Secondary	110(28.9)	50(34.5)	60(25.5)		
Tertiary	90(23.7)	20(13.8)	70(29.8)		
Occupation				2.700, 2	0.259
Unemployed	60(15.8)	35(24.1)	25(10.6)		
Self-employed	235(61.8)	85(58.6)	150(63.8)		
Salary work	85(22.4)	25(17.2)	60(25.5)		
Vaccination status				0.004, 1	1.000
No	300(78.9)	115(79.3)	185(78.7)		
Yes	80(21.1)	30(20.7)	50(21.3)		

The results are presented as frequency (per cent). Chi-square or Fisher's Exact tests were performed to determine differences in the distribution of the data between the columns.

Table 2
Comparing maternal age, total testosterone and birth order stratified by the offspring's sex at birth.

Variable	Mothers	Sons	t	P-value	Hedge's g
	Daughters				
Age (years)	29.1 ± 6.0	29.2 ± 5.3	−0.109	0.913	−0.03
TT (pg/mL)	0.32 ± 0.13	0.32 ± 0.27	0.001	0.991	0.00
Birth order	2.5 ± 1.2	2.7 ± 1.5	−0.812	0.420	−0.190

The results are presented as mean ± SD. The differences in the distribution of data between the groups were determined using the unpaired student t-test (2-tailed). The effect size between means is reported in Hedge's g: similar ($g < 0.20$), small ($0.20 \leq g < 0.50$), moderate ($0.50 \leq g < 0.80$), large ($g \geq 0.80$). TT: total testosterone.

Table 3
The association between the maternal hepatitis B status and the offspring's sex at birth.

HBV Test	Mothers	Live-births	Sons	$\chi2$, df	P-value
		Daughters			
HBsAg				0.531, 1	0.472
Negative	340(89.5)	125(86.2)	215(91.5)		
Positive	40(10.5)	20(13.8)	20(8.5)		
HBsAb				2.655, 1	0.140
Negative	245(64.5)	110(75.9)	135(57.4)		
Positive	135(35.5)	35(24.1)	100(42.6)		
HBeAg					
Negative	380 (100)	145(100)	235(100)		
Positive	0(0.0)	0(0.0)	0(0.0)		
HBeAb				0.251, 1	0.633
Negative	360(94.7)	135(93.1)	225(95.7)		
Positive	20(5.3)	10(6.9)	10(4.3)		
HBcAb				0.101, 1	1.000
Negative	335(88.2)	130(89.7)	205(87.2)		
Positive	45(11.8)	15(10.3)	30(12.8)		

The results are presented as frequency (per cent). Chi-square or Fisher's Exact tests were performed to determine differences in the distribution of the data between the columns.

0.472). Regarding hepatitis B surface antibody, 135 mothers (35.5 %) tested positive, while the rest tested negative. Although more mothers with sons tested positive for hepatitis B surface antibody compared to mothers with daughters (100 vs. 35), this difference did not reach statistical significance (P = 0.140). Similarly, only a minority of women tested positive for hepatitis B envelope antibody (5.3 %) and hepatitis B core antibody (11.8 %), with no notable disparity between mothers with daughters and those with sons (P = 0.633 and P = 1.000, respectively). Conversely, none of the mothers tested positive for hepatitis B envelope antigen. Table 4 presents the maternal serum testosterone level, stratified by their hepatitis B status. No significant differences were found between seropositive mothers and those who were seronegative either for the hepatitis B antigen or antibody.

5. Discussion

The study sought to determine whether maternal hepatitis B status is associated with the offspring's sex at birth. It was observed that there were no significant associations between maternal hepatitis B status and the offspring sex at birth. This was independent of maternal age, sociodemographic characteristics and their offspring's birth order.

The observed lack of association between the offspring sex at birth and maternal hepatitis B status is consistent with previous

Table 4
Serum testosterone level stratified by hepatitis B antigen or antibody seropositivity.

Variable	HBV status	Positive	t	P-value	Hedge's g
	Negative				
HBsAg	0.32 ± 0.23	0.28 ± 0.20	0.488	0.627	0.18
HBsAb	0.33 ± 0.25	0.30 ± 0.17	0.575	0.567	0.14
HBeAg*	0.32 ± 0.23	–			
HBeAb	0.32 ± 0.23	0.28 ± 0.10	0.310	0.757	0.16
HBcAb	0.32 ± 0.23	0.29 ± 0.18	0.370	0.710	0.13

Results are summarized as mean ± standard deviation. The differences in the distribution of data between the groups were determined using the unpaired student t-test (2-tailed). The effect size between means is reported in Hedge's g: similar ($g < 0.20$), small ($0.20 \leq g < 0.50$), moderate ($0.50 \leq g < 0.80$), large ($g \geq 0.80$). *All the samples tested negative.

studies [4,8,20]. Sub-Saharan Africa, including Ghana, is known to have low sex ratio despite the relative high hepatitis B prevalence. The low sex ratio in SSA, may be due to the observation that women of Black-African ancestry, regardless of location, tend to give birth to more girls than boys [26]. Higher fertility rates in these populations may account for the low sex ratio. The more a woman gives birth, the less likely she will give birth to a boy. Another explanation may be that increasing paternal age is associated with a low sex ratio. Older men are more likely to produce children in populations in SSA than other populations [26]. In addition, low caloric intake is associated with female sex at birth, which may be the case in SSA as caloric intake may be relatively low compared to other countries or regions of the world [26].

The consensus is that maternal hepatitis B status cannot explain the male-bias sex ratio in many populations [20]. This conclusion is, however, at variance with findings from previous studies [9,11,12]. One possible explanation is that there are significant differences in the number of samples used in the studies. Most of the previous studies that found a positive association between sex ratio and hepatitis B infection involved a few hundred or thousand samples [4]. In addition, poor data quality, errors in statistical analysis and confounding factors in previous studies have been suggested as possible sources of disparity in their findings [8,21]. Some authors, however, argued, from evidence adduced from their studies that paternal rather than maternal hepatitis B status may be responsible for the male-bias sex ratio [11,27]. However, in a cohort of about 67,000 individuals where the relationship between both paternal and maternal hepatitis B status and the sex ratio was examined, the effect of hepatitis B status on the sex at birth was close to zero with small standard errors. Moreover, the findings were independent of age, township and offspring's birth order [20].

It has been observed from demographic data, that women who previously gave birth to a girl were more likely to give birth to a boy [4]. For the argument of Oster [9] to be true, then women who had given birth to a girl will be more prone to contracting hepatitis B or that hepatitis B infection in women will first lead to the birth of a girl and then followed by the birth of a boy [4]. This cannot, however, be true since the impact of hepatitis B infection on sex order is fairly constant across birth order. Thus, the impact of HBV on the sex ratio is not affected by the sex composition of previous births [4]. A probable explanation for the high sex ratio in Asian countries at the time when Oster, Chen [20] made their observation may be due to social discrimination against girls where parents preferred boys to girls and thus adjusted the sex composition of the children by any means possible. It was observed that girls with no older sisters had an equal chance as boys to survive, however, girls were likely to be aborted or die early in families that already had a daughter [4,28]. Moreover, the sex at birth or sex ratio can be affected by many factors including exposure to toxicants or hormones, malnutrition of the mother, ethnicity and socioeconomic factors [8]. For example, women of low-income status will have a strong preference for a son, however, such a woman is likely to have a higher risk of hepatitis B infection due to her exposure to an unclean environment. In such instances, the impact of hepatitis B status on offspring's sex at birth will be overly estimated [8].

The current study is significant in many ways; the true value of the current study is that the data presented here are probably the first to come from Ghana. In addition, most previous studies relied on only the maternal seropositivity of HBsAg. In the current study, in addition to HBsAg, the maternal status of HBsAb, HBeAg, HBeAb and HBcAb were also determined. HBeAg is a fragment of the viral capsid protein. The hepatitis B envelop antigen may be a more potent determinant of the sex ratio than the surface antigen given its smaller size and ability to cross the placental barrier [8]. The envelop antigen is also associated with a phase of the disease where the viral load is high due to the rapid replication of the virus while the surface antigen is only a mark of a chronic carrier status [29,30]. The mechanism may be that high viral load may affect the viability of female foetus than male [8]. Moreover, confounding factors such as maternal age, location or city and birth order did not markedly affect the results as these variables did not differ significantly between mothers with sons and those with daughters. The determination of both hepatitis B antigens and antibodies satisfies the suggestion that carriers of hepatitis B produce excess sons while immune persons produce excess daughters [12]. Both observations were tested in this study by testing for the hepatitis B antigen and antibodies. The study may, however, be limited by not using molecular techniques to detect occult hepatitis B in the mothers. In addition, mothers who were vaccinated against hepatitis B were included in the study. While this could be a limitation, those mothers were included to investigate the association between maternal hepatitis B antibody seropositivity and the offspring's sex at birth. Moreover, employing a random or simple stratified sampling technique could have reduced potential bias and confounders in the study. Measures should be taken to address all these potential limitations in future studies.

6. Conclusion

There was no significant association between offspring sex at birth and the maternal seropositivity for hepatitis B surface antigen, surface antibody, envelop antigen, envelop antibody and the core antibody. It appears maternal hepatitis B status is not associated with the offspring sex at birth in the studied population.

Data availability statement

The data supporting these findings can be obtained from the corresponding author upon a reasonable request.

CRediT authorship contribution statement

Moses Banyeh: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Moses Kofi Woli:** Writing – review & editing. **Benjamin N. Mayeem:** Writing – review & editing, Writing – original draft, Validation, Formal analysis. **Augusta S. Kolekang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis. **Ruth Nimota Nukpezah:** Writing – review & editing. **Nadia Habib:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Emmanuel Ansah Owusu:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Muniru Mohammed Tanko:** Writing – review & editing. **Clement Binwatin Dagungong:** Writing – review & editing, Writing – original draft, Validation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31566.

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