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SEASON OF BIRTH AND OTHER PERINATAL RISK FACTORS FOR MELANOMA

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ratio), SD (standard deviation), ultraviolet radiation (UVR)

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SUMMARY

Background: Ultraviolet radiation (UVR) exposure is the main risk factor for cutaneous malignant melanoma (CMM), but its specific effect in infancy is unknown. We examined whether season of birth, a proxy for solar UVR exposure in the first few months of life, is associated with CMM in childhood through young adulthood.

Methods: National cohort study of 3,571,574 persons born in Sweden in 1973-2008, followed up for CMM incidence through 2009 (maximum age 37 years) to examine season of birth and other perinatal factors.

Results: There were 1,595 CMM cases in 63.9 million person-years of follow-up. We found a sinusoidal pattern in CMM risk by season of birth (P=0.006), with peak risk corresponding to birthdates in spring (March-May). Adjusted odds ratios for CMM by season of birth were 1.21 (95% CI, 1.05-1.39; P=0.008) for spring, 1.07 (95% CI, 0.92-1.24; P=0.40) for summer, and 1.12 (95% CI, 0.96-1.29; P=0.14) for winter, relative to fall. Spring birth was associated with superficial spreading subtype (P=0.02), whereas there was no seasonal association with nodular subtype (P=0.26). Other CMM risk factors included family history of CMM in a sibling (>6-fold) or parent (>3-fold), female gender, high fetal growth, and high paternal education level.

Conclusions: In this large cohort study, persons born in spring had increased risk of CMM in childhood through young adulthood, suggesting that the first few months of life may be a critical period of UVR susceptibility. Sun avoidance in early infancy may play an important role in the prevention of CMM in high-risk populations.

INTRODUCTION

The incidence of cutaneous malignant melanoma (CMM) has increased in Western countries over the past five decades.[1] Although ultraviolet radiation (UVR) exposure is the main risk factor, the effect of UVR exposure during infancy on CMM risk in later life is unknown. Previous studies have reported that childhood sun exposures are a strong determinant of CMM risk in later life but have not specifically examined exposures in infancy.[2-3] Recent evidence that UVR-related pigmentation begins in the first summer of life[4] has suggested that solar UVR exposures in infancy may play an important role in the development of CMM, particularly in susceptible populations that lack the protective effect of high skin melanin concentration.[5-6] Direct assessment of UVR exposures on the individual level is usually infeasible in cohorts that are sufficiently large to test this hypothesis. However, season of birth is a useful proxy for solar UVR exposures in the first few months of life. We hypothesized that persons born just prior to summer, preceding the period of highest solar UVR exposures, would have an increased risk of CMM in later life. If confirmed, this would suggest that the first few months of life are an important period of UVR susceptibility, and would help target preventive interventions.

In addition to UVR exposure and genetic susceptibility,[7] other perinatal and familial risk factors for CMM have also been hypothesized, including high birth weight,[8-9] older parental age,[8, 10] and early birth order.[8, 11-12] Previous studies of these putative risk factors have yielded mixed results, due in part to differences in study design or sample selection, and insufficient sample sizes. Large population-based cohort studies have the potential to clarify these risk factors and improve the understanding of mechanisms involved in the development of CMM. We conducted a national cohort study of 3.5 million people in Sweden to examine whether

season of birth and other perinatal and familial factors are associated with CMM in childhood through young adulthood.

METHODS

Study Population

We identified 3,595,055 individuals in the Swedish Birth Registry who were born from 1973 through 2008. Month and day of birth information was complete for the entire cohort. We excluded 10,438 (0.3%) individuals who had missing information for birth weight, and 7,704 (0.2%) others who had missing information for gestational age at birth. To remove possible coding errors, we also excluded 5,339 (0.1%) others who had a reported birth weight more than four standard deviations (SD) above or below the mean birth weight for gestational age and gender based on a Swedish reference growth curve.[13] A total of 3,571,574 individuals (99.3% of the original cohort) remained for inclusion in the study. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

Melanoma Ascertainment

The study cohort was followed for CMM incidence from birth through December 31, 2009 (maximum attained age was 37 years). All incident CMM cases were identified using the *International Classification of Diseases, 7th revision*, code 190, in the Swedish Cancer Registry. This registry includes all primary incident cancers in Sweden since 1958, with compulsory reporting nationwide. CMM subtypes that were sufficiently common for separate analysis were identified using standard ICD-O codes (8743 for superficial spreading melanoma, and 8721 for

nodular melanoma). Information on Breslow's thickness (a prognostic indicator for melanoma) was unavailable.

Perinatal and Familial Variables

Perinatal and familial characteristics that may be associated with CMM were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number.[14] The following variables were examined as predictors of interest or adjustment variables: gender; birth year (modeled simultaneously as continuous and categorical [1973-1979, 1980-1984, 1985-1989, 1990-2008] variables to allow for a non-linear effect); season of birth (modeled as a sinusoidal function, as described below); fetal growth (a standardized fetal growth variable defined as the number of standard deviations from the mean birth weight for gestational age and gender based on a Swedish reference growth curve,[13] modeled alternatively as a categorical [<-2; -2 to <-1; -1 to <0; 0 to <1; 1 to <2; ≥2 SD] or continuous variable); gestational age at birth (based primarily on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s; modeled alternatively as a categorical [<37, 37-42, ≥43 weeks] or continuous variable); birth weight (modeled alternatively as a categorical [<2500, 2500-3999, ≥4000 g] or continuous variable); birth length (crown-heel length in cm, modeled alternatively as a categorical [<48, 48-52, ≥53 cm] or continuous variable); multiple birth (singleton vs. twin or higher order); birth order (1, 2, 3, 4, ≥5); maternal and paternal age at birth (<20, 20-24, 25-29, 30-34, 35-39, ≥40 years; examined separately for mothers and fathers); parental country of birth (both parents born in Sweden, both born in Europe/U.S./Canada but not both in Sweden, 1 or both born in other countries; note that other specific information on

ethnicity was unavailable); maternal and paternal education level (compulsory high school or

less [≤9 years], practical high school or some theoretical high school [10-11 years], theoretical

high school and/or some college [12-14 years], college and/or post-graduate study [≥15 years];

examined separately for mothers and fathers); and family history of CMM in a parent or sibling

(yes or no; identified from the Swedish Cancer Registry from 1958 through 2009, not self-

reported, thus enabling highly complete and unbiased ascertainment during this time period, and

examined separately for parents and siblings).

Statistical Analysis

We explored different statistical models to identify the best fit to the data. Logistic

regression was a good fit in all models using the Pearson chi-squared or Hosmer-Lemeshow

tests.[15] In contrast, Poisson regression violated goodness-of-fit tests in all models; and Cox

proportional hazards regression was a poor fit in most models, whereas it gave essentially

identical results as logistic regression in others in which the proportional hazards assumption was

satisfied. As a result, logistic regression was used in the final models to estimate odds ratios

(ORs) and 95% confidence intervals (CIs) for associations between the predictor variables and

CMM.

Season of birth was modeled using standard methods for seasonal data. First, date of

birth (DOB, coded as an integer from 1 to 365) was modeled as a sinusoidal function in the

logistic regression model, using an iterative method to identify the peak date for CMM relative

risk and to test for an overall seasonal association, as previously described.[16] In the case of a

leap year, February 29 was recoded as calendar day 59 so that the respective year had 365 days.

Specifically, the trigonometric term entered into the logistic model was

$$x = \cos[2 \times \arccos(-1) \times ((DOB\text{-}t_{max})/365)]$$

where t_{max} (the peak birthdate for CMM risk) was determined iteratively by finding the value

from 1 to 365 that maximized the model coefficient.[16] After identifying the peak date in this

manner, the 3-month period of maximum risk was identified by centering on this date.

Two different adjusted models were used: The first was adjusted for birth year, and the

second was further adjusted for other variables that were found to be associated with CMM

(gender, season of birth, parental country of birth, paternal education level, and family history of

CMM in a parent or sibling). First-order interactions between gender or season of birth and

other variables were explored using a likelihood ratio test. In addition, multinomial logistic

regression was used to test for heterogeneity in the association between each risk factor and

earlier-onset (age <15 years) vs. later-onset (age ≥15 years) CMM. We also repeated the same

models described above to explore associations between perinatal or familial variables and the

most common CMM subtypes (superficial spreading and nodular melanoma). All statistical tests

were 2-sided and used an α-level of 0.05. All analyses were conducted using Stata version

13.0.[17]

RESULTS

Among the 3,571,574 persons in this cohort, 1,595 CMM cases were identified in 63.9

million person-years of follow-up. The mean age at CMM diagnosis was 26.3 years (SD 5.6,

median 26.8, range 1.4 to 36.8 years). CMM incidence by season or month of birth is shown in

Table 1, and was highest among persons born in April or May (2.79 and 2.82 cases per 100,000

person-years, respectively). In the logistic model, we found a sinusoidal pattern in CMM risk by

season of birth (*P*=0.006, adjusted for birth year), with peak risk corresponding to a birthdate of

April 13, and lowest risk corresponding to a birthdate of October 12. Figure 1 shows the

seasonal pattern in relative risk of CMM from the sinusoidal model. The 3-month period of

maximum risk, identified by centering around the peak date (April 13), coincided nearly exactly

with March through May, and the 3-month period of minimum risk with September through

November. As a result, season of birth was examined in subsequent models as spring (March-

May), summer (June-August), or winter (December-February), relative to fall (September-

November).

Unadjusted ORs for CMM by season of birth were 1.25 (95% CI, 1.09-1.44; *P*=0.002) for

spring, 1.04 (95% CI, 0.90-1.21; *P*=0.56) for summer, and 1.13 (95% CI, 0.98-1.31; *P*=0.10) for

winter, relative to fall (not shown in the tables). The distribution of season of birth varied

comparing earlier with later birth cohorts, hence birth year was considered as a potential

confounder. After adjusting for birth year (Table 2, adjusted model 1), ORs for CMM by season

of birth were 1.22 (95% CI, 1.06-1.40; *P*=0.005) for spring, 1.07 (95% CI, 0.92-1.24; *P*=0.38)

for summer, and 1.12 (95% CI, 0.96-1.30; *P*=0.13) for winter, relative to fall. Further

adjustment for other variables had a negligible effect on these risk estimates (Table 2, adjusted

model 2). For spring relative to fall birth, the fully adjusted OR for early-onset CMM (age <15

years) was 2.13 (95% CI, 0.89-5.11; P=0.09; based on 42 cases) and for later-onset CMM (≥15

years) was 1.19 (95% CI, 1.03-1.37; P=0.02; based on 1,553 cases) (test for heterogeneity

between aORs, *P*=0.19; not shown in the tables).

The strongest overall risk factors for CMM were a family history of CMM in a sibling or

parent (>6-fold and >3-fold risks, respectively; Table 2, adjusted model 2). A parental history of

CMM appeared to be more strongly associated with earlier-onset CMM (age <15 years, aOR,

8.27; 95% CI, 2.91-23.44; *P*<0.001; based on 42 cases) compared with later-onset CMM (age

≥15 years, aOR, 3.12; 95% CI, 2.41-3.90; *P*<0.001) (test for heterogeneity between aORs, *P*=0.07; not shown in the tables). There was no heterogeneity in the association between CMM in a sibling and earlier-onset (<15 years) vs. later-onset (≥15 years) CMM in the proband. We also found no evidence that the association between family history and CMM varied by whether the affected family member was male or female (*P*=0.86), or by whether the affected family member was the same or opposite sex as the proband (*P*=0.19).

Other risk factors for CMM in the fully adjusted model included female gender (2-fold risk relative to males), high fetal growth (P_{trend}=0.02), high birth weight (P_{trend} <0.001), high birth length (P_{trend}=0.006), and high paternal education level (P_{trend}=0.03) (Table 2, adjusted model 2). Risk of CMM also was lower among those who had 1 or both parents born outside of Sweden (and especially with a parent born outside of Europe, U.S., or Canada), relative to those whose parents were both Swedish-born (Table 2). Only 3,317 (<0.1%) persons (and only 1 with CMM) had a parent who was born in Australia or New Zealand, which precluded separate analysis of this group.

High gestational age at birth was associated with CMM before but not after adjusting for covariates in the fully adjusted model (Table 2). A modest trend of decreasing CMM risk by later birth order was also noted (P_{trend}=0.07; Table 2, adjusted model 2). Multiple birth, maternal and paternal age, and maternal education level were not associated with CMM.

We found no interactions between gender or season of birth and any other variables with respect to CMM risk, including none directly between gender and season of birth (*P*=0.09). Also, with the possible exceptions of season of birth and parental history of CMM (as noted above), there was no evidence of heterogeneity in the association between any other variable and earlier-onset (<15 years) vs. later-onset (≥15 years) CMM.

CMM subtype information was available for 864 (54.2%) cases. The most common

subtypes were superficial spreading (n=744) and nodular (n=89) melanoma, whereas there were

too few cases of lentigo maligna melanoma (n=18) or other known subtypes (n=13) for

meaningful analysis. A sinusoidal pattern in the risk of superficial spreading subtype was found

by season of birth (*P*=0.02, adjusted for birth year), with peak risk corresponding to a birthdate

of April 20. For spring relative to fall birth, the fully adjusted OR for superficial spreading

subtype was 1.24 (95% CI, 1.01-1.52; *P*=0.04). Other risk factors for superficial spreading

subtype were consistent with the overall CMM findings except that the associations with fetal

growth and paternal education were attenuated, although the trends were in the same direction

(see eTable 1 in supplemental data for full results). In contrast, there was no clear sinusoidal

pattern in the risk of nodular subtype by season of birth (*P*=0.26, adjusted for birth year). Other

results for nodular subtype differed from those for CMM overall or superficial spreading subtype

in that there was no increased risk among females, nor a positive trend by higher paternal

education level, although precision was limited due to the small number of cases (see eTable 2 in

supplemental data for full results).

DISCUSSION

In this large national cohort study, we found that the risk of CMM in childhood through

young adulthood had a sinusoidal pattern by season of birth, with highest risk among persons

born in spring (March-May). Because spring precedes the several month period of highest solar

UVR exposure (the main known risk factor for CMM), these findings suggest that the first few

months of life may be a critical period of UVR susceptibility for the development of CMM in

later life. These findings have implications for the prevention of CMM through avoidance of

direct sunlight exposures among infants, especially those <6 months of age or in high-risk families, consistent with current clinical recommendations.[18] We also found other risk factors for CMM, including family history of CMM, female gender, high fetal growth, and high paternal education level.

The only previous study of season of birth and CMM included 210 cases (ages 15 to 24 years) in northern England, and reported a sinusoidal variation among females only (P=0.03), with peak risk for birthdates in March.[19] Relative risk estimates for the association between season of birth and CMM were not reported. Our larger national cohort study found that CMM risk was similarly highest among persons born in spring (March-May). However, this was found in the entire population, irrespective of gender, and across a wider age range. In addition, we found that spring birth was specifically associated with superficial spreading (but not nodular) subtype. Because superficial spreading melanoma has been more strongly associated with sun exposures,[19-20] this finding also supports a solar UVR mechanism for the seasonal variation that we observed.

The link we found between spring birth and CMM is consistent with experimental evidence for the effects of UVR exposure in infancy. UVR is capable of directly stimulating melanin production in neonatal melanocytes or melanoma cells *in vitro*.[20] A pigmentation response to solar UVR exposure has also been observed *in vivo* in the first summer of life.[4] These effects may increase the risk of CMM in individuals who lack the protective mechanism of high basal concentrations of melanin.[3-4] Our population-based findings support the hypothesis that early infancy is an important period of UVR susceptibility for the development of CMM. Later sun exposure patterns and Vitamin D levels may modify these relationships and warrant further study to elucidate their relative influences.

We also found that high fetal growth was a risk factor for CMM in childhood through young adulthood. This is consistent with some[8, 22] but not all[9-10, 23] previous smaller studies, most of which were case-control studies[8-10] or examined older adults.[21] The largest previous cohort study included 847 CMM cases in Denmark, and reported a modest positive trend for CMM risk by higher birth weight (RR per 500 g increase = 1.14; 95% CI, 1.00-1.31).[22] Differences in sun exposure patterns are a possible explanation for this finding, although high birth weight has also been associated with other cancers, especially breast cancer, via other putative mechanisms.[22, 24] These mechanisms are not well-established but may involve a larger number of tissue stem cells which carry a greater capacity for oncogenic mutations later in life,[25] or increased levels of growth factors such as insulin-like growth factors I and II which are correlated with birth weight and have been shown to inhibit cell apoptosis and promote tumor growth.[26-27]

The strong associations we found with family history of CMM are consistent with earlier findings[28] and may reflect shared sun exposure patterns as well as possible genetic factors. An estimated 5% of all CMM cases occur in a familial setting with two or more close relatives affected, and susceptibility genes (e.g., CDKN2A and CDK4) have been identified in such families.[7] Consistent with other European studies and in contrast to Australia, New Zealand, or North America, we found a higher risk of CMM among females,[8-9, 28] likely related to gender differences in sun exposure patterns which vary across different countries.[1, 7] High paternal education level (an indicator of high socioeconomic status) was also a risk factor and may be related to more frequent recreational sun exposure.[7]

We found a possible trend of decreasing CMM risk by later birth order, which is in the same direction as that reported in several other studies.[8, 10-12, 28] Various hypotheses have been

proposed, including an immunoprotective effect resulting from earlier exposure to infectious agents from older siblings,[8] or decreased opportunities for recreational sun exposure in larger families.[28] In contrast to other studies, we found no relation between older maternal age and CMM in the offspring,[8, 10] or a lower risk among twins compared with singletons.[29-32]

Important strengths of this study were its population-based national cohort design and large sample size, enabling more robust and generalizable inferences. The use of season of birth as a proxy for UVR exposures in early infancy is a relatively novel approach to help elucidate a specific period of susceptibility. Linkage of birth and cancer registries provided detailed information on perinatal factors and CMM incidence that was nearly 100% complete nationwide.[33-34] A cohort design prevented selection bias that may potentially occur in case-control studies, and the use of registry-based data prevented bias that may result from self-reporting. Family history of CMM was also based on registry data with virtually complete ascertainment, thus improving the reliability of those risk estimates. CMM subtype information enabled exploratory analyses of the most common subtypes.

Study limitations included the unavailability of direct assessments of solar UVR exposures. The use of season of birth as a proxy for UVR exposures in the first few months of life is inherently imprecise and involves misclassification which is non-differential with respect to the outcome (CMM). Consequently, the reported risk estimates are expected to be conservatively biased toward the null hypothesis. The risk of CMM from actual solar UVR exposures in early infancy (i.e., with reduced misclassification) may be higher. Other seasonally varying environmental exposures such as infectious agents, however, also cannot be excluded as possible contributors to the seasonal patterns we observed. In addition, the specific comparisons

in our analyses (e.g., cutpoints for season of birth groups) were data-determined, hence the findings should be interpreted with caution and will require confirmation in other large cohorts.

In summary, this large national cohort study identified several risk factors for CMM among persons born in Sweden during 1973-2008, including spring birth, high fetal growth, and family history of CMM. The increased risk we observed among persons born in spring, preceding the period of highest solar UVR exposures, suggests that the first few months of life may be a critical period of UVR susceptibility for the development of CMM in later life. Avoidance of sun exposures in early infancy may play an important role in the prevention of CMM in high-risk populations.

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Table 1. Incidence of cutaneous malignant melanoma (CMM) in 1973-2009 by season or month of birth

	Births	Person-years	CMM cases	
	N (%)	(in millions)	n (%)	No. per 100,000 person-years
Overall	3,571,574 (100.0)	63.95	1,595 (100.0)	2.49
Spring	990,773 (27.7)	18.17	498 (31.2)	2.74
March	334,787 (9.4)	6.20	162 (10.2)	2.61
April	331,520 (9.3)	6.09	170 (10.7)	2.79
May	324,466 (9.1)	5.88	166 (10.4)	2.82
Summer	915,888 (25.6)	16.15	384 (24.1)	2.38
June	305,267 (8.6)	5.45	127 (8.0)	2.33
July	310,043 (8.7)	5.44	131 (8.2)	2.41
August	300,578 (8.4)	5.26	126 (7.9)	2.40
Fall	822,327 (23.0)	14.38	330 (20.7)	2.29
September	291,196 (8.2)	5.13	116 (7.3)	2.26
October	278,533 (7.8)	4.84	115 (7.2)	2.37
November	252,598 (7.1)	4.41	99 (6.2)	2.25
Winter	842,586 (23.6)	15.25	383 (24.0)	2.51
December	253,596 (7.1)	4.42	100 (6.3)	2.26
January	297,241 (8.3)	5.47	144 (9.0)	2.63
February	291,749 (8.2)	5.36	139 (8.7)	2.59

Table 2. Adjusted odds ratios for associations between perinatal or familial characteristics and cutaneous malignant melanoma (CMM) in 1973-2009

	Total population N (%)	CMM cases n (%)	Adjusted Model 1[a]			Adjusted Model 2[b]		
			OR	95% CI	*P*	OR	95% CI	*P*
Age at diagnosis (years)								
<5		4 (0.3)						
5-9		6 (0.4)						
10-14		32 (2.0)						
15-19		181 (11.4)						
20-24		395 (24.8)						
25-29		505 (31.7)						
≥30		472 (29.6)						
Gender								
Male	1,835,588 (51.4)	553 (34.7)	1.00			1.00		
Female	1,735,986 (48.6)	1,042 (65.3)	2.00	1.80, 2.21	<0.001	2.00	1.80, 2.21	<0.001
Season of birth								
Spring (Mar-May)	990,773 (27.7)	498 (31.2)	1.22	1.06, 1.40	0.005	1.21	1.05, 1.39	0.008
Summer (Jun-Aug)	915,888 (25.6)	384 (24.1)	1.07	0.92, 1.24	0.38	1.07	0.92, 1.24	0.40
Fall (Sep-Nov)	822,327 (23.0)	330 (20.7)	1.00			1.00		
Winter (Dec-Feb)	842,586 (23.6)	383 (24.0)	1.12	0.97, 1.30	0.13	1.12	0.96, 1.29	0.14
Fetal growth (SD)								
<-2	112,440 (3.1)	57 (3.6)	0.69	0.52, 0.91		0.70	0.53, 0.93	
-2 to <-1	535,817 (15.0)	291 (18.2)	0.93	0.81, 1.08		0.93	0.81, 1.08	
-1 to <0	1,266,800 (35.5)	542 (34.0)	0.87	0.77, 0.98		0.87	0.77, 0.98	
0 to <1	1,118,797 (31.3)	493 (30.9)	1.00			1.00		
1 to <2	428,757 (12.0)	162 (10.2)	0.92	0.77, 1.10		0.93	0.77, 1.11	
≥2	108,963 (3.1)	50 (3.1)	1.16	0.87, 1.55		1.17	0.87, 1.56	
Per SD (trend test)			1.06	1.01, 1.10	0.02	1.06	1.01, 1.10	0.02
Gestational age at birth (weeks)								
<37	206,835 (5.8)	71 (4.5)	0.84	0.66, 1.07		0.89	0.70, 1.13	
37-42	3,323,840 (93.1)	1,488 (93.3)	1.00			1.00		
≥43	40,899 (1.1)	36 (2.3)	0.88	0.63, 1.22		0.88	0.63, 1.22	

<2500	149,359 (4.2)	52 (3.3)	0.81	0.61, 1.07		0.82	0.62, 1.09	
2500-3999	2,779,681 (77.8)	1,265 (79.3)	1.00			1.00		
≥4000	642,534 (18.0)	278 (17.4)	1.07	0.94, 1.22		1.15	1.01, 1.31	
Per 1000 g (trend test)			1.12	1.03, 1.23	0.01	1.18	1.08, 1.29	<0.001
Birth length (cm)								
<48	359,988 (10.1)	138 (8.7)	0.88	0.74, 1.05		0.86	0.72, 1.03	
48-52	2,601,357 (72.8)	1,199 (75.2)	1.00			1.00		
≥53	577,004 (16.2)	255 (16.0)	0.96	0.84, 1.10		1.09	0.95, 1.25	
Unknown	33,225 (0.9)	3 (0.2)	0.45	0.15, 1.40		0.49	0.16, 1.53	
Per cm (trend test)			1.01	0.99, 1.03	0.30	1.03	1.01, 1.05	0.006
Multiple birth								
Singleton	3,487,043 (97.6)	1,569 (98.4)	1.00			1.00		
Twin or higher order	84,474 (2.4)	26 (1.6)	0.93	0.63, 1.38	0.73	0.92	0.63, 1.36	0.69
Birth order								
1	1,411,435 (39.5)	691 (43.3)	1.00			1.00		
2	1,224,253 (34.3)	618 (38.7)	1.04	0.93, 1.16		1.02	0.91, 1.14	
3	509,759 (14.3)	223 (14.0)	0.97	0.83, 1.13		0.95	0.82, 1.11	
4	148,413 (4.2)	48 (3.0)	0.79	0.59, 1.06		0.80	0.60, 1.07	
≥5	67,533 (1.9)	15 (0.9)	0.59	0.36, 0.99		0.64	0.38, 1.06	
Unknown	210,181 (5.9)	0 (0.0)	NE	NE		NE	NE	
Per each higher category (trend test)			0.95	0.90, 1.01	0.09	0.95	0.90, 1.00	0.07
Maternal age at birth (years)								
<20	84,008 (2.3)	67 (4.2)	0.91	0.71, 1.17		1.02	0.79, 1.32	
20-24	678,209 (19.0)	375 (23.5)	0.82	0.73, 0.94		0.87	0.77, 0.99	
25-29	1,251,782 (35.1)	654 (41.0)	1.00			1.00		
30-34	1,034,457 (29.0)	375 (23.5)	0.98	0.86, 1.11		0.96	0.85, 1.09	
35-40	432,425 (12.1)	107 (6.7)	0.87	0.71, 1.07		0.86	0.70, 1.06	
≥40	86,575 (2.4)	17 (1.1)	0.82	0.51, 1.33		0.84	0.52, 1.36	
Unknown	4,118 (0.1)	0 (0.0)	NE	NE		NE	NE	
Per each higher category (trend test)			1.03	0.98, 1.08	0.25	1.00	0.95, 1.05	0.98
Paternal age at birth (years)								
<20	16,949 (0.5)	9 (0.6)	0.80	0.41, 1.54		0.92	0.47, 1.78	
20-24	327,052 (9.2)	209 (13.1)	0.96	0.82, 1.12		1.01	0.86, 1.18	

25-29	1,021,995 (28.6)	569 (35.7)	1.00			1.00		
30-34	1,161,825 (32.5)	517 (32.4)	1.10	0.97, 1.24		1.07	0.95, 1.21	
35-40	657,548 (18.4)	192 (12.0)	0.97	0.82, 1.14		0.96	0.81, 1.13	
≥40	357,578 (10.0)	88 (5.5)	0.92	0.73, 1.15		0.93	0.74, 1.17	
Unknown	28,627 (0.8)	11 (0.7)	0.88	0.49, 1.61		1.30	0.67, 2.50	
Per each higher category (trend test)			1.01	0.96, 1.05	0.79	0.99	0.95, 1.04	0.75
Parental country of birth								
Both born in Sweden	2,854,201 (79.9)	1,416 (88.8)	1.00			1.00		
Both born in Europe/U.S./Canada (but not both Sweden)	417,438 (11.7)	164 (10.3)	0.71	0.60, 0.83	<0.001	0.76	0.65, 0.90	0.001
1 or both born in other countries	299,901 (8.4)	15 (0.9)	0.34	0.20, 0.57	<0.001	0.37	0.22, 0.62	<0.001
Maternal education (years)								
≤9	675,199 (18.9)	474 (29.7)	1.00			1.00		
10-11	1,150,381 (32.2)	542 (34.0)	0.92	0.81, 1.04		0.90	0.80, 1.02	
12-14	1,045,489 (29.3)	329 (20.6)	1.02	0.89, 1.18		0.95	0.82, 1.10	
≥15	554,895 (15.5)	200 (12.5)	1.09	0.92, 1.29		0.98	0.81, 1.19	
Unknown	145,610 (4.1)	50 (3.1)	0.54	0.40, 0.72		0.60	0.45, 0.81	
Per each higher category (trend test)			1.03	0.98, 1.08	0.25	0.99	0.93, 1.05	0.73
Paternal education (years)								
≤9	767,733 (21.5)	495 (31.0)	1.00			1.00		
10-11	1,129,269 (31.6)	399 (25.0)	0.94	0.83, 1.08		0.94	0.83, 1.08	
12-14	960,319 (26.9)	400 (25.1)	1.15	1.01, 1.32		1.14	1.00, 1.30	
≥15	538,137 (15.1)	237 (14.9)	1.15	0.98, 1.34		1.12	0.96, 1.31	
Unknown	176,116 (4.9)	64 (4.0)	0.64	0.49, 0.82		0.76	0.58, 0.99	
Per each higher category (trend test)			1.06	1.01, 1.12	0.01	1.05	1.01, 1.11	0.03
CMM in a parent								
No	3,535,454 (99.0)	1,510 (94.7)	1.00			1.00		
Yes	36,120 (1.0)	85 (5.3)	3.39	2.73, 4.23	<0.001	3.21	2.58, 4.00	<0.001
CMM in a sibling								
No	3,569,772 (99.9)	1,583 (99.2)	1.00			1.00		
Yes	1,802 (<0.1)	12 (0.8)	7.39	4.18, 13.08	<0.001	6.53	3.68, 11.58	<0.001

[a]Adjusted for birth year (modeled simultaneously as continuous and categorical variables).
[b]Adjusted for birth year (as noted above), gender, season of birth, parental country of birth, paternal education, and family history of CMM in a parent or sibling.

The reference category for all variables is indicated by an odds ratio of 1.00. Missing data were excluded for trend tests.
CI = confidence interval, NE = not estimable, OR = odds ratio.
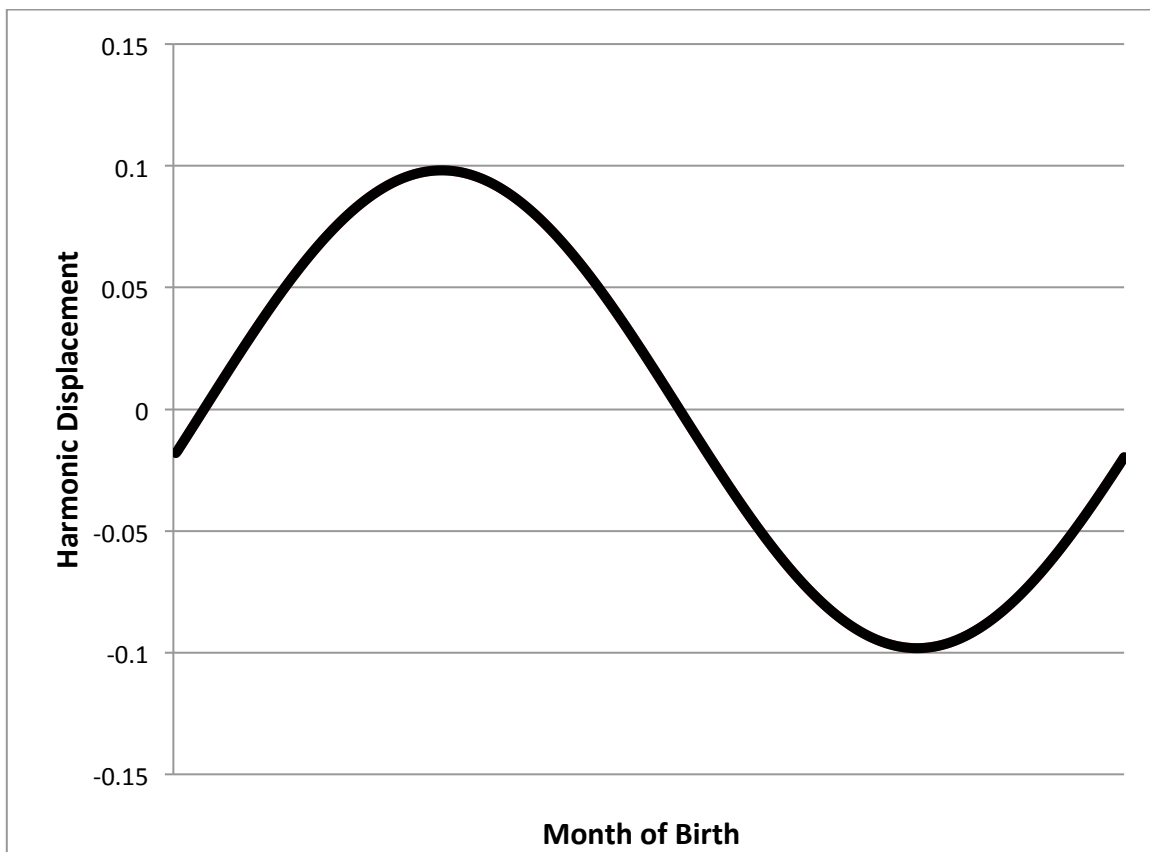
Figure 1. Sinusoidal logistic regression results for association between birthdate and cutaneous malignant melanoma (CMM) in childhood through young adulthood, adjusted for birth year (P=0.006 for overall seasonal association). Harmonic displacement represents the log odds ratio for a given time point relative to the mean risk across the entire calendar year.

SUPPLEMENTARY DATA

eTable 1. Adjusted odds ratios for associations between perinatal or familial characteristics and superficial spreading melanoma (n=744 cases) in 1973-2009

	Total population N (%)	Cases n (%)	Adjusted Model 1[a]			Adjusted Model 2[b]		
			OR	95% CI	*P*	OR	95% CI	*P*
Age at diagnosis (years)								
<5		0 (0.0)						
5-9		0 (0.0)						
10-14		2 (0.3)						
15-19		67 (9.0)						
20-24		191 (25.7)						
25-29		243 (32.7)						
≥30		241 (32.4)						
Gender								
Male	1,835,588 (51.4)	243 (32.7)	1.00			1.00		
Female	1,735,986 (48.6)	501 (67.3)	2.18	1.87, 2.54	<0.001	2.18	1.87, 2.54	<0.001
Season of birth								
Spring	990,773 (27.7)	239 (32.1)	1.25	1.02, 1.53	0.03	1.24	1.01, 1.52	0.04
Summer	915,888 (25.6)	175 (23.5)	1.04	0.84, 1.30	0.70	1.04	0.84, 1.29	0.71
Fall	822,327 (23.0)	154 (20.7)	1.00			1.00		
Winter	842,586 (23.6)	176 (23.7)	1.10	0.89, 1.37	0.37	1.10	0.89, 1.37	0.39
Fetal growth (SD)								
<-2	112,440 (3.1)	34 (4.6)	0.91	0.63, 1.30		0.92	0.64, 1.32	
-2 to <-1	535,817 (15.0)	139 (18.7)	0.99	0.80, 1.23		0.99	0.80, 1.22	
-1 to <0	1,266,800 (35.5)	249 (33.5)	0.90	0.75, 1.08		0.89	0.74, 1.07	
0 to <1	1,118,797 (31.3)	218 (29.3)	1.00			1.00		
1 to <2	428,757 (12.0)	76 (10.2)	0.98	0.76, 1.28		0.99	0.76, 1.28	
≥2	108,963 (3.1)	28 (3.8)	1.48	1.00, 2.19		1.49	1.00, 2.21	
Per SD (trend test)			1.04	0.98, 1.12	0.19	1.05	0.98, 1.12	0.17
Gestational age at birth (weeks)								
<37	206,835 (5.8)	32 (4.3)	0.82	0.58, 1.17		0.87	0.61, 1.24	
37-42	3,323,840 (93.1)	693 (93.1)	1.00			1.00		
≥43	40,899 (1.1)	19 (2.6)	0.96	0.61, 1.51		0.95	0.60, 1.50	
Per week (trend test)			1.04	1.00, 1.09	0.04	1.03	0.99, 1.07	0.12
Birth weight (g)								

<2500	149,359 (4.2)	22 (3.0)	0.74	0.48, 1.13		0.75	0.49, 1.15	
2500-3999	2,779,681 (77.8)	588 (79.0)	1.00			1.00		
≥4000	642,534 (18.0)	134 (18.0)	1.12	0.93, 1.35		1.22	1.01, 1.47	
Per 1000 g (trend test)			1.12	0.98, 1.28	0.10	1.19	1.04, 1.36	0.01
Birth length (cm)								
<48	359,988 (10.1)	65 (8.7)	0.89	0.69, 1.15		0.86	0.67, 1.12	
48-52	2,601,357 (72.8)	563 (75.7)	1.00			1.00		
≥53	577,004 (16.2)	115 (15.5)	0.92	0.76, 1.13		1.06	0.86, 1.30	
Unknown	33,225 (0.9)	1 (0.1)	0.34	0.05, 2.44		0.38	0.05, 2.69	
Per cm (trend test)			1.01	0.98, 1.04	0.51	1.03	1.00, 1.07	0.04
Multiple birth								
Singleton	3,487,043 (97.6)	737 (99.1)	1.00			1.00		
Twin or higher order	84,474 (2.4)	7 (0.9)	0.54	0.26, 1.14	0.11	0.54	0.25, 1.13	0.10
Birth order								
1	1,411,435 (39.5)	328 (44.1)	1.00			1.00		
2	1,224,253 (34.3)	278 (37.4)	0.99	0.84, 1.16		0.97	0.83, 1.14	
3	509,759 (14.3)	111 (14.9)	1.03	0.83, 1.28		1.01	0.82, 1.26	
4	148,413 (4.2)	20 (2.7)	0.71	0.45, 1.11		0.72	0.46, 1.13	
≥5	67,533 (1.9)	7 (0.9)	0.59	0.28, 1.26		0.64	0.30, 1.35	
Unknown	210,181 (5.9)	0 (0.0)	NE	NE		NE	NE	
Per each higher category (trend test)			0.95	0.88, 1.03	0.23	0.95	0.88, 1.03	0.24
Maternal age at birth (years)								
<20	84,008 (2.3)	34 (4.6)	0.95	0.67, 1.38		1.06	0.74, 1.51	
20-24	678,209 (19.0)	176 (23.7)	0.81	0.67, 0.97		0.85	0.70, 1.02	
25-29	1,251,782 (35.1)	310 (41.7)	1.00			1.00		
30-34	1,034,457 (29.0)	162 (21.8)	0.91	0.75, 1.10		0.90	0.74, 1.09	
35-40	432,425 (12.1)	52 (7.0)	0.92	0.69, 1.24		0.93	0.69, 1.25	
≥40	86,575 (2.4)	10 (1.3)	1.07	0.57, 2.01		1.11	0.59, 2.09	
Unknown	4,118 (0.1)	0 (0.0)	NE	NE		NE	NE	
Per each higher category (trend test)			1.03	0.96, 1.11	0.39	1.01	0.94, 1.09	0.80
Paternal age at birth (years)								
<20	16,949 (0.5)	5 (0.7)	0.97	0.40, 2.36		1.12	0.46, 2.71	
20-24	327,052 (9.2)	111 (14.9)	1.12	0.90, 1.40		1.18	0.94, 1.47	
25-29	1,021,995 (28.6)	256 (34.4)	1.00			1.00		
30-34	1,161,825 (32.5)	242 (32.5)	1.16	0.97, 1.38		1.14	0.96, 1.36	
35-40	657,548 (18.4)	83 (11.2)	0.96	0.75, 1.23		0.96	0.75, 1.24	

≥40	357,578 (10.0)	42 (5.6)	1.01	0.73, 1.40		1.04	0.75, 1.45	
Unknown	28,627 (0.8)	5 (0.7)	0.89	0.37, 2.17		1.31	0.50, 3.45	
Per each higher category (trend test)			0.99	0.93, 1.06	0.79	0.98	0.92, 1.05	0.62
Parental country of birth								
Both born in Sweden	2,854,201 (79.9)	661 (88.8)	1.00			1.00		
Both born in Europe/U.S./Canada (but not both Sweden)	417,438 (11.7)	77 (10.3)	0.71	0.56, 0.90	0.004	0.76	0.60, 0.97	0.03
1 or both born in other countries	299,901 (8.4)	6 (0.8)	0.32	0.14, 0.72	0.006	0.35	0.16, 0.79	0.01
Maternal education (years)								
≤9	675,199 (18.9)	229 (30.8)	1.00			1.00		
10-11	1,150,381 (32.2)	259 (34.8)	0.93	0.78, 1.11		0.89	0.74, 1.07	
12-14	1,045,489 (29.3)	153 (20.6)	1.02	0.83, 1.25		0.93	0.75, 1.15	
≥15	554,895 (15.5)	80 (10.8)	0.92	0.72, 1.19		0.81	0.60, 1.08	
Unknown	145,610 (4.1)	23 (3.1)	0.52	0.34, 0.81		0.67	0.43, 1.04	
Per each higher category (trend test)			0.99	0.92, 1.07	0.78	0.95	0.87, 1.03	0.20
Paternal education (years)								
≤9	767,733 (21.5)	225 (30.2)	1.00			1.00		
10-11	1,129,269 (31.6)	199 (26.7)	1.07	0.88, 1.29		1.07	0.88, 1.29	
12-14	960,319 (26.9)	185 (24.9)	1.19	0.98, 1.45		1.18	0.97, 1.43	
≥15	538,137 (15.1)	105 (14.1)	1.14	0.90, 1.44		1.11	0.88, 1.40	
Unknown	176,116 (4.9)	30 (4.0)	0.67	0.45, 0.97		0.79	0.54, 1.17	
Per each higher category (trend test)			1.06	0.99, 1.14	0.10	1.05	0.98, 1.13	0.16
CMM in a parent								
No	3,535,454 (99.0)	704 (94.6)	1.00			1.00		
Yes	36,120 (1.0)	40 (5.4)	3.35	2.44, 4.61	<0.001	3.17	2.30, 4.36	<0.001
CMM in a sibling								
No	3,569,772 (99.9)	737 (99.1)	1.00			1.00		
Yes	1,802 (<0.1)	7 (0.9)	9.10	4.31, 19.21	<0.001	8.05	3.81, 17.01	<0.001

[a]Adjusted for birth year (modeled simultaneously as continuous and categorical variables).

[b]Adjusted for birth year (as noted above), gender, season of birth, parental country of birth, paternal education, and family history of CMM in a parent or sibling.

The reference category for all variables is indicated by an odds ratio of 1.00. Missing data were excluded for trend tests.

CI = confidence interval, NE = not estimable, OR = odds ratio.

eTable 2. Adjusted odds ratios for associations between perinatal or familial characteristics and nodular melanoma (n=89 cases) in 1973-2009

	Total population N (%)	Cases n (%)	Adjusted Model 1[a]			Adjusted Model 2[b]		
			OR	95% CI	*P*	OR	95% CI	*P*
Age at diagnosis (years)								
<5		0 (0.0)						
5-9		1 (1.1)						
10-14		3 (3.4)						
15-19		6 (6.7)						
20-24		33 (37.1)						
25-29		22 (24.7)						
≥30		24 (27.0)						
Gender								
Male	1,835,588 (51.4)	51 (57.3)	1.00			1.00		
Female	1,735,986 (48.6)	38 (42.7)	0.79	0.52, 1.20	0.27	0.79	0.52, 1.20	0.26
Season of birth								
Spring	990,773 (27.7)	25 (28.1)	0.81	0.46, 1.41	0.45	0.80	0.46, 1.39	0.42
Summer	915,888 (25.6)	22 (24.7)	0.81	0.45, 1.43	0.46	0.80	0.45, 1.42	0.44
Fall	822,327 (23.0)	25 (28.1)	1.00			1.00		
Winter	842,586 (23.6)	17 (19.1)	0.66	0.35, 1.22	0.18	0.65	0.35, 1.21	0.17
Fetal growth (SD)								
<-2	112,440 (3.1)	5 (5.6)	1.14	0.44, 2.96		1.17	0.45, 3.04	
-2 to <-1	535,817 (15.0)	14 (15.7)	0.83	0.44, 1.59		0.86	0.45, 1.64	
-1 to <0	1,266,800 (35.5)	29 (32.6)	0.86	0.51, 1.45		0.87	0.52, 1.47	
0 to <1	1,118,797 (31.3)	27 (30.3)	1.00			1.00		
1 to <2	428,757 (12.0)	10 (11.2)	1.03	0.50, 2.14		1.02	0.50, 2.11	
≥2	108,963 (3.1)	4 (4.5)	1.69	0.59, 4.82		1.67	0.58, 4.76	
Per SD (trend test)			1.08	0.90, 1.31	0.40	1.07	0.89, 1.30	0.47
Gestational age at birth (weeks)								
<37	206,835 (5.8)	1 (1.1)	0.21	0.03, 1.50		0.21	0.03, 1.53	
37-42	3,323,840 (93.1)	84 (94.4)	1.00			1.00		
≥43	40,899 (1.1)	4 (4.5)	1.80	0.66, 4.94		1.79	0.65, 4.92	
Per week (trend test)			1.06	0.95, 1.20	0.30	1.06	0.94, 1.20	0.33
Birth weight (g)								
<2500	149,359 (4.2)	1 (1.1)	0.26	0.04, 1.88		0.27	0.04, 1.95	
2500-3999	2,779,681 (77.8)	75 (84.3)	1.00			1.00		
≥4000	642,534 (18.0)	13 (14.6)	0.84	0.47, 1.51		0.80	0.44, 1.44	

Per 1000 g (trend test)			1.35	0.92, 1.99	0.12	1.29	0.88, 1.90	0.20
Birth length (cm)								
<48	359,988 (10.1)	6 (6.7)	0.64	0.28, 1.48		0.68	0.29, 1.56	
48-52	2,601,357 (72.8)	71 (79.8)	1.00			1.00		
≥53	577,004 (16.2)	12 (13.5)	0.77	0.42, 1.42		0.72	0.39, 1.33	
Unknown	33,225 (0.9)	0 (0.0)	NE	NE		NE	NE	
Per cm (trend test)			1.02	0.94, 1.12	0.58	1.01	0.93, 1.10	0.82
Multiple birth								
Singleton	3,487,043 (97.6)	89 (100.0)	1.00			1.00		
Twin or higher order	84,474 (2.4)	0 (0.0)	NE	NE	NE	NE	NE	NE
Birth order								
1	1,411,435 (39.5)	40 (44.9)	1.00			1.00		
2	1,224,253 (34.3)	35 (39.3)	1.02	0.65, 1.61		1.00	0.63, 1.57	
3	509,759 (14.3)	12 (13.5)	0.89	0.47, 1.70		0.86	0.45, 1.64	
4	148,413 (4.2)	1 (1.1)	0.28	0.04, 2.03		0.27	0.04, 1.97	
≥5	67,533 (1.9)	1 (1.1)	0.67	0.09, 4.89		0.68	0.09, 4.95	
Unknown	210,181 (5.9)	0 (0.0)	NE	NE		NE	NE	
Per each higher category (trend test)			0.88	0.70, 1.12	0.32	0.87	0.68, 1.11	0.27
Maternal age at birth (years)								
<20	84,008 (2.3)	3 (3.4)	0.71	0.22, 2.29		0.73	0.22, 2.39	
20-24	678,209 (19.0)	22 (24.7)	0.82	0.49, 1.38		0.82	0.49, 1.40	
25-29	1,251,782 (35.1)	39 (43.8)	1.00			1.00		
30-34	1,034,457 (29.0)	20 (22.5)	0.86	0.50, 1.48		0.88	0.51, 1.51	
35-40	432,425 (12.1)	5 (5.6)	0.65	0.26, 1.67		0.67	0.26, 1.71	
≥40	86,575 (2.4)	0 (0.0)	NE	NE		NE	NE	
Unknown	4,118 (0.1)	0 (0.0)	NE	NE		NE	NE	
Per each higher category (trend test)			0.96	0.78, 1.18	0.68	0.96	0.78, 1.18	0.70
Paternal age at birth (years)								
<20	16,949 (0.5)	0 (0.0)	NE	NE		NE	NE	
20-24	327,052 (9.2)	10 (11.2)	0.71	0.35, 1.42		0.70	0.35, 1.42	
25-29	1,021,995 (28.6)	37 (41.6)	1.00			1.00		
30-34	1,161,825 (32.5)	28 (31.5)	0.90	0.55, 1.48		0.91	0.56, 1.50	
35-40	657,548 (18.4)	10 (11.2)	0.74	0.37, 1.50		0.76	0.38, 1.55	
≥40	357,578 (10.0)	4 (4.5)	0.61	0.22, 1.72		0.65	0.23, 1.83	
Unknown	28,627 (0.8)	0 (0.0)	NE	NE		NE	NE	
Per each higher category (trend test)			0.97	0.80, 1.17	0.73	0.98	0.80, 1.19	0.82

Parental country of birth								
Both born in Sweden	2,854,201 (79.9)	82 (92.1)	1.00			1.00		
1 or both born in other countries	717,339 (20.1)	7 (7.9)	0.44	0.20, 0.95	0.04	0.52	0.24, 1.13	0.10
Maternal education (years)								
≤9	675,199 (18.9)	27 (30.3)	1.00			1.00		
10-11	1,150,381 (32.2)	41 (46.1)	1.19	0.73, 1.94		1.17	0.71, 1.91	
12-14	1,045,489 (29.3)	13 (14.6)	0.68	0.35, 1.33		0.66	0.33, 1.32	
≥15	554,895 (15.5)	7 (7.9)	0.66	0.29, 1.52		0.60	0.23, 1.53	
Unknown	145,610 (4.1)	1 (1.1)	0.19	0.03, 1.40		0.31	0.04, 2.34	
Per each higher category (trend test)			0.86	0.68, 1.07	0.17	0.84	0.65, 1.09	0.20
Paternal education (years)								
≤9	767,733 (21.5)	32 (36.0)	1.00			1.00		
10-11	1,129,269 (31.6)	27 (30.3)	0.95	0.57, 1.60		0.95	0.57, 1.60	
12-14	960,319 (26.9)	18 (20.2)	0.79	0.44, 1.41		0.78	0.44, 1.40	
≥15	538,137 (15.1)	11 (12.4)	0.81	0.41, 1.61		0.80	0.40, 1.59	
Unknown	176,116 (4.9)	1 (1.1)	0.15	0.02, 1.11		0.20	0.03, 1.47	
Per each higher category (trend test)			0.92	0.75, 1.12	0.41	0.91	0.74, 1.12	0.37
CMM in a parent								
No	3,535,454 (99.0)	87 (97.8)	1.00			1.00		
Yes	36,120 (1.0)	2 (2.2)	1.40	0.35, 5.71	0.64	1.31	0.32, 5.33	0.71
CMM in a sibling								
No	3,569,772 (99.9)	87 (97.8)	1.00			1.00		
Yes	1,802 (<0.1)	2 (2.2)	23.03	5.66, 93.71	<0.001	22.09	5.42, 90.07	<0.001

[a]Adjusted for birth year (modeled simultaneously as continuous and categorical variables).

[b]Adjusted for birth year (as noted above), gender, season of birth, parental country of birth, paternal education, and family history of CMM in a parent or sibling.

The reference category for all variables is indicated by an odds ratio of 1.00. Missing data were excluded for trend tests.

CI = confidence interval, NE = not estimable, OR = odds ratio.