Title

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David J. Cote, Rong Wang, Libby M. Morimoto, Catherine Metayer, Jessica Stempel, Gabriel Zada[®], Xiaomei Ma[†], and Joseph L. Wiemels[†]

Department of Neurosurgery, Keck School of Medicine of the University of Southern California, Los Angeles, California, USA (D.J.C., G.Z.); Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut, USA (R.W., X.M.); Department of Epidemiology, School of Public Health, University of California, Berkeley, California, USA (L.M.M., C.M.); Center for Genetic Epidemiology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA (D.J.C., J.L.W.); Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA (J.S.)

Corresponding Author: David J. Cote, MD, PhD, Department of Neurosurgery, Keck School of Medicine, University of Southern California, 1200 N State Street, Suite 3300, Los Angeles, CA 90033, USA (david.cote@med.usc.edu).

[†]These authors contributed equally to this work.

Abstract

Background. We evaluated the potential role of birth characteristics in the etiology of early-onset meningioma.

Methods. Leveraging a population-based linkage of California birth records (from 1978 to 2015) and cancer registry data (from 1988 to 2015), we identified 362 nonmalignant meningioma cases aged 0–37 years and selected 18 100 controls matched on year of birth. Cases and controls were compared with regard to birth characteristics, with adjusted odds ratios (ORs) and 95% confidence intervals (CIs) estimated from unconditional multivariable logistic regression models. We also conducted stratified analyses by race/ethnicity and age.

Results. Female sex (compared to male: OR = 1.43, 95% CI: 1.16 to 1.79; *P* < .01) and Black race (compared to White: OR = 1.46, 95% CI: 1.02 to 2.07; *P* = .04) were associated with higher risk of meningioma. Higher birth order (OR = 0.90, 95% CI: 0.81 to 0.99 per additional birth position; *P* = .04) was associated with a lower risk. No significant associations were observed between birthweight, gestational age, delivery mode, maternal age, or maternal education and meningioma risk. In the non-Latino White subgroup, higher birthweight was associated with a higher risk of meningioma (OR = 1.20, 95% CI: 1.02 to 1.41 per 500 grams; *P* = .03), but this was not recapitulated in the Latino subgroup. In age-stratified analyses, female sex was a risk factor for those diagnosed at the age of 20–37 years but not among younger individuals.

Conclusions. In this large population-based study less prone to selection and recall bias, higher birth order was associated with a reduced risk of early-onset meningioma, while female sex and Black race were linked to an increased risk. There were also indications of differential associations by race/ethnicity and age of diagnosis.

Key Points

- The association between early-life exposures and risk of nonmalignant meningioma has not been explored.
- Higher birth order was associated with a lower risk of meningioma.
- Higher birth weight was associated with a higher risk of meningioma among non-Latino participants.

Importance of the Study

Identification of risk factors for brain tumors has the potential to improve risk stratification and elucidate underlying mechanisms of pathogenesis. The association between early-life exposures and risk of meningioma has not been explored in prior studies. Here, we used a population-based data source less subject to selection and recall bias to examine associations between birth characteristics and risk of meningioma. We demonstrated inverse associations between birth order and meningioma risk. In stratified analyses, we also demonstrated positive associations between birthweight and meningioma risk among non-Latino White patients.

Meningioma is the most commonly diagnosed intracranial tumor, accounting for approximately one-third of all primary brain and central nervous system tumors.[1–3] Although most often histologically benign, they can cause substantial morbidity due to their location adjacent to important neurovascular structures.[4] In general, the incidence of meningioma increases with age, but diagnosis during young adulthood remains relatively common, particularly among women.[2]

The epidemiology of meningioma has been investigated in a variety of prospective and retrospective cohort and case-control studies, with convincing evidence for inherited susceptibility as well as for some environmental and behavioral risk factors, such as ionizing radiation.[5] Women have been consistently shown to be approximately twice at risk developing of meningioma as men across the lifespan, suggesting the possibility that sex hormones may also play a role in pathogenesis.[6]

To date, few studies have examined early-life exposures, such as birth characteristics or parental sociodemographic features, and risk of meningioma. Early-life exposures are of interest, given that they have been indicated in the etiology of other tumors, such as pituitary tumors, sarcoma, and lymphoma.[7–9] There has also been strong evidence for the developmental origin of breast cancer and other hormone-related cancers, suggesting that they begin in utero.[10] Using the California Linkage Study of Early-onset Cancers (CALSEC), which links California statewide birth records with all cancer diagnoses reported to the statewide cancer registry, we examined potential associations between birth characteristics and risk of early-onset, nonmalignant meningioma.

Methods

Data Source

Detailed methods related to CALSEC data collection have been published elsewhere.[8,11,12] In brief, statewide information on cancer diagnosis from 1988 to 2015 from the California Cancer Registry (CCR) were linked to California birth records maintained by the Vital Statistics Advisory Committee of the California Department of Public Health from 1978 to 2015. Reporting of birth and cancer diagnosis are both mandated by law, and are considered complete at the population level. Beginning in 2001, the CCR records incidence of nonmalignant tumors. From CALSEC, we identified cases who were born during 1978–2015 and diagnosed with first primary and incident meningioma during 1988–2015, at the age of 0–37 years, as well as 50 times as many controls who were frequency matched to cases on year of birth. For all participants, we extracted data on gestational age, birth weight, mode of delivery, birth plurality, and birth order. Parental sociodemographic information was also extracted, including parental race and ethnicity, maternal age at delivery, maternal education, and maternal nativity. The study protocol was approved by the Institutional Review Boards at the California Health and Human Services Agency, University of California, Berkeley (Berkeley, CA), and Yale University (New Haven, CT).

Outcomes

Diagnoses of nonmalignant brain tumors were recorded in CCR beginning in 2001. All patients diagnosed with nonmalignant meningioma in the CCR were included as cases according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), codes, using site "Any" and codes 9530/0,1, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0, 9538/0, 9539/1. These ICD-O-3 codes specify nonmalignant meningioma of various types, including fibrous, angiomatous, psammomatous, and others. We excluded patients who had diagnoses of other benign or malignant tumors prior to the diagnosis of meningioma, out of concern that treatment for previous tumors might lead to a higher risk of second tumors. We identified a total of 362 cases who were born during 1978–2015 and diagnosed with meningioma during 2001–2015, to which 18 100 controls were matched on the birth year with a 50:1 ratio. The controls were randomly selected from statewide birth records, and none of the controls had been diagnosed with any cancer per CCR record at the time of linkage.

Statistical Analysis

Case and control characteristics were presented with frequencies and percentages, and Pearson's χ^2 test were used to compare groups. We computed odds ratio (OR) estimates and 95% confidence intervals (CIs) using unconditional multivariable logistic regression models that adjusted for year of birth (ie, the matching variable). Such models provide valid and more efficient estimates of risk than conditional models in matched case-control studies.[13] The multivariable models additionally included sex at birth, maternal race/ethnicity (Latino/Hispanic, non-Latino White, non-Latino Black, non-Latino Asian/Pacific Islander, and

other), birthweight (grams), gestational age (weeks), birth plurality (singleton vs multiple), birth order (first, second, third or higher), mode of delivery (Cesarean vs vaginal), maternal age (years), maternal education (years), and maternal nativity (US vs other). Race/ethnicity stratification used in this study reflects the categorization allowed by the categories used by the federal Office of Management and Budget data collection available from the period of the study.[14] Additional models were constructed stratified by ethnicity (non-Latino White vs Latino) and age (≤19, 20–37 years). All analyses were performed using SAS (version 9.4, SAS Institute). All tests were two-sided, and the threshold for statistical significance was 0.05.

Results

In our study population, the largest subgroup by race/ethnicity were non-Latino White individuals (43%), followed by Latinos (35%). Cases were more likely than controls to be female and less likely to have foreign-born mothers (Table 1).

Based on results from a multivariable logistic regression model, female sex (compared to male: OR = 1.43, 95% CI: 1.16 to 1.79; $P < .01$) and Black race (compared to White: OR = 1.46, 95% CI: 1.02 to 2.07; $P = .04$) were associated with a higher risk of meningioma. Higher birth order (OR = 0.90, 95% CI: 0.81 to 0.99 per additional birth position; $P = .04$) was associated with lower meningioma risk. No significant associations were observed between birthweight, gestational age, mode of delivery, maternal age, or maternal education and risk of meningioma (Figure 1). A nonsignificant inverse association was observed between multiplicity and meningioma risk (OR = 0.38, 95% CI: 0.12 to 1.20, $P = .10$ comparing multiple births to singletons).

When stratified by race/ethnicity (Supplementary Tables 1 and 2), power was significantly reduced. Among non-Latino White participants, there were 157 cases. Higher birthweight was associated with a higher risk of meningioma (OR = 1.20, 95% CI: 1.02 to 1.41 per 500 grams; $P = .03$), as was low maternal education (OR = 5.15, 95% CI: 1.29 to 20.45; $P = .02$). These observations were not recapitulated in the subgroup of 128 Latino cases and 6400 Latino controls, but the statistical comparison was limited by small numbers in the Latino subgroup.

Stratified analyses by age at meningioma diagnosis (≤19 vs ≥20 years, Supplementary Tables 3 and 4) demonstrated that female sex was not a risk factor for pediatric meningioma (OR = 1.05, 95% CI: 0.68 to 1.66; $P = .81$). The observed disparity comparing Black to non-Latino White race was smaller and not statistically significant among those who are aged ≤ 19 years (OR = 0.97, 95% CI: 0.41 to 2.27, $P = .94$), but remained statistically significant among those who are ≥ 20 years (OR = 1.62, 95% CI: 1.10 to 2.39, $P = .04$).

Discussion

This study examines potential associations between birth characteristics, parental sociodemographic features, and risk of early-onset meningioma, the most common primary intracranial tumor. Using population-based data that are less prone to selection or recall bias, we identified an inverse association between birth order and risk of meningioma, and a positive association between Black race and meningioma. Among non-Latino White individuals, higher birthweight was also associated with a higher risk of meningioma. Stratification by age in this relatively young cohort of patients with meningioma further demonstrated that disparities in incidence by sex and race were not present in those who are aged ≤ 19 years.

Prior work examining risk factors for meningioma has similarly identified disparities in incidence by race/ethnicity, with higher incidence among Black individuals compared to those of other racial and ethnic backgrounds.[3] High-dose radiation and radiation from dental X-rays have both been established as risk factors, as well as higher body mass index and a variety of familial cancer syndromes, such as neurofibromatosis type 2.[5,6,15] Additionally, atopic diseases such as allergies, asthma, and eczema may play a protective role, perhaps through heightened immune surveillance.[16–18] Although investigated extensively, head injury, alcohol use, and cell phone exposure are likely not risk factors for meningioma based on the current literature.[6] It is important to note that most previous studies included predominantly older patients. Our study is the first that focused on early-onset meningioma.

Despite restriction to early-onset meningioma (ie, those diagnosed at 0–37 years), we nevertheless demonstrated similar disparities in incidence by race as those reported elsewhere in the literature. Specifically, risk of early-onset meningioma was about 50% higher in Black compared to non-Latino White individuals, driven solely by differential risk in those older than 20 years, though tests for statistical interaction were limited by small subgroups. Therefore, if driven primarily by differential access to care or neuroimaging, our data suggest that these differences are not present during childhood, given the lack of differences by race among those who are younger than 20 years. If driven by exposure to an as-yet unidentified risk factor, these data suggest that such a risk factor would have an effect solely among young adults and older, which may inform future studies. Similarly, our study is in line with others that describe the disparity in meningioma incidence by sex as a post-pubertal phenomenon, with no significant difference in incidence by sex for those younger than 20 years, but 30% lower risk among men compared to women in those aged 20 years or older.

Novel findings of the current study include a 10% reduced risk of meningioma for each additional increase in birth order, meaning that compared to firstborns, later-born children were at a lower risk of early-onset meningioma. Although not specified as an a *priori* hypothesis given the exploratory nature of this analysis, similar findings have been identified for early-onset synovial sarcoma,[8] early-onset non-Hodgkin lymphoma,[9] and pediatric thyroid cancer.[11] In general, birth order is not thought to be a causal risk factor for tumor development, but rather a proxy for other factors that may influence tumorigenesis. Compared to first-borns, later-born children have a higher degree of nutrition while in utero due to more efficient placentation.[19] As a result of this overall in utero nutritional restriction, first-born children tend to have reduced insulin

Table 1. Characteristics of Meningioma Cases and Controls in the California Linkage Study of Early-Onset Cancers

		Case (n = 362)		Control (n = 18 100)		P
		n	%	n	%	
Age at diagnosis (years)	0–4	7	1.9			
	5–9	8	2.2			
	10–14	19	5.2			
	15–19	48	13.3			
	20–24	87	24.0			
	25–29	98	27.1			
	30–34	79	21.8			
	35–36	16	4.4			
Sex	Female	207	57.2	8870	49.0	<.01
	Male	155	42.8	9230	51.0	
Race/ethnicity	Non-Latino White	157	43.4	7772	42.9	.08
	Non-Latino Black	44	12.2	1588	8.8	
	Latino	128	35.4	6834	37.8	
	Non-Latino Asian	24	6.6	1596	8.8	
	Other	9	2.5	310	1.7	
Birthweight (grams)	250–2499	22	6.1	1063	5.9	.65
	2500–2999	49	13.5	2724	15.0	
	3000–3499	132	36.5	6940	38.3	
	3500–3999	110	30.4	5314	29.4	
	4000+	49	13.5	2059	11.4	
Gestational age (weeks)	22–36	33	9.1	1564	8.6	.91
	37–41	253	69.9	12 825	70.9	
	42–44	41	11.3	1975	10.9	
	Unknown	35	9.7	1736	9.6	
Birth plurality	Singleton	359	99.2	17 713	97.9	.09
	Multiple	3	0.8	387	2.1	
Birth order	1st	165	45.6	7605	42.0	.39
	2nd	109	30.1	5729	31.7	
	3rd and higher	88	24.3	4766	26.3	
Mode of delivery	Vaginal	279	77.1	14 472	80.0	.18
	C-section	83	22.9	3628	20.0	
Year of birth	1978–1982	138	38.1	6900	38.1	1.00
	1983–1987	103	28.5	5150	28.5	
	1988–1992	60	16.6	3000	16.6	
	1993–2013	61	16.9	3050	16.9	
Maternal age (years)	<20	46	12.7	2240	12.4	.57
	20–24	104	28.7	5322	29.4	
	25–29	115	31.8	5359	29.6	
	30–34	60	16.6	3552	19.6	
	>=35	37	10.2	1627	9.0	
Maternal education	Up to 8 years	14	3.9	954	5.3	.68
	9–11 years	22	6.1	1178	6.5	
	12 years	44	12.2	2035	11.2	
	13–15 years	27	7.5	1315	7.3	
	16 or more years	25	6.9	1067	5.9	
	Unknown	230	63.5	11 551	63.8	
Mother's place of birth	US	259	71.5	11 764	65.0	<.01
	Foreign	103	28.5	6336	35.0	

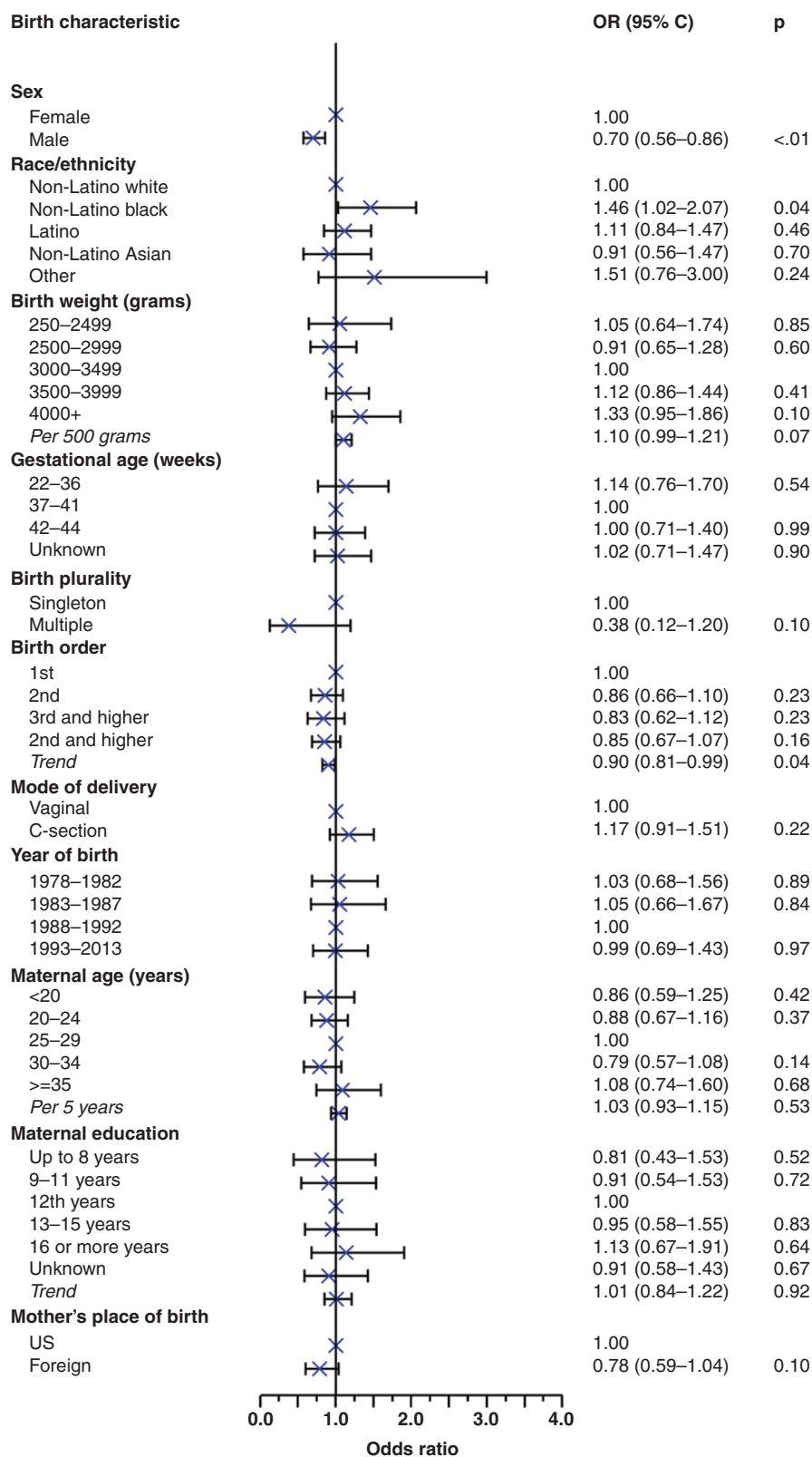| Birth characteristic	OR (95% C)	p
Sex		
Female	1.00	
Male	0.70 (0.56–0.86)	<.01
Race/ethnicity		
Non-Latino white	1.00	
Non-Latino black	1.46 (1.02–2.07)	0.04
Latino	1.11 (0.84–1.47)	0.46
Non-Latino Asian	0.91 (0.56–1.47)	0.70
Other	1.51 (0.76–3.00)	0.24
Birth weight (grams)		
250–2499	1.05 (0.64–1.74)	0.85
2500–2999	0.91 (0.65–1.28)	0.60
3000–3499	1.00	
3500–3999	1.12 (0.86–1.44)	0.41
4000+	1.33 (0.95–1.86)	0.10
Per 500 grams	1.10 (0.99–1.21)	0.07
Gestational age (weeks)		
22–36	1.14 (0.76–1.70)	0.54
37–41	1.00	
42–44	1.00 (0.71–1.40)	0.99
Unknown	1.02 (0.71–1.47)	0.90
Birth plurality		
Singleton	1.00	
Multiple	0.38 (0.12–1.20)	0.10
Birth order		
1st	1.00	
2nd	0.86 (0.66–1.10)	0.23
3rd and higher	0.83 (0.62–1.12)	0.23
2nd and higher	0.85 (0.67–1.07)	0.16
Trend	0.90 (0.81–0.99)	0.04
Mode of delivery		
Vaginal	1.00	
C-section	1.17 (0.91–1.51)	0.22
Year of birth		
1978–1982	1.03 (0.68–1.56)	0.89
1983–1987	1.05 (0.66–1.67)	0.84
1988–1992	1.00	
1993–2013	0.99 (0.69–1.43)	0.97
Maternal age (years)		
<20	0.86 (0.59–1.25)	0.42
20–24	0.88 (0.67–1.16)	0.37
25–29	1.00	
30–34	0.79 (0.57–1.08)	0.14
>=35	1.08 (0.74–1.60)	0.68
Per 5 years	1.03 (0.93–1.15)	0.53
Maternal education		
Up to 8 years	0.81 (0.43–1.53)	0.52
9–11 years	0.91 (0.54–1.53)	0.72
12th years	1.00	
13–15 years	0.95 (0.58–1.55)	0.83
16 or more years	1.13 (0.67–1.91)	0.64
Unknown	0.91 (0.58–1.43)	0.67
Trend	1.01 (0.84–1.22)	0.92
Mother's place of birth		
US	1.00	
Foreign	0.78 (0.59–1.04)	0.10

Figure 1. Forest plot demonstrating the odds ratios resulting from a multivariable logistic regression model examining the association between various birth characteristics and incidence of meningioma. All variables were included as categorical variables in the model for mutual adjustment, with *P*-trends calculated to assess semicontinuous associations between characteristics and meningioma incidence.

sensitivity at birth and greater concentrations of IGF-1, which may play a role in tumorigenesis.[20] Firstborns are also taller on average, which itself may be a risk marker for meningioma, possibly through a similar association with circulating growth factors.[21]

In addition, later birth order is associated with a higher amount of exposure to infectious agents on average (through the earlier-born children, ie, the older siblings), which may affect the development of the immune system and conditions that depend on it, such as allergy and atopic disease.[17] Given that these conditions themselves may have a protective association with meningioma and are likely more common in first-born than in later-born children, it is less likely that this underlying mechanism explains the observed finding for meningioma.[6,16]

Finally, levels of circulating estrogen are higher in first-borns than in later borns.[22] This is particularly of interest for meningioma, where a consistently higher risk in women compared to men during adulthood has long suggested the possibility that circulating estrogens/progesterones may play a causal role. Some reports have even identified regression of meningioma after cessation of exogenous hormones, but in population studies, the association remains less clear.[23] Some case-control studies have identified relatively strong positive associations between the use of exogenous hormones and incidence of meningioma,[24–26] while others have not.[27] Overall, there is a suggestive positive association with menopausal hormone therapy and more limited data for oral contraceptives.[2] In our data, some observations may be related to estrogen exposure including the 5-fold risk for meningioma in less educated non-Latino White individuals (<8 years compared to 12 years of education), given known associations between high body mass index and low education levels in Californians.[28] Estrogens and early hormonal risk factors are associated with body mass index among adolescents and young adults,[29] which may accelerate development in girls with delays in boys, mirroring the sex-specific meningioma incidence trends that appear after puberty and extend through the reproductive years.[2]

Interestingly, despite relatively strong findings demonstrating an association between higher adult body mass index and later incidence of meningioma, we found a statistically significant positive association between birthweight, which is itself associated with adult body mass index, and meningioma only among non-Latino White individuals, with the noted limitation that the Latino subgroup was small enough to prohibit adequate statistical comparison.[15,24,27]

This study is distinguished by its population-based design, and conceptually it is a nested case-control study within the California birth cohort. The linkage covered all births and cancer diagnoses in California, the most populous and racially/ethnically diverse state in the United States, over a long period of time. No cases or controls had to be traced or consented to for participation in this study, minimizing selection bias. All data on birth characteristics are retrieved from existing birth records that were collected before meningioma diagnosis, eliminating recall bias. In addition, data on race/ethnicity and age at diagnosis allowed for stratified analyses to delineate more clearly various associations of interest. Despite this, limitations of our study include the younger age of participants, with the oldest being only 37 years. Given that meningioma is more common in older age, it is possible that the findings reported here may not be generalizable. In addition, because this was a hypothesis-generating study, we conducted statistical tests on several different strata, making it possible that some of the statistically significant results could be false positives. For validation, future studies should aim to examine these same factors, particularly if data on incidence and risk factors are available across the entire lifespan.

Conclusion

In this large population-based study not prone to selection and recall bias, higher birth order was associated with a reduced risk of early-onset meningioma, while female sex and Black race were linked to an increased risk. There were also indications of differential associations by race/ethnicity and age of diagnosis. Future studies with a large number of early-onset cases may help shed light on the possible underlying mechanisms.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* online.

Keywords

birth characteristics | birth order | birthweight | epidemiology | meningioma.

Conflict of Interest: The authors have nothing to disclose.

Author Contributions

Conceptualization (All authors), Methodology (R.W., L.M.M., C.M., X.M., J.L.W.), Formal Analysis (D.J.C., R.W.), Writing—Original Draft (D.J.C.), Writing—Review and Editing (All authors), Supervision (X.M., J.L.W.). The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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